



(51) International Patent Classification:

C07K 16/28 (2006.01) A61K 39/395 (2006.01)

A61P 35/02 (2006.01)

(21) International Application Number:

PCT/US2021/035069

(22) International Filing Date:

31 May 2021 (31.05.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/032,302 29 May 2020 (29.05.2020) US

63/044,833 26 June 2020 (26.06.2020) US

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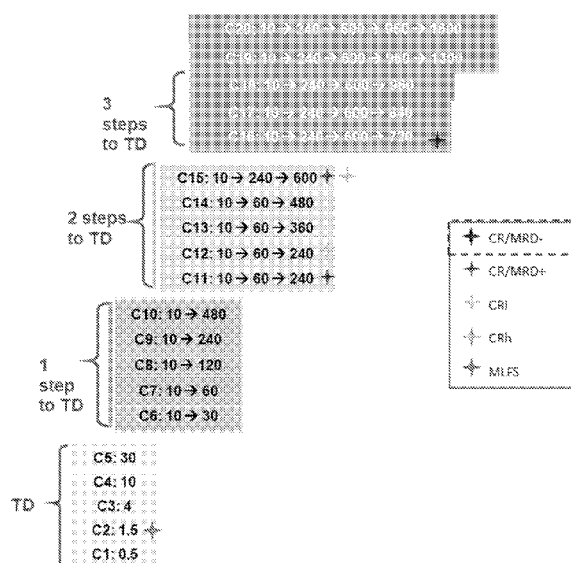
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

(54) Title: ADVERSE EFFECTS-MITIGATING ADMINISTRATION OF A BISPECIFIC ANTIBODY CONSTRUCT BINDING TO CD33 AND CD3

Fig. 1



(57) Abstract: The present invention provides a bispecific construct comprising a first binding domain specifically binding to a target such as CD33 and a second binding domain specifically binding to an effector such as CD3 for use in a method for the treatment of myeloid leukemia, wherein the construct is administered in one or more treatment cycles of more than 14 days applying a step dosing comprising at least two, preferably steps, wherein the first step is higher than the second step with respect to the previous dosage, and wherein the second step is higher than the optional but preferred third step with respect to the previous dosage, a treatment cycle optionally followed by a period without administration of the construct. Moreover, the invention provides a method for the treatment of myeloid leukemia comprising the administration of a therapeutically efficient amount of such bispecific construct and the use of such bispecific construct for the preparation of a pharmaceutical composition for the treatment of myeloid leukemia.



SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(88) **Date of publication of the international search report:**

17 February 2022 (17.02.2022)

Adverse effects-mitigating administration of a bispecific construct binding to CD33 and CD3

Field of the Invention

The present invention relates to a bispecific construct comprising a first binding domain specifically binding to a target such as CD33 and a second binding domain specifically binding to an effector such as CD3, preferably for use in a method for the treatment of acute myeloid leukemia. Moreover, the invention relates to a method for the treatment of acute myeloid leukemia comprising the administration of a therapeutically efficient amount of such bispecific construct and the use of such bispecific construct for the preparation of a pharmaceutical composition for the treatment of acute myeloid leukemia.

Background of the Invention

Bispecific constructs such as BiTE[®] (bispecific T cell engager) constructs are recombinant protein constructs made from two flexibly linked antibody derived binding domains. One binding domain of bispecific constructs is specific for a selected tumor-associated surface antigen on target cells; the second binding domain is specific for CD3, a subunit of the T cell receptor complex on T cells. By their particular design BiTE[®] constructs are uniquely suited to transiently connect T cells with target cells and, at the same time, potently activate the inherent cytolytic potential of T cells against target cells. The first generation of bispecific constructs (see WO 99/54440 and WO 2005/040220) developed into the clinic as blinatumomab and solitomab. These bispecific constructs are administered via continuous intravenous infusion. For example, blinatumomab is administered in B acute lymphoblastic leukemia as 4-week infusing with a lower initial dose in the 1st week and a higher dose in the remaining treatment for the 1st cycle and in all other cycles from start. Before starting a second cycle, there is a treatment-free period of two weeks. A similar administration schema has been used for solitomab which was administered as continuous intravenous infusion over at least 28 days with increasing doses and also a treatment-free period of two weeks between two cycles.

An important further development of the first generation of bispecific constructs was the provision of bispecific constructs binding to a context independent epitope at the N-terminus of the CD3ε chain of human and *Callithrix jacchus*, *Saguinus oedipus* or *Saimiri sciureus* (WO 2008/119567). Hence, such bispecific constructs have become versatile means to address so-far unmet therapeutic needs.

One such need is an efficient and safe therapy of Acute Myeloid Leukemia (AML), in particular relapsed or refractory AML (r/r AML), or AML with minimal residual disease (MRD) or myelodysplastic syndrome (MDS). Acute myeloid leukemia, whereof MDS is a typical precursor condition, is the most common form of acute leukemia in adults in the United States (US), with a rising incidence attributed to an aging population, an increase in environmental exposure, and an increase in the population of cancer survivors previously exposed to chemotherapy and therapeutic radiation. In the US, an estimated 21450 new cases of AML and 10920 deaths from AML were expected in 2019 (Siegel et al, 2019).

Prognosis of patients with relapsed or refractory AML is poor as no standard salvage therapy exists except in the case of AML with specific mutations such IDH1/2 mutations. Most trials of investigational agents begin in r/r AML and have accrued a wide range of patients with different characteristics. Historical context for outcomes can be used as a reference for the development of future protocols and novel agents. Analysis of such historical context reveals that overall survival and event free survival were modest and decreased with subsequent salvage. Age, cytogenetics, antecedent disease, De novo/therapy-induced AML, duration of first remission, and platelet count were associated with survival. Importantly, in the vast majority of cases, patients, in particular a majority of r/r AML patients, are unable to achieve a sustained second or subsequent remission, i.e. a long-term amelioration or even cure of the disease. Hence, there is a need for further therapeutic means and an optimized use thereof.

CD33 is a sialic-acid-dependent cytoadhesion molecule known as a myeloid differentiation antigen found inter alia on AML blasts in most patients and leukemic stem cells. Therefore, CD33 has been identified as a promising marker for myeloid leukemia and a target molecule in the treatment of such diseases. To this end, Mylotarg® (gemtuzumab ozogamcin), a cytotoxic antibiotic linked to a recombinant monoclonal antibody directed against the CD33 antigen present on leukemic myeloblasts, had been approved in the United States for patients with AML through accelerated approval. However, following the drug's failure to demonstrate clinical benefit in the confirmatory trial, and an increased risk of venoocclusive disease observed in the postmarketing setting, the drug was temporarily withdrawn voluntarily by the manufacturer from the United States market. Frequently reported toxicities observed with gemtuzumab ozogamcin included neutropenia and thrombocytopenia, and less frequently reported toxicities included events related to acute infusion-related reactions (anaphylaxis), hepatotoxicity, and veno-occlusive disease. A promising CD33xCD3 bispecific construct has been proposed before for use in the treatment of AML. While first encouraging results indicated clinical efficacy in terms of observed complete remissions, cytokine release syndrome (CRS) is the key toxicity which is typically associated with such bispecific constructs, as the resulting activation of T cells involves the transient release of inflammatory cytokines. During treatment with a CD33xCD3 bispecific construct, signs and symptoms of CRS typically occur within the first 24 hours after initiation of the therapy, and may include pyrexia, rash, chills, hypoxia, dyspnea, tachycardia, headache, nausea, vomiting, hypotension, hypertension, AST and/or ALT elevations, and hyperbilirubinemia. CRS may be life-threatening or fatal. For better comparability of CRS events, grading of CRS is typically done from 1 (least severe) to 5 (most severe, death).

CRS has been shown to be a key toxicity for bispecific therapy in AML including CD33xCD3 bispecific construct in subjects with R/R AML. For example, too high starting doses as a single dose without prior lower dose-step and/or without premedication can be intolerable due to dose limiting toxicities (DLT) including grade 4 CRS and/or grade 3 colitis. Hence, it is the objective of the present invention to provide an improved administration, i.e. a schedule of administration of the CD33xCD3 bispecific construct to

mitigate the risk of CRS while allowing higher CD33xCD3 bispecific construct dosages for better therapeutic outcome in the treatment of AML.

Summary of the invention

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In a first aspect, the present invention refers to a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 preferably for use in a method for the treatment of (i.) myeloid leukemia, selected from relapsed/refractory AML (R/R AML) and AML with minimal residual disease (MRD) , or (ii.) myelodysplastic syndrome (MDS), wherein the bispecific construct is administered in one or more treatment cycles, wherein at least one treatment cycle comprises more than 14 days of administration of the bispecific construct in at least three, preferably four or five different dosages applying at least two, preferably three or four dosage steps, optionally followed by a period without administration of the bispecific construct,

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15 wherein the bispecific construct is administered in at least one of the one or more treatment cycles according to a schedule comprising the following steps:

(a) administration of a first dosage of the bispecific construct of at least 10 µg per day for use in the treatment of R/R AML or at least 30 µg per day for use in the treatment of MRD or MDS, followed by

20 (b) administration of a second dosage of the bispecific construct, wherein said second dosage is at least 240 µg per day and/or preferably exceeds said first dose at least 10-fold for use in the treatment of R/R AML or at least 8-fold for use in the treatment of MRD or MDS, and/or wherein the delta between the first and the second dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, followed by

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(c) administration of a third dosage of the bispecific construct, wherein said third dosage is at least 600 per day and/or preferably exceeds said second dosage at most three-fold and/or wherein the delta between the second and the third dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day for use in the treatment of R/R AML, and wherein said third dosage is in the range of 600 to 1600 µg/d for use in the treatment of MRD or MDS, preferably followed by

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(d) administration of a forth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional forth dose is at least 720 µg per day and/or exceeds said third dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, optionally followed by

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- (e) administration of a fifth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional fifth dose is at least 960 µg per day and/or exceeds said fourth dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day, optionally followed by
- (f) administration of a sixth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional sixth dose is at least 1200 µg per day and/or exceeds said fifth dosage and/or wherein the delta between the fifth and the sixth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day.

It is envisaged in one aspect of the present invention that the time of administering the bispecific construct in one treatment cycle including all steps (a) to (c) or (d) or (e) or (f) is at least 15 days, preferably 15 to 60 days, more preferably 28 to 56 days, most preferably 28 days wherein the bispecific construct is for use in the treatment of R/R AML or MRD AML or 56 days wherein the bispecific construct is for use in the treatment MDS.

It is envisaged in one aspect of the present invention that, preferably wherein the bispecific construct is for use in the treatment of R/R AML, the first dosage in step (a) is at least 10 µg per day, preferably in the range of 10 to 20 µg per day, preferably 10 µg per day, the second dosage in step (b) is at least 240 µg per day, preferably in the range of 240 to 600 µg per day, the third dosage in step (c) of at least 600 µg per day, preferably in the range of 600 to 1000 µg per day, and preferably the fourth dosage in step (d) of at least 720 µg per day, preferably 720 to 1600 µg per day, more preferably in the range of 960 to 1080 µg per day, more preferably 960 µg per day, optionally the fifth dosage in step (e), of at least 960 µg per day, preferably at least 1200 or 1300 µg per day, and optionally the sixth dosage in step (f), of at least 1200 µg per day, preferably at least 1300 or 1600 µg per day.

It is envisaged in one aspect of the present invention that the period of administration of the first dosage in step (a) is 1 to 5 days, preferably 2 or 3 days, the period of administration of the second dosage in step (b) is 2 to 5 days, preferably 2 or 3 days, and the period of administration of the third dosage in step (c) and the preferred and optional fourth, fifth and sixth dosage in step (d), (e) and (f), respectively, together is 7 to 52 days, preferably 14 to 23 or 52 days, more preferably 22, 23 wherein the use is for the treatment of R/R AML or MRD or 52 days wherein the use is for the treatment of MDS.

It is envisaged in one aspect of the present invention that the treatment of the myeloid leukemia, preferably acute myeloid leukemia, comprises two or more treatment cycles, preferably two, three, four, five, six or seven treatment cycles, whereof at least one, two, three, four five, six or seven treatment cycles comprise more than 14 days of bispecific construct administration.

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It is envisaged in one aspect of the present invention that the at least one treatment cycle is followed by a period without administration of the bispecific construct, preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days without treatment.

10 It is envisaged in one aspect of the present invention that at least one treatment cycle is not followed by the period without administration of the construct, preferably where the bispecific construct is for use in the treatment of MDS.

15 It is envisaged in one aspect of the present invention that only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dosage according to step (b).

It is envisaged in one aspect of the present invention that the first binding domain of the bispecific construct is a single chain bispecific construct.

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It is envisaged in one aspect of the present invention that the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 an 98 to 100, preferably 94 to 96 an 98 to 100.

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It is envisaged in one aspect of the present invention that the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 148-153, 154-159, 160-165, 166-171, 172-177, 178-183, 184- 189, 190-195, 196-201 and 202-207, preferably 202-207.

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It is envisaged in one aspect of the present invention that the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 94 to 96 or 98 to 100 **and** the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 202-207.

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It is envisaged in one aspect of the present invention that the first binding domain of the bispecific construct comprises a VH of SEQ ID NO 93 and a VL of SEQ ID NO 97, and wherein the second binding domain of the bispecific construct comprises a VH of SEQ ID NO 208 and a VL of SEQ ID NO 209.

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It is envisaged in one aspect of the present invention that the bispecific construct is a single chain construct comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108, preferably selected from the group consisting of SEQ ID NOs: 104, 105, 106, 107 and 108, more preferably SEQ ID NO 104.

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It is envisaged in one aspect of the present invention that the bispecific construct is administered in combination with a PD-1 inhibitor, a PDL-1 inhibitor and/or one or more epigenetic factors selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid) and wherein:

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- (a) the PD-1 inhibitor, a PDL-1 inhibitor and/or one or more epigenetic factors are administered prior to the administration of the bispecific construct;
- (b) the PD-1 inhibitor, a PDL-1 inhibitor and/or one or more epigenetic factors are administered subsequent to the administration of the bispecific construct; or
- (c) the PD-1 inhibitor, a PDL-1 inhibitor and/or one or more epigenetic factors and the bispecific construct are administered simultaneously.

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It is envisaged in one aspect of the present invention that the PD-1 inhibitor, a PDL-1 inhibitor and/or one or more epigenetic factors are administered prior to the administration of the bispecific construct, preferably 1, 2, 3, 4, 5, 6, or 7 days prior to the administration of the bispecific construct.

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It is envisaged in one aspect of the present invention that the epigenetic factor is hydroxyurea.

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It is envisaged in one aspect of the present invention that the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, preferably relapsed or refractory acute myeloid leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic

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syndrome, acute panmyeloic leukemia, myeloid sarcoma, and mixed phenotypic acute leukemia.

It is envisaged in another aspect of the present invention that a method for the treatment of myeloid diseases, preferably related one or more of the diseases (i.) myeloid leukemia, selected from relapsed/refractory AML (R/R AML) and AML with minimal residual disease (MRD) AML, or
5 (ii.) myelodysplastic syndrome (MDS) in a patient in need thereof is provided, the method comprising administering a therapeutically efficient amount of a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 in one or more treatment cycles, wherein the at least one treatment cycle
10 comprises more than 14 days of administration of the bispecific construct in at least three different dosages applying at least two dosage steps,

wherein the bispecific construct is administered in one treatment cycle according to a schedule comprising the following steps:

- (a) administration of a first dosage of the bispecific construct of at least 10 µg per day in the
15 treatment of R/R AML or at least 30 µg per day used in the treatment of MRD or MDS, followed by
- (b) administration of a second dosage of the bispecific construct, wherein said second dosage is at least 240 µg per day and/or preferably exceeds said first dose at least 10-fold in the treatment of R/R AML or at least 8-fold used in the treatment of MRD or MDS and/or wherein the delta
20 between the first and the second dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, followed by
- (c) administration of a third dosage of the bispecific construct, wherein said third dosage is at least 600 per day and/or preferably exceeds said second dosage at most three-fold and/or wherein the delta between the second and the third dosage is preferably at least 50 µg per day, preferably at
25 least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day in the treatment of R/R AML, and wherein said third dosage is in the range of 600 to 1600 µg/d used in the treatment of MRD or MDS, preferably followed by
- (d) administration of a forth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional forth dose is at least
30 720 µg per day and/or exceeds said third dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, optionally followed by

- (e) administration of a fifth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional fifth dose is at least 960 μg per day and/or exceeds said fourth dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 μg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 μg per day, optionally followed by
- (f) administration of a sixth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional sixth dose is at least 1200 μg per day and/or exceeds said fifth dosage and/or wherein the delta between the fifth and the sixth dosage is at least 50 μg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 μg per day.

It is envisaged in another aspect of the present invention that the time of administering the bispecific construct in one treatment cycle including all steps (a) to (c) or (d) or (e) or (f) is at least 15 days, preferably 15 to 60 days, more preferably 28 to 56 days, more preferred 28 days wherein the bispecific construct is used in the treatment of R/R AML or MRD AML or 56 days wherein the bispecific construct is used in the treatment MDS.

It is envisaged in one aspect of the present invention that preferably wherein the bispecific construct is for use in the treatment of R/R AML the first dosage in step (a) is at least 10 μg per day, preferably in the range of 10 to 20 μg per day, preferably 10 μg per day, the second dosage in step (b) is at least 240 μg per day, preferably in the range of 240 to 600 μg per day, the third dosage in step (c) of at least 600 μg per day, preferably in the range of 600 to 1000 μg per day, and preferably the fourth dosage in step (d) of at least 720 μg per day, preferably 720 to 1600 μg per day, more preferably in the range of 960 to 1080 μg per day, more preferably 960 μg per day, optionally the fifth dosage in step (e), of at least 960 μg per day, preferably at least 1200 or 1300 μg per day, and optionally the sixth dosage in step (f), of at least 1200 μg per day, preferably at least 1300 or 1600 μg per day.

It is envisaged in another aspect of the present invention that the period of administration of the first dosage in step (a) is 1 to 5 days, preferably 2 or 3 days, the period of administration of the second dosage in step (b) is 2 to 5 days, preferably 2 or 3 days, and the period of administration of the third and the optional fourth dose in step (c) and optional step (d), respectively, is 7 to 52 days, preferably 14 to 23 days, more preferably 21, 22 or 23 days wherein used for the treatment of R/R AML or MRD or 50 or 52 days wherein used for the treatment of MDS.

It is envisaged in another aspect of the present invention that the treatment of the myeloid leukemia comprises two or more treatment cycles, preferably 2, 3, 4, 5, 6 or 7 treatment cycles, whereof

at least 1, 2, 3, 4, 5, 6 or 7 treatment cycles which each comprises more than 14 days of bispecific construct administration.

It is envisaged in another aspect of the present invention that the treatment is followed by the period without administration of the bispecific construct, preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,
5 11, 12, 13, or 14 days without treatment.

It is envisaged in another aspect of the present invention that the treatment is not followed by the period of at least 14 days without administration of the bispecific construct, preferably where the bispecific construct is for use in the treatment of MDS, preferably in order to extend exposure which is typically safer in an MDS setting than in an R/R AML setting.

10 It is envisaged in another aspect of the present invention that only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dose according to step (b).

It is envisaged in another aspect of the present invention that the construct is a single chain bispecific construct.

15 It is envisaged in another aspect of the present invention that the first binding domain of the bispecific construct used in the method of treatment comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100, preferably 94 to 96 and 98 to 100.

20 It is envisaged in another aspect of the present invention that the second binding domain of the bispecific construct used in the method of treatment comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 148-153, 154-159, 160-165, 166-171, 172-177, 178-183, 184- 189, 190-195, 196-201 and 202-207, preferably 202-207.

It is envisaged in one aspect of the present invention that the first binding domain of the bispecific
25 construct used in the method of treatment comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 94 to 96 or 98 to 100 and the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 202-207.

It is envisaged in one aspect of the present invention that the first binding domain of the bispecific
30 construct used in the method of treatment comprises a VH of SEQ ID NO 93 and a VL of SEQ ID NO 97, and wherein the second binding domain of the bispecific construct comprises a VH of SEQ ID NO 208 and a VL of SEQ ID NO 209.

It is envisaged in one aspect of the present invention that the bispecific construct is a single chain construct used in the method of treatment comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108, preferably selected from the group consisting of SEQ ID NOs: 104, 105, 106, 107 and 108, more preferably SEQ ID NO 104.

Brief description of the drawings

Fig. 1: Overview of a Phase I clinical study on CD33xCD3 bispecific construct for use in the treatment of R/R AML comprising 20 patient cohorts. “C” stands for cohort, numbers following the cohort number stand for administered dose levels [μg per day]. One arrow indicates one step to target dose (TD), two arrows indicate two steps to target dose and 3 arrows indicate three steps to target dose. Further abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; PK, pharmacokinetic; R/R, relapsed/refractory; TD, targeted dose. CR: Complete Remission, CRi: Complete Remission with Incomplete Count Recovery, CRh: Complete Remission with Partial Hematologic Recovery, MLFS: Morphologic Leukemia-Free State.

Fig. 2: Overview of anti-tumor activity with respect to the first 16 patient cohorts in a Phase I clinical study. (A) Best overall response (B) Treatment duration in responders. Anti-tumor efficacy with respect to study cohort:

8 patients responded to CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) treatment: CR (n=3, cohorts 11, 15, and 16), CRi (n=4, cohorts 8, 9, 12, and 15) and MLFS (n=1, cohort 2) with 3 responders out of 14 treated patients (21%) in cohorts 15-17. For patients achieving CR/CRi (n=7), minimal efficacious dose was established at the 120 $\mu\text{g}/\text{day}$ dose level. Response was observed after 1st cycle and sustained for a median 38.5 days (range of 14 –121 days) during the on-study period. Following CRi, 1 patient treated in cohort 15 was bridged to allogeneic hematopoietic stem cell transplant (HSCT)

Fig. 3: Correlation of CRS with (A) leukemic burden, (B) E:T (effector-target cell) ratio and (C) Correlation of CRS with IL-10.

Fig. 4: CR/CRi Response to CD33xCD3 bispecific construct (SEQ ID NO: 104), correlation of CR/CRi response with SEQ ID NO: 104 exposures and leukemic burden: (A) SEQ ID NO: 104 exposures, (B) Bone Marrow and (C) peripheral blood.

Fig. 5: Overview on frequency and severity of CRS depended on a schedule (number of dose steps, i.e. one up to four, and dose discrepancies between dose levels, respectively).

Fig. 6: Population PK model parameters and diagnostic plots: Model diagnostics plots

Fig. 7: (A) Baseline tumor burden, (B) Steady-state CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures and (C) Baseline E:T ratio were compared for responders vs non-responders to assess whether it influences efficacy of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) .

Fig. 8: (A) Baseline tumor burden, (B) Steady-state CD33xCD3 bispecific construct exposures and (C) Baseline CD33 expression on blast cells were plotted against the worst grade CRS on treatment for each patient to explore its influence on safety of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104)

Fig. 9: Probability of CRS Grade by CD33xCD3 bispecific construct exposures: Solid line represents mean; dashed line represents 95% CI. Worst grade CRS for each patient was modeled with CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures using a proportional odds logistic regression model. The effect of baseline patient characteristics was tested as a covariate in the logistic regression model.

Detailed Description of the Invention

For an efficient treatment of (i.) myeloid leukemia such as AML, preferably R/R AML or minimal residual disease (MRD+) AML and/or (ii.) myelodysplastic syndrome (MDS), using a CD33⁺ cell eliminating therapy approach, safety and tolerability of the employed CD33xCD3 bispecific construct has to be established at dosages which are also clinically effective.

This problem was solved, e.g., by providing a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 (CD33/CD3) for use in a method for the treatment of (i.) myeloid leukemia or (ii.) MDS, wherein the bispecific construct is administered in one or preferably more treatment cycles, wherein one treatment cycle comprises more than 14 days of administration of the bispecific construct in at least three different, preferably four dosages applying at least two, preferably three dosage steps or even four, five, six, seven, eight, nine or ten dosage steps, optionally followed by a period without administration of the construct.

The addressed disease in the context of the present invention is preferably R/R AML, minimal residual disease (MRD+) AML and/or MDS. Advantageously, a CD33xCD3 bispecific construct according to the present invention is suitable for use in the treatment of more than one bone marrow failure syndrome

including myeloid leukemia and its typical precursor MDS and can versatily be used as needed and accordingly dosed as described herein.

Using an administration schedule in line with the present invention, dose steps are intermediate CD33xCD3 bispecific construct dose levels administered with 1–5 day intervals prior to the target dose.

5 Preferred dose steps herein are, for example, at least 10 µg per day in the 1st step, at least 240 µg per day in the 2nd step and at least 600 µg per day in the 3rd step. Typically, a dosage step is at most 400 µg per day higher than the previous dosage step in order to mitigate CRS adverse events in the context of the present invention. A higher number of steps reduces the risk of CRS adverse events in the context of the present invention. Hence, if a target dose, i.e. the highest dose of a dosage regimen which
10 preferably facilitates clinical efficacy with respect to AML, of e.g. 1600 µg per day should be reached, it is safest in line with the present invention, to start with a low dose of 10 µg per day and then perform a series of escalating steps wherein the steps differ in at most 400 µg per day. Further steps might be added in between in line with the present invention, i.e. adding further mini steps in between the at least two, three, four or five steps as disclosed herein in detail. This is particularly useful for use in the
15 treatment of R/R AML where an increased number of steps, such as two or more, typically three, four or even five steps (leading, in consequence, to three, four, five or even six different ascending dosages) typically and advantageously leads to increased safety in terms of reduced risk of CRS as significant side effect. The same applies in principle also to the use in the treatment of MRD and MDS, where advantageously less steps are required to mitigate CRS as disclosed herein.

20 According to the present invention, optimized dose steps in the -preferably continuous infusion-administration of a CD33xCD3 bispecific construct allow higher target dose levels with manageable safety profile. In detail, the first step should comprise administration of at least 10 µg per day. Preferably, said dosage should be 10 µg per day or not much above, i.e. below 30 µg per day, because subjects with
25 R/R AML typically have tumor burden ranges from 5% to > 50%. Higher tumor burden typically correlates with a higher risk of developing CRS in R/R AML patients. Without wanting to be bound by theory, patients with R/R AML will be at lower risk of developing CRS when treated with a low run in dose of only about 10 µg per day, i.e. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 µg per day, preferably 10 µg per day. This typically facilitates the tolerability of an about
30 10-fold higher second dose, which can be 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or even 30-times higher than the first dose in order to reach the ultimate target dose quickly, but may typically not exceed the previous dosage by more than 400 µg per day in order to avoid CRS adverse effects. For example, a second dosage of 240 µg per day is preferably tolerated if the first dosage was as low as 10 µg per day. In consequence, a tolerated larger first step then requires only a
35 smaller second step. Hence, in line with the present invention, the third dosage is typically only two-, three, four- or five-fold the second dosage, but preferably only at most three-fold, e.g. at least 600 µg per day or 720 µg per day but might be up to 1080 µg per day. A further optional but preferred third

step is again significantly lower than the second step, i.e. typically the fourth dosage is below two-fold or three-fold higher than the third dosage, i.e. typically the third dosage is at least 720 µg per day, 840 µg per day or 960 µg per day but could be as high as about 400 µg per day higher than the second dose to allow for optimal therapeutic efficacy in the treatment of AML, preferably R/R AML. Further steps in between are envisaged in the context of the present invention to reach a higher target dose such at least 1100, 1200, 1300, 1400, 1500 or 1600 µg per day.

Hence, in the context of the present invention a low run in dose followed by a large first step, a second smaller step and a preferred even smaller step, preferably in combination with an immunomodulator such as a cytokine or cytokine receptor blocking agent, e.g. in form of early intervention with tocilizumab, preferably mitigates CRS challenges and still facilitates beneficial clinical outcomes with respect to the treatment of AML, preferably R/R AML. While a minimal efficacious dose of 120 µg per day has been found to reach a clinical effect such as CRi, in order to obtain a more sustainable clinical effect and an improved safety profile at the same time, the administration according to the present invention is more likely to be beneficial for so treated patients. In particular in terms of percental change from baseline, response is superior for higher dosages applied in more steps as described herein. For example, an administration schedule comprising four subsequent rising dosages, wherein the first is at least 10 µg per day, the second is at least 10-fold the first dosage, e.g. at least 240 µg per day, the third is at most 3-fold the second dosage such as at least 600 µg per day and the fourth exceeds the third dosage, as the previous ones did, by not more than 400 µg per day, e.g. at least 720 or 840 µg per day, then percental changes from baseline beyond -80%, preferably -90% or even -100% can be achieved. As exemplified herein, such beneficial and surprising results are, e.g., seen in cohorts 15 and 16.

Accordingly, applying an administration regimen as described herein, preferably at least 25%, or even at least 30% or at least 50% of the treated patients achieve a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi). At the same time, preferably, only up to 20%, preferably only up to 5% of all treated patients suffer from CRS grade 3 or higher, while not more than up to 50% preferably only up to 40% or 15% require intensive care due to CRS as adverse effect. In view thereof, it is a particular advantage of the present invention to preferably keep overall the rate of CRS grade 2 or higher adverse effects below 50% of all patients treated according to an administration regimen comprising at let three steps, wherein the first step is larger than the second, and the second is larger than the third, and wherein the start (run in) dose is low enough not to initially trigger CRS adverse effects.

For example, in the context of the present invention, it has been observed that an administration schedule according to the present invention such as 10 µg per day as step 1 dose, 240 µg as step 2 dose, 600 µg as step 3 dose and 720 or 840 µg per day as target dose (cohort 16 and 17), wherein the entire schedule administered over 28 days, and preferably given under early intervention by tocilizumab, the CRS adverse effects of moderate grade 2 or higher could be kept at or even below 50% of patient incidence. This is especially remarkable because lower target doses such as 480 µg per day (cohort 14) exhibited

Grade 2 or higher CRS patient incidence of 100%. However, there the dosing steps were not adjusted to each other as required by the present invention, i.e. that the first step is significantly larger than the second step and that there is preferably also at least a third step in order to mitigate CRS and provide sufficient clinical efficacy. In this regard, it was observed that frequency and severity of CRS depended on a schedule (number of dose steps) and a Target Dose level. At later cohorts, frequency and severity of CRS may be further mitigated by early use of a cytokine or cytokine receptor blocking agent such as tocilizumab. Also, higher grades of CRS were observed in patients with higher leukemic burden and with higher Effector:Target (E:T) ratio.

Hence, by means of the at least a twofold step dosing with at least three increasing dosage levels, it is possible to preferably efficiently eliminate myeloid leukemic cells during the more than 14 days of CD33/CD3 bispecific construct (e.g. SEQ ID NO: 104) administration period, while still allowing the patient to recover the myeloid compartment in a period without administration of the construct between treatment cycles. Employing a target dosage, i.e. the maximum dosage of the last step within a treatment cycle, of at least 720 µg per day preferably enables a complete remission of the disease as demonstrated herein. At the same time, the step dosing according to the present invention preferably significantly reduces the risk of severe immunologic side effects such as a cytokine release syndrome or symptoms thereof despite longer exposure to the target dose than what has previously been expected to be tolerable. By applying the step dosing according to the present invention, i.e. applying at least two dosage steps resulting in at least three increasing dosages, the patient can be exposed to the target dosage for a prolonged period of time, such as a maximum of 52 days. Said maximum period of time results from the first and the second step lasting for two days, respectively, and the third step lasting 24 days of the remaining first treatment cycle and another 28 days of target dosage of a subsequent (second) treatment cycle which comprises only the third dosage without previous step dosing. Hence, at least one of the treatment-free periods between treatment cycles (i.e. when the bispecific construct according to the present invention is uninterrupted administered) can be dispensable. Accordingly, the target dosage of the first concerned treatment cycle is immediately followed by the same target dosage of the subsequent, i.e. second concerned treatment cycle without interruption. Thereby, exposure of the patient to the target dosage is significantly expanded in order to fulfil the therapeutic goal to eradicate AML blasts and leukemic stem cells as a precondition for long-lasting therapeutic effect and eventually eradication of the AML disease in the affected and so-treated patient. Hence, the method according to the present invention provides a method which balances the need for a preferably long-lasting therapeutic effect, i.e. to eradicate the hematopoietic and the myeloid leukemic stem cells effective, and the avoidance or attenuation of severe and potentially therapy-ending side effects such as CRS. In particular, CRS events of the highest grade 5 (as commonly defined in the art) can be preferably avoided and CRS events of a higher grade 3 and 4 be significantly reduced in occurrence, i.e. grade 3 occurring typically in at most 10% of treated patients and grade 4 typically in at most 5% of treated patients, respectively.

In the context of the present invention, the duration of exposure of a patient to the bispecific construct in one treatment cycle is longer than 14 days and can be up to 60 days, if two treatment cycles are not separated by a treatment-free period. Typically, each treatment cycle comprising at least two, preferably three dosage steps is followed by a treatment-free period to allow for patient recovery. However, when prolong target dosage exposure is required to address leukemic stem cells in addition to AML blasts, two treatment cycles are connected to each other by leaving the treatment-free period away. However, preferably not more than two treatment cycles follow each other without a treatment-free period in order to allow for sufficient patient recovery but still prolong target dosage exposure time.

When said two treatment cycles are connected, the later treatment cycle following the earlier treatment cycle is characterized by having only one dosage and no step dosing. This is facilitated by the fact that the step dosing of the earlier treatment cycle reduces the risk for side effects such as CRS (especially of higher grades 3 and 4 and highest grade 5) also for the immediately following treatment cycle (i.e. with no treatment-free period between the two connected cycles) because the treatment cycle following the earlier treatment cycle profits from the earlier treatment cycle's applied step dosing. Hence, side effect CRS of the highest grade could be avoided completely and the higher grades 3 and 4 attenuated to infrequent single digit occurrences. A treatment interruption could be avoided in the majority of treated patients and ensure continuous effective dose administration to treat high patients suffering from highly progressive r/r AML.

Hence, in the context of the present invention, at least one of the treatment cycles has to fulfil the requirements for the specific step dosing as described herein. In case only one treatment cycle is applied, said one treatment cycle comprises the step dosing. In case two treatment cycles are applied which are not separated by a treatment-free period, then it is sufficient for only the first of the two treatment cycles to fulfil the requirements of the specific at least three-step specific step dosing as described herein.

The period of exposure as referred to herein typically refers to the total exposure to all at least three different dosages applied through one treatment cycle. Typical exposure to the target dose is shorter, i.e. shortened by the duration of the first and second (and optionally third) dosage before the third or optional forth maximum (target) dosage within the treatment cycle is reached. Such exposure of the target dosage may last for, for example, 56, 55, 54, 53, 52, 51, 50, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15 or 14 days, which at the same time allows for full exploitation if the anti-tumor efficacy of the CD33xCD3 bispecific construct (e.g. SEQ ID NO: 104) according to the present invention. Consequently, the present dosage regimen allows for a prolonged exposure of the treated patient to the target dose while minimizing the side effects during the initial phase of drug administration, such as cytokine release syndrome and symptoms thereof, by using step dosing as described herein. At the same time, the superior efficacy,

which is confined by the administration schedule or dosage regimen as described herein, is preferably demonstrated by a significant reduction in tumor burden in treated patients, more preferably in partial or even complete remission or even repeated complete remissions after one treatment cycle or a plurality of treatment cycles, respectively.

5

A typical treatment cycle according to the present invention, which has clinically demonstrated complete remission of disease (AML) comprises administering the CD33xCD3 bispecific construct (e.g. SEQ ID NO: 104) a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 µg per day for 2, 3 or 4 days, immediately followed by a third dosage of 240 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 µg per day for 2, 3 or 4 days, immediately followed by a third dosage of 480 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 µg per day for 2, 3 or 4 days, immediately followed by a third dosage of 600 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60, 120 or 240 µg per day for 2, 3 or 4 days, immediately followed by a third dosage of 720 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60, 120 or 240 µg per day for 2, 3 or 4 days, immediately followed by a third dosage of 840 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 or 120 µg and a third dosage of 120 or 240 µg per day for together 2 days, immediately followed by a forth dosage of 840 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 or 120 µg and a third dosage of 120 or 240 µg per day for together 2 days, immediately followed by a forth dosage of 960 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Such treatment cycles are also represented in Fig. 5 for better illustration.

It has been a remarkable finding in the context of the present invention that already a target dosage of 240 µg per day can lead to complete remissions of disease AML, being MRD+ but preferably also MRD-. Higher target dosages such as described herein, e.g. from 600 µg per day for the MRD+ AML indication or e.g. from 720 µg per day for the R/R AML indication, do typically even more quantitatively

eradicate leukemic stem cells in addition to AML blasts and likely reduce the risk of relapse and thus, provide a longer disease-free state for the patient, improving their quality of life.

Preferably, in the context of the present invention, the dose toxicity limiting (DLT) window can be shortened to a standard of 4 weeks (with at least 14 days on the target dose) allowing for monitoring the onset of CRS and its resolutions, efficient intra-subject escalation, and overall patient safety.

As it is known in the art, the expression of CD33 on the surface of myeloid cells comprising the *common myeloid progenitor* cells, *Myeloblasts*, *Monocytes* has been demonstrated in the literature by flow cytometry. Moreover, CD33 expression on the surface of Macrophages has been demonstrated via immunohistochemistry.

For a successful treatment of a myeloid leukemia a significant exposure of a patient (i.e. a certain length of exposure) with the bispecific constructs described herein is required to induce T cell activation/proliferation and cytotoxic activity of those T cells. However, based on the above described observations the longer the administration period of the bispecific constructs last, the longer pancytopenia is to be expected. This in mind, the solution to the problem underlying this invention is to balance the length of exposure and the dose of the bispecific constructs which enable the effective elimination of the leukemic cells with an off treatment period during which the myeloid compartment of a patient is allowed to recover. This is reflected by the above described administration scheme.

The time period without administration serves as recovery period for the myeloid compartment in order to rebuild myeloid cells important, e.g., for the defense against bacterial infection. The length of the required minimum time period without administration typically depends on the residual tumor burden. For example, patients who have shown a partial response, the time period may be as short as 7 days or less, such as 1, 2, 3, 4, 5, or 6 days, preferably 7 days, while those patients with higher residual tumor burden and more damage to the myeloid compartment typically require a longer period to rebuild myeloid cells, typically at least 8, 9, 10, 11, 12, 13 or 14 days, preferably 14 days. In general, it is envisaged that exposure of the patient to the target dose is maximized, and at the same time to limit the duration of a single treatment cycle including the treatment free recovery period as much as possible to allow for overall quick sequence of treatment cycles for patients who often are in a critical condition and typically need quick efficacy.

In a particular embodiment of the present invention, a first treatment cycle comprising an administration time of more than 14 days, offers a longer exposure of the patient to the target dose and thereby reduces the tumor burden to such a level that subsequent treatment cycles may not require administration times of more than 14 days. In such a case, treatment cycles after the first treatment cycle may last at most 14 days which reduces the risk of side effects by longer treatment to recovery time ratio within one cycle,

provided sufficient efficiency has been reached. Alternatively, the second, third, fourth or any subsequent treatment cycle may last more than 14 days followed by one or more treatment cycles of at most 14 days in length. Also, treatment cycles of more than 14 days of administration may alternate with treatment cycles of at most 14 days of administration in order to level efficacy and mitigation of side effects.

It is a specific achievement of the invention as described herein to provide a dosage scheme which does not lose time to reach an effective dose to target cancer cells and at the same time reduces the risk of triggering severe side effects such as CRS. Wasting time would not be in the interest of the treated patient who is suffering from a severe and aggressively progressing disease. On the other hand, triggering side effects such as CRS by too quick step dosing likely leads to the interruption or abandonment of treatment due to undue toxicity. Both disadvantages are mitigated by the method according to the present invention. Also, by adding a fourth step, the delta between the dosages is reduced whereby also the probability of CRS is reduced. Hence, in the context of the present invention, where a high target dosage of, for example, at least 480, 720 or 960 µg per day is applied, a step dosing comprising four steps (e.g. 30-240-600-900 µg per day) is preferred to a step dosing comprising three steps (e.g. 30-240-900 µg per day), even if conducted over the same time period due to a smaller delta between the dosage of a previous step and a target dosage.

The method according to the present invention avoids or attenuates severe side effects such as CRS. In particular, CRS events of the highest grade 5 (as commonly defined in the art) can be preferably avoided and CRS events of a higher grade 3 and 4 be significantly reduced in occurrence, i.e. grade 3 occurring typically in at most 10% of treated patients and grade 4 typically in at most 5% of treated patients undergoing a method as described herein, respectively.

As the person skilled in the art is aware of, after each relapse, a new complete remission is more and more difficult to achieve. Given the fact that patients undergoing presently described therapy by the bispecific construct have typically already undergone standard chemotherapy and might have gone through remissions and relapses, a profound activity needs to be conferred by the method according to the present invention. Hence, prolonged exposure to a high dosage of bispecific construct, e.g. SEQ ID NO 104, is preferred as described herein. This typically requires a step dosing comprising three dosing steps meaning 4 different and ascending dosages, i.e. a first, second, third and fourth dose. Hence, such a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 or 120 µg and a third dosage of 120 or 240 µg per day for together 2 days, immediately followed by a fourth dosage of 840 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. Alternatively, a preferred treatment cycle comprises a first dosage of 10 µg per day for two or three consecutive days, immediately followed by a second dosage of 60 or 120 µg and a third dosage of 120 or 240 µg per day for together 2 days,

immediately followed by a forth dosage of 960 µg per day for 21, 22 or 23 days, wherein the total treatment cycle duration is 28 days. When two treatment cycles are combined and following each other without an intermittent administration-free period, the application of the forth, effective dosage has a duration of up to 52 days. Suh parameters are, for example, considered a prolonged exposure to a high dosage of bispecific construct, e.g. SEQ ID NO 104, is preferred as described herein.

It is envisaged in the context of the present invention that a significant unmet medical need exists for patients with MRD+ AML who are ineligible for HSCT, as there are no approved treatment options for this population. A CD33xCD3 bispecific construct dosed according to the present invention is advantageously effective in treating patients with MRD+ AML which are converted MRD+ to MRD-status, which may improve survival outcomes. Treating subjects who achieved CR with complete hematologic recovery allow to assess the effect of the CD33xCD3 bispecific construct such as SEQ ID NO: 104 on normal myeloid cells and describe any potential changes including the onset, severity, and duration of myelosuppression. Treating subjects who achieved CRi allow to assess the effect of the CD33xCD3 bispecific construct treatment on the recovery of normal myeloid cells.

MDS as defined by the WHO classification, (patients with intermediate, high and very high risk MDS per IPSS-R), who are refractory to hypomethylating agents (HMAs), and who are not eligible for allogeneic HSCT (per investigator assessment, lack of a donor, or declined the offered procedure).

As discussed in Section 2.1.2 of Appendix 1, a significant unmet medical need exists for patients with MDS who failed HMA treatment and are ineligible for HSCT. Although HMAs are considered the standard of care treatment for MDS, only half of patients respond to this treatment. Moreover, all patients will eventually become refractory to HMAs (Gil Perez and Montalban Bravo, 2019). Patients who failed HMA treatment have a poor prognosis and limited therapeutic options, as there are no approved interventions for HMA refractory MDS (Montalban-Bravo and Garcia-Manero, 2018). Although allogeneic HSCT is potentially curative, it is typically only available to younger, fit patients due to the high risk of HSCT associated morbidity and mortality. The Center for International Bone Marrow Transplant Registry (CIBMTR) reported approximately 1150 transplants for MDS and myeloproliferative neoplasms in the US in 2017 (D'Souza and Fretham, 2018). When considered in the context of the entire patient population of high-risk MDS patients in the US, statistics suggest a low use of transplantation in this population, with a cross-sectional survey and prospective feasibility study reporting 4% to 5% of MDS patients receiving transplants (Sekeres et al, 2008; Estey et al, 2007).

Therefore, novel therapeutic options are needed for patients with MDS who have progressive or refractory disease following treatment with HMAs and who are ineligible for allogeneic HSCT. Because CD33 is expressed on both MDS blasts and myeloid derived suppressor cells (Section 2.2 of Appendix 1), AMG 330 will be evaluated for the treatment of patients with MDS.

The baseline tumor burdens in patients with either MRD+ AML or MDS (typically about < 5% and < 20% blasts in the bone marrow, respectively) may differ and are typically lower compared with the higher tumor burdens found in those with R/R AML (range, 5% to > 50% blasts in the bone marrow).

Therefore, a lower incidence and severity of CRS is typically found in the MRD+ AML and MDS populations after treatment with a CD33xCD3 bispecific construct according to the present invention compared with that observed in subjects with R/R AML. As such, these three patient populations will each require a step dose schedule according to the present invention with specifically preferred start and final target dose. Alternatively, subjects with either MDS or MRD+ AML will require fewer dose steps and a higher target dose compared with subjects with R/R AML.

While a starting step dose of CD33xCD3 bispecific construct (e.g. SEQ ID NO: 104) of typically at least 10 µg is being used for subjects with a myeloid leukemia, e.g. R/R AML, or a precursor disease thereof, a continuously infused dose of at least 10 µg per day can be further specified, i.e. increased, for use in the treatment of MRD+ AML for best efficacy while maintaining safety as described herein. CD33xCD3 bispecific constructs of the present invention (e.g. SEQ ID NO: 104) typically have steady-state concentrations (C_{ss}) of 1.5 to 2 ng/mL (~240 µg/day) which are considered both safe and efficacious, as these exposures are 4 to 5 times lower than those observed at the highest nonseverely toxic dose (HNSTD) of 10 µg/kg/day in healthy monkeys (average C_{ss} = 8.36 ng/mL) and above the human dose with 50% tumor growth inhibition (ED₅₀; based on a PK-tumor dynamic model) of 1.44 ng/mL. Hence, it has been established herein for the first time that at least 30 µg per day as a dose level can be used as an advantageous starting dose. Furthermore, a dose of 240 µg/day is supported by the clinical safety and efficacy experience of CD33xCD3 bispecific construct in the R/R AML population, as this dose was well tolerated, with no cases of grade greater or equal to 3 CRS (0 of 15 subjects) and a 20% rate of CR with A CD33xCD3 bispecific construct dose of about 240 µg/day might lead approximately to a 28% risk of developing grade greater or equal to 2 CRS in patients with R/R AML who have a < 20% baseline tumor burden. Because patients with MRD+ AML have a baseline tumor burden < 5%, the risk of CRS is expected to be even lower in this population than in the R/R AML and MDS populations, which have 5% to > 50% and < 20% blasts at baseline, respectively. Thus, an at least 240 µg dose level can used as a second dose step prior to the target dose. Because the safety of the at least 600 µg/day target dose was already shown in R/R AML (typically at least 10 µg/day for 2 days, at least 240 µg/day for up to 5 days, and at least 600 µg/day starting at day 8 in a, for example, 28 day treatment cycle) as shown herein, a starting target dose of at least 600 µg/day is found tolerable and effective in the context of the present invention. Preferably, the target dose of at least 600 µg/d is, for example, at least 720, at least 840, at least 960, at least 1080 µg/d, at least 1300 µg/d, or at least 1600 µg/d.

Surprisingly, already applying a two-step dosage regimen of CD33xCD3 bispecific construct (as exemplified herein by SEQ ID NO 104), wherein one treatment cycle comprises at least 28 days, the

cycle comprising three different dosages of at least 30 μ /d as initial dose followed by a dose of at least 240 μ g/d followed of a target dose of at least 600 μ g/d may effectively convert an AML patient of MRD+ status to MRD- status and, thus, reduce the patients risk of a future disease progression. It is a further particular advantage that a low number of three different dosages, i.e. to dosage steps, is typically sufficient to reach the target dose for use in the treatment of MRD AML. A lower number of steps may reduce the level of complexity of treatment and may further increase patient compliance. Also, with fewer number of steps, a fewer number of infusions of premedication, i.e. typically dexamethasone, are required as CRS prophylaxis. Since the premedication typically is an immunosuppressant, it may potentially reduce efficacy of the treatment. Further advantageously, the bispecific construct for use in the treatment of MRD AML involving a step dosing as described herein typically leads to a lower risk in MRD patients to develop severe side effects such as higher degree CRS than in a comparable R/R setting. Typically, CRS is observed of grade 2 or lower, preferably at most grade 1 or lower under a two-step dosage regimen of CD33xCD3 bispecific construct (as exemplified herein by SEQ ID NO 104). Hence, the present bispecific construct is particularly preferred for use in the treatment of MRD AML, even more preferred in a dosage regimen as described herein.

For use of a CD33xCD3 bispecific construct in the treatment of MDS, the preferred starting dose of at least 10 μ g/d is preferably at least 30 μ g/day. Because patients with MDS have a lower tumor burden than those with R/R AML, patients with MDS are found to be at lower risk of developing CRS than those with R/R AML. As such, subjects with MDS are found to typically tolerate a higher starting dose of the CD33xCD3 bispecific construct (e.g. SEQ ID NO: 104), typically allow a dosing schedule which does not exceed the minimum amount of at least three or at least four steps, i.e. may typically require fewer step doses, and a higher MTD than for use in the treatment of R/R AML. In the context of the present invention, the for use in treatment of MDS typically comprises at least the dosing steps of at least 10 μ g/d, preferably at least 30 μ g/day for at least 1 day or at least 2 days, then at least 240 μ g/day for up to 5 days, and then at least 600 μ g/d, preferably at least 720, 840, 960, 1080, 1300 or 1600 μ g/day as target dose for up to 21 days per cycle, wherein typically at least one cycle is performed.

The end of the period of administration is understood to be reached, when the serum level of the active compound, e.g. the bispecific compound drops under a defined threshold. An example for such threshold is a serum level below an EC_{90} value, preferably below an EC_{50} value, more preferably below an EC_{10} value. Such EC values can be defined in a cytotoxic assay using CD33⁺ target cells and human PBL as effector cells in line with the assays.

In case of a bispecific single chain construct such as a preferred CD33xCD3 bispecific construct in the context of the present invention (see SEQ ID NO: 104), which is known to have a short serum half-life the half-life of CD33XCD3 bispecific construct in mice is 6.5 to 8.7h, while the predicted half-life of CD33XCD3 bispecific construct in human is about 2 hours), the serum level would fall below the above

discussed threshold value within short time after stopping a continuous iv administration, i.e. almost immediately after the end of the administration phase.

An assay for the determination of a specific EC_x value of a bispecific construct suitable for the present invention is described in the examples herein below.

5 The term “dose” is understood herein as a measured quantity of the agents described herein, i.e. a bispecific construct, typically in units of mass such as microgram [μ g].

The term “dosage” is understood herein as the rate of application of a dose of the agents described herein, i.e. a bispecific construct, typically in units of mass per time such as microgram per day [μ g/d].

10 In the context of the present invention, the application is IV infusion, preferably continuous IV infusion (CIV). Therein, administration, i.e. submission of the therapeutic bispecific construct, is not interrupted during the provided period of administration.

The term “treatment cycle” is understood herein as a period of treatment, comprising at least two dosage steps resulting in at least three dosages to be applied, wherein the dosages are increasing by order of their sequence. Said dosages within one treatment cycle are preferably not interrupted by any treatment-free period between the different dosages administered within one treatment cycle applying step dosing as described herein. Instead, the continuous infusion continues with respect to the treated patient preferably uninterrupted for the entire length of the treatment cycle. After completion, said treatment cycle may then typically be followed by a period of rest (administration-free period, i.e. no treatment), and that combination of treatment period and treatment-free period is repeated on a regular schedule.

20 For example, treatment given for four weeks followed by two weeks of rest is one treatment cycle. When this cycle is repeated multiple times on a regular schedule, it makes up a course of treatment.

The term “step dosing” is understood herein as the application of a series of increasing dosages, preferably within one treatment cycle, in order to avoid treatment-associated side effects such as CRS.

25 The term “dosage step” is understood herein as the change from one dosage to another. Hence, if the step dosing provides three different dosages, two dosage steps have to be applied, i.e. the change from the first to the second dosage step and from the second to the third dosage step, respectively.

In the context of the present invention, remission is understood either as the reduction or disappearance of the signs and symptoms of the disease AML. The term may also be used to refer to the period during which this diminution occurs. Herein, a remission may be considered a partial remission or a complete remission. For example, a partial remission for AML may be defined as a 50% or greater reduction in the measurable parameters of AML as may be found, for example, on physical examination, radiologic study, or by biomarker levels from a blood or urine test.

30 In the context of the present invention, complete remission, is typically a total disappearance of the manifestations of a disease. A patient whose condition is in complete remission might be considered cured or recovered, notwithstanding the possibility of a relapse, i.e. the reappearance of a disease.

In the context of the present invention, complete remission (CR) without a number typically means a first CR e.g. a newly diagnosed patient with AML receives chemotherapy in one or more cycles -i.e.

before receiving a bispecific construct according to the present invention, and goes into remission, that is the first CR (usually only called CR), then relapses, receives some other therapy and goes into remission again, that is now the second complete remission (CR2) and so forth.

The term “cohort” is understood in the context of the present invention as a group of patients who share a defining characteristic, i.e. who undergo the same treatment cycles characterized by same step dosing, dosages and application duration.

The term “effective dosage” is the target dose of at which the AML blasts and leukemic stem cells are effectively killed. This dose is typically the highest and preferably last dosage of one treatment cycle.

The term “Acute myeloid leukemia” (AML) is understood herein as a common form of acute leukemia, with a rising incidence attributed to an aging population, an increase in environmental exposure, and an increase in the population of cancer survivors previously exposed to chemotherapy and therapeutic radiation.

The term “measurable residual disease” or equivalently “minimal residual disease” (MRD) is understood herein as the persistence of detectable leukemic blasts below the threshold for CR. A patient under such condition may designated as “MRD+”. MRD is a proven risk factor for relapse and poor survival in patients with acute lymphoblastic leukemia (ALL), and the concept of MRD is gaining wider acceptance in the AML community (Richard-Carpentier et al, 2019; Buccisano et al, 2018). Hence, it is an object of the present invention to provide a CD33xCD3 bispecific construct -and its specific dosage regimen- for use in the treatment of MRD+ AML patients. The preferred endpoint of such use for the treatment of AML is the conversion of an AML patient from MRD+ status to MRD- status which is typically characterized by the absence of detectable leukemic blasts. Such abnormal blasts are referred herein simply as blasts if nothing else is mentioned.

The term “myelodysplastic syndrome represents” (MDS) is understood herein as a common class of acquired bone marrow failure syndromes, primarily in adults, and is typically defined by a diverse group of clonal disorders of hematopoietic progenitor cells. MDS is typically characterized by cytopenias, abnormal cell morphology, and progression to AML, typically with up to 30% of MDS cases progressing to AML (Greenberg et al, 1997). Approximately 40 000 new cases of MDS occur annually, with an estimated prevalence of 60 000 to 120 000 cases in the US (Bejar and Steensma, 2014).

The term “bispecific construct” refers to a molecule having a structure suitable for the specific binding of two individual target structures. In the context of the present invention such bispecific constructs specifically bind to a target, preferably CD33 on the cell surface of target cells and an effector, preferably CD3 on the cell surface of T cells. However, the preferred administration as described herein, i.e. a step dosing to mitigate side effects such as a cytokine release syndrome, and a prolonged exposition to

maximize efficacy, applies also to other bispecific constructs targeting another target than CD33 in addition to CD3 on the cell surface of T cells. In a preferred embodiment of a bispecific construct at least one, more preferably both binding domains of the bispecific construct are is/are based on the structure and/or function of an antibody. Such constructs may be designated as “bispecific constructs” in line with the present invention.

The term “construct” refers to a molecule in which the structure and/or function is/are based on the structure and/or function of an antibody, e.g., of a full-length or whole immunoglobulin molecule. A construct is hence capable of binding to its specific target or antigen and/or is/are drawn from the variable heavy chain (VH) and/or variable light chain (VL) domains of an antibody or fragment thereof. Furthermore, the domain which binds to its binding partner according to the present invention is understood herein as a binding domain of a construct according to the invention. Typically, a binding domain according to the present invention comprises the minimum structural requirements of an antibody which allow for the target binding. This minimum requirement may e.g. be defined by the presence of at least the three light chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region) and/or the three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region), preferably of all six CDRs. An alternative approach to define the minimal structure requirements of an antibody is the definition of the epitope of the antibody within the structure of the specific target, respectively, the protein domain of the target protein composing the epitope region (epitope cluster) or by reference to an specific antibody competing with the epitope of the defined antibody. The antibodies on which the constructs according to the invention are based include for example monoclonal, recombinant, chimeric, deimmunized, humanized and human antibodies.

The binding domain of an construct according to the invention may e.g. comprise the above referred groups of CDRs. Preferably, those CDRs are comprised in the framework of an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH); however, it does not have to comprise both. Fd fragments, for example, have two VH regions and often retain some antigen-binding function of the intact antigen-binding domain. Additional examples for the format of antibody fragments, antibody variants or binding domains include (1) a Fab fragment, a monovalent fragment having the VL, VH, CL and CH1 domains; (2) a F(ab')₂ fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) an Fd fragment having the two VH and CH1 domains; (4) an Fv fragment having the VL and VH domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) Nature 341 :544-546), which has a VH domain; (6) an isolated complementarity determining region (CDR), and (7) a single chain Fv (scFv) , the latter being preferred (for example, derived from an scFV-library). Examples for embodiments of constructs according to the invention are e.g. described in WO 00/006605, WO 2005/040220, WO 2008/119567, WO 2010/037838, WO 2013/026837, WO 2013/026833, US 2014/0308285, US 2014/0302037, WO 2014/144722, WO 2014/151910, and WO 2015/048272.

Furthermore, the definition of the term “constructs” includes monovalent, bivalent and polyvalent / multivalent constructs and, thus, monospecific constructs, specifically binding to only one antigenic structure, as well as bispecific and polyspecific/multispecific constructs, which specifically bind more than one antigenic structure, e.g. two, three or more, through distinct binding domains. Moreover, the definition of the term “constructs” includes molecules consisting of only one polypeptide chain as well as molecules consisting of more than one polypeptide chain, which chains can be either identical (homodimers, homotrimers or homooligomers) or different (heterodimer, heterotrimer or heterooligomer). Examples for the above identified antibodies and variants or derivatives thereof are described *inter alia* in Harlow and Lane, Antibodies a laboratory manual, CSHL Press (1988) and Using Antibodies: a laboratory manual, CSHL Press (1999), Kontermann and Dübeler, Antibody Engineering, Springer, 2nd ed. 2010 and Little, Recombinant Antibodies for Immunotherapy, Cambridge University Press 2009.

The constructs of the present invention are preferably “*in vitro* generated constructs”. This term refers to a construct according to the above definition where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection, e.g., an *in vitro* phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen. This term thus preferably excludes sequences generated solely by genomic rearrangement in an immune cell in an animal. A “recombinant antibody” is an antibody made through the use of recombinant DNA technology or genetic engineering.

An embodiment of the bispecific construct of the present invention is a “single chain constructs”. Those single chain constructs include only above described embodiments of constructs, which consist of a single peptide chain.

The term “monoclonal antibody” (mAb) or monoclonal construct as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site or determinant on the antigen, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (or epitopes). In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, hence uncontaminated by other immunoglobulins. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

For the preparation of monoclonal antibodies, any technique providing antibodies produced by continuous cell line cultures can be used. For example, monoclonal antibodies to be used may be made by the hybridoma method first described by Koehler *et al.*, Nature, 256: 495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Patent No. 4,816,567). Examples for further techniques to produce human monoclonal antibodies include the trioma technique, the human B-cell hybridoma technique (Kozbor, Immunology Today 4 (1983), 72) and the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), 77-96).

Hybridomas can then be screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (BIAcore™) analysis, to identify one or more hybridomas that produce an antibody that specifically binds with a specified antigen. Any form of the relevant antigen may be used as the immunogen, *e.g.*, recombinant antigen, naturally occurring forms, any variants or fragments thereof, as well as an antigenic peptide thereof. Surface plasmon resonance as employed in the BIAcore system can be used to increase the efficiency of phage antibodies which bind to an epitope of a target antigen, such as the target cell surface antigen CD33 or CD3 epsilon (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmborg, J. Immunol. Methods 183 (1995), 7-13).

Another exemplary method of making monoclonal antibodies includes screening protein expression libraries, *e.g.*, phage display or ribosome display libraries. Phage display is described, for example, in Ladner *et al.*, U.S. Patent No. 5,223,409; Smith (1985) Science 228:1315-1317, Clackson *et al.*, Nature, 352: 624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222: 581-597 (1991).

In addition to the use of display libraries, the relevant antigen can be used to immunize a non-human animal, *e.g.*, a rodent (such as a mouse, hamster, rabbit or rat). In one embodiment, the non-human animal includes at least a part of a human immunoglobulin gene. For example, it is possible to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig (immunoglobulin) loci. Using the hybridoma technology, antigen-specific monoclonal antibodies derived from the genes with the desired specificity may be produced and selected. See, *e.g.*, XENOMOUSE™, Green *et al.* (1994) Nature Genetics 7:13-21, US 2003-0070185, WO 96/34096, and WO96/33735.

A monoclonal antibody can also be obtained from a non-human animal, and then modified, *e.g.*, humanized, deimmunized, rendered chimeric etc., using recombinant DNA techniques known in the art. Examples of modified constructs include humanized variants of non-human antibodies, "affinity matured" antibodies (see, *e.g.* Hawkins *et al.* J. Mol. Biol. 254, 889-896 (1992) and Lowman *et al.*,

Biochemistry 30, 10832- 10837 (1991)) and antibody mutants with altered effector function(s) (see, *e.g.*, US Patent 5,648,260, Kontermann and Dübel (2010), *loc. cit.* and Little (2009), *loc. cit.*).

In immunology, affinity maturation is the process by which B cells produce antibodies with increased affinity for antigen during the course of an immune response. With repeated exposures to the same antigen, a host will produce antibodies of successively greater affinities. Like the natural prototype, the *in vitro* affinity maturation is based on the principles of mutation and selection. The *in vitro* affinity maturation has successfully been used to optimize antibodies, constructs, and antibody fragments. Random mutations inside the CDRs are introduced using radiation, chemical mutagens or error-prone PCR. In addition, the genetic diversity can be increased by chain shuffling. Two or three rounds of mutation and selection using display methods like phage display usually results in antibody fragments with affinities in the low nanomolar range.

A preferred type of an amino acid substitutional variation of the constructs involves substituting one or more hypervariable region residues of a parent antibody (e. g. a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e. g. 6-7 sites) are mutated to generate all possible amino acid substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e. g. binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the binding domain and, e.g., human the target cell surface antigen CD33. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

The monoclonal antibodies and constructs of the present invention specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the

desired biological activity (U.S. Patent No. 4,816, 567; Morrison et al., Proc. Natl. Acad. Sci. USA, 81: 6851-6855 (1984)). Chimeric antibodies of interest herein include "primitized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g., Old World Monkey, Ape etc.) and human constant region sequences. A variety of approaches for making chimeric antibodies have been described. See *e.g.*, Morrison *et al.*, Proc. Natl. Acad. Sci. U.S.A. 81:6851, 1985; Takeda *et al.*, Nature 314:452, 1985, Cabilly *et al.*, U.S. Patent No. 4,816,567; Boss *et al.*, U.S. Patent No. 4,816,397; Tanaguchi *et al.*, EP 0171496; EP 0173494; and GB 2177096.

An antibody, construct or antibody fragment may also be modified by specific deletion of human T cell epitopes (a method called "deimmunization") by the methods disclosed in WO 98/52976 and WO 00/34317. Briefly, the heavy and light chain variable domains of an antibody can be analyzed for peptides that bind to MHC class II; these peptides represent potential T cell epitopes (as defined in WO 98/52976 and WO 00/34317). For detection of potential T cell epitopes, a computer modeling approach termed "peptide threading" can be applied, and in addition a database of human MHC class II binding peptides can be searched for motifs present in the VH and VL sequences, as described in WO 98/52976 and WO 00/34317. These motifs bind to any of the 18 major MHC class II DR allotypes, and thus constitute potential T cell epitopes. Potential T cell epitopes detected can be eliminated by substituting small numbers of amino acid residues in the variable domains, or preferably, by single amino acid substitutions. Typically, conservative substitutions are made. Often, but not exclusively, an amino acid common to a position in human germline antibody sequences may be used. Human germline sequences are disclosed *e.g.* in Tomlinson, *et al.* (1992) J. Mol. Biol. 227:776-798; Cook, G.P. *et al.* (1995) Immunol. Today Vol. 16 (5): 237-242; and Tomlinson *et al.* (1995) EMBO J. 14: 14:4628-4638. The V BASE directory provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, L.A. *et al.* MRC Centre for Protein Engineering, Cambridge, UK). These sequences can be used as a source of human sequence, *e.g.*, for framework regions and CDRs. Consensus human framework regions can also be used, for example as described in US Patent No. 6,300,064.

"Humanized" antibodies, constructs or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) are antibodies or immunoglobulins of mostly human sequences, which contain (a) minimal sequence(s) derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region (also CDR) of the recipient are replaced by residues from a hypervariable region of a non-human (*e.g.*, rodent) species (donor antibody) such as mouse, rat, hamster or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, "humanized antibodies" as used herein may also comprise residues which are found neither in the recipient antibody

nor the donor antibody. These modifications are made to further refine and optimize antibody performance. The humanized antibody may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, Nature, 321: 522-525 (1986); Reichmann *et al.*, Nature, 332: 323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2: 593-596 (1992).

Humanized antibodies or fragments thereof can be generated by replacing sequences of the Fv variable domain that are not directly involved in antigen binding with equivalent sequences from human Fv variable domains. Exemplary methods for generating humanized antibodies or fragments thereof are provided by Morrison (1985) Science 229:1202-1207; by Oi *et al.* (1986) BioTechniques 4:214; and by US 5,585,089; US 5,693,761; US 5,693,762; US 5,859,205; and US 6,407,213. Those methods include isolating, manipulating, and expressing the nucleic acid sequences that encode all or part of immunoglobulin Fv variable domains from at least one of a heavy or light chain. Such nucleic acids may be obtained from a hybridoma producing an antibody against a predetermined target, as described above, as well as from other sources. The recombinant DNA encoding the humanized antibody molecule can then be cloned into an appropriate expression vector.

Humanized antibodies may also be produced using transgenic animals such as mice that express human heavy and light chain genes, but are incapable of expressing the endogenous mouse immunoglobulin heavy and light chain genes. Winter describes an exemplary CDR grafting method that may be used to prepare the humanized antibodies described herein (U.S. Patent No. 5,225,539). All of the CDRs of a particular human antibody may be replaced with at least a portion of a non-human CDR, or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to a predetermined antigen.

A humanized antibody can be optimized by the introduction of conservative substitutions, consensus sequence substitutions, germline substitutions and/or back mutations. Such altered immunoglobulin molecules can be made by any of several techniques known in the art, (e.g., Teng *et al.*, Proc. Natl. Acad. Sci. U.S.A., 80: 7308-7312, 1983; Kozbor *et al.*, Immunology Today, 4: 7279, 1983; Olsson *et al.*, Meth. Enzymol., 92: 3-16, 1982, and EP 239 400.

The term "human antibody", "human construct" and "human binding domain" includes antibodies, constructs and binding domains having antibody regions such as variable and constant regions or domains which correspond substantially to human germline immunoglobulin sequences known in the art, including, for example, those described by Kabat *et al.* (1991) (*loc. cit.*). The human antibodies, constructs or binding domains of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis

in vitro or by somatic mutation *in vivo*), for example in the CDRs, and in particular, in CDR3. The human antibodies, constructs or binding domains can have at least one, two, three, four, five, or more positions replaced with an amino acid residue that is not encoded by the human germline immunoglobulin sequence. The definition of human antibodies, constructs and binding domains as used
5 herein also contemplates fully human antibodies, which include only non-artificially and/or genetically altered human sequences of antibodies as those can be derived by using technologies or systems such as the Xenomouse.

In some embodiments, the constructs of the invention are "isolated" or "substantially pure" constructs.
10 "Isolated" or "substantially pure" when used to describe the construct disclosed herein means an construct that has been identified, separated and/or recovered from a component of its production environment. Preferably, the construct is free or substantially free of association with all other components from its production environment. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere
15 with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. The constructs may e.g constitute at least about 5%, or at least about 50% by weight of the total protein in a given sample. It is understood that the isolated protein may constitute from 5% to 99.9% by weight of the total protein content, depending on the circumstances. The polypeptide may be made at a significantly higher concentration through the use of an inducible
20 promoter or high expression promoter, such that it is made at increased concentration levels. The definition includes the production of an construct in a wide variety of organisms and/or host cells that are known in the art. In preferred embodiments, the construct will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using
25 Coomassie blue or, preferably, silver stain. Ordinarily, however, an isolated construct will be prepared by at least one purification step.

The term "binding domain" characterizes in connection with the present invention a domain which (specifically) binds to / interacts with / recognizes a given target epitope or a given target site on the
30 target molecules (antigens) and CD3, respectively. The structure and function of the first binding domain (recognizing the target cell surface antigen CD33), and preferably also the structure and/or function of the second binding domain (CD3), is/are based on the structure and/or function of an antibody, e.g. of a full-length or whole immunoglobulin molecule. According to the invention, the first binding domain is characterized by the presence of three light chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region)
35 and three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region). The second binding domain preferably also comprises the minimum structural requirements of an antibody which allow for the target binding. More preferably, the second binding domain comprises at least three light chain

CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region) and/or three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region). It is envisaged that the first and/or second binding domain is produced by or obtainable by phage-display or library screening methods rather than by grafting CDR sequences from a pre-existing (monoclonal) antibody into a scaffold.

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According to the present invention, binding domains are preferably in the form of polypeptides. Such polypeptides may include proteinaceous parts and non-proteinaceous parts (e.g. chemical linkers or chemical cross-linking agents such as glutaraldehyde). Proteins (including fragments thereof, preferably biologically active fragments, and peptides, usually having less than 30 amino acids) comprise two or more amino acids coupled to each other via a covalent peptide bond (resulting in a chain of amino acids). The term "polypeptide" as used herein describes a group of molecules, which usually consist of more than 30 amino acids. Polypeptides may further form multimers such as dimers, trimers and higher oligomers, i.e. consisting of more than one polypeptide molecule. Polypeptide molecules forming such dimers, trimers etc. may be identical or non-identical. The corresponding higher order structures of such multimers are, consequently, termed homo- or heterodimers, homo- or heterotrimers etc. An example for a heteromultimer is an antibody molecule, which, in its naturally occurring form, consists of two identical light polypeptide chains and two identical heavy polypeptide chains. The terms "peptide", "polypeptide" and "protein" also refer to naturally modified peptides / polypeptides / proteins wherein the modification is effected e.g. by post-translational modifications like glycosylation, acetylation, phosphorylation and the like. A "peptide", "polypeptide" or "protein" when referred to herein may also be chemically modified such as pegylated. Such modifications are well known in the art and described herein below.

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Antibodies and constructs comprising at least one human binding domain avoid some of the problems associated with antibodies or constructs that possess non-human such as rodent (e.g. murine, rat, hamster or rabbit) variable and/or constant regions. The presence of such rodent derived proteins can lead to the rapid clearance of the antibodies or constructs or can lead to the generation of an immune response against the antibody or construct by a patient. In order to avoid the use of rodent derived antibodies or constructs, human or fully human antibodies / constructs can be generated through the introduction of human antibody function into a rodent so that the rodent produces fully human antibodies.

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The ability to clone and reconstruct megabase-sized human loci in YACs and to introduce them into the mouse germline provides a powerful approach to elucidating the functional components of very large or crudely mapped loci as well as generating useful models of human disease. Furthermore, the use of such technology for substitution of mouse loci with their human equivalents could provide unique insights into the expression and regulation of human gene products during development, their communication with other systems, and their involvement in disease induction and progression.

An important practical application of such a strategy is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to study the mechanisms underlying programmed expression and assembly of antibodies as well as their role in B-cell development. Furthermore, such a strategy could provide an ideal source for production of fully human monoclonal antibodies (mAbs) – an important milestone towards fulfilling the promise of antibody therapy in human disease. Fully human antibodies or constructs are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized mAbs and thus to increase the efficacy and safety of the administered antibodies / constructs. The use of fully human antibodies or constructs can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as inflammation, autoimmunity, and cancer, which require repeated compound administrations.

One approach towards this goal was to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci in anticipation that such mice would produce a large repertoire of human antibodies in the absence of mouse antibodies. Large human Ig fragments would preserve the large variable gene diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains should yield high affinity antibodies against any antigen of interest, including human antigens. Using the hybridoma technology, antigen-specific human mAbs with the desired specificity could be readily produced and selected. This general strategy was demonstrated in connection with the generation of the first XenoMouse mouse strains (see Green et al. *Nature Genetics* 7:13-21 (1994)). The XenoMouse strains were engineered with yeast artificial chromosomes (YACs) containing 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. The human Ig containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig genes. This was demonstrated by their ability to induce B cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human mAbs. These results also suggested that introduction of larger portions of the human Ig loci containing greater numbers of V genes, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively. See Mendez *et al.* *Nature Genetics* 15:146-156 (1997) and U.S. patent application Ser. No. 08/759,620.

The production of the XenoMouse mice is further discussed and delineated in U.S. patent applications Ser. No. 07/466,008, Ser. No. 07/610,515, Ser. No. 07/919,297, Ser. No. 07/922,649, Ser. No. 08/031,801, Ser. No. 08/112,848, Ser. No. 08/234,145, Ser. No. 08/376,279, Ser. No. 08/430,938, Ser. No. 08/464,584, Ser. No. 08/464,582, Ser. No. 08/463,191, Ser. No. 08/462,837, Ser. No. 08/486,853, Ser. No. 08/486,857, Ser. No. 08/486,859, Ser. No. 08/462,513, Ser. No. 08/724,752, and Ser. No. 08/759,620; and U.S. Pat. Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. See also Mendez *et al.* Nature Genetics 15:146-156 (1997) and Green and Jakobovits J. Exp. Med. 188:483-495 (1998), EP 0 463 151 B1, WO 94/02602, WO 96/34096, WO 98/24893, WO 00/76310, and WO 03/47336.

In an alternative approach, others, including GenPharm International, Inc., have utilized a "minilocus" approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more VH genes, one or more DH genes, one or more JH genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Pat. No. 5,545,807 to Surani *et al.* and U.S. Pat. Nos. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,877,397, 5,874,299, and 6,255,458 each to Lonberg and Kay, U.S. Pat. Nos. 5,591,669 and 6,023,010 to Krimpenfort and Berns, U.S. Pat. Nos. 5,612,205, 5,721,367, and 5,789,215 to Berns *et al.*, and U.S. Pat. No. 5,643,763 to Choi and Dunn, and GenPharm International U.S. patent application Ser. No. 07/574,748, Ser. No. 07/575,962, Ser. No. 07/810,279, Ser. No. 07/853,408, Ser. No. 07/904,068, Ser. No. 07/990,860, Ser. No. 08/053,131, Ser. No. 08/096,762, Ser. No. 08/155,301, Ser. No. 08/161,739, Ser. No. 08/165,699, Ser. No. 08/209,741. See also EP 0 546 073 B1, WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Pat. No. 5,981,175. See further Taylor *et al.* (1992), Chen *et al.* (1993), Tuailon *et al.* (1993), Choi *et al.* (1993), Lonberg *et al.* (1994), Taylor *et al.* (1994), and Tuailon *et al.* (1995), Fishwild *et al.* (1996).

Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. See European Patent Application Nos. 773 288 and 843 961. Xenerex Biosciences is developing a technology for the potential generation of human antibodies. In this technology, SCID mice are reconstituted with human lymphatic cells, e.g., B and/or T cells. Mice are then immunized with an antigen and can generate an immune response against the antigen. See U.S. Pat. Nos. 5,476,996; 5,698,767; and 5,958,765.

Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. It is however expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide constructs comprising a fully human binding domain against the target cell surface antigen and a fully human binding domain against CD3 in order to vitiate concerns and/or effects of HAMA or HACA response.

The terms “(specifically) binds to”, “(specifically) recognizes”, “is (specifically) directed to”, and “(specifically) reacts with” mean in accordance with this invention that a binding domain interacts or specifically interacts with one or more, preferably at least two, more preferably at least three and most preferably at least four amino acids of an epitope located on the target protein or antigen (the target cell surface antigen CD33 / CD3).

The term “epitope” refers to the site on an antigen to which a binding domain, such as an antibody or immunoglobulin or derivative or fragment of an antibody or of an immunoglobulin, specifically binds. An “epitope” is antigenic and thus the term epitope is sometimes also referred to herein as “antigenic structure” or “antigenic determinant”. Thus, the binding domain is an “antigen interaction site”. Said binding/interaction is also understood to define a “specific recognition”. The term “epitope” is understood in connection with this application as describing the complete antigenic structure, whereas the term “part of the epitope” may be used to describe one or more subgroups of the specific epitope of a given binding domain.

“Epitopes” can be formed both by contiguous amino acids or non-contiguous amino acids juxtaposed by tertiary folding of a protein. A “linear epitope” is an epitope where an amino acid primary sequence comprises the recognized epitope. A linear epitope typically includes at least 3 or at least 4, and more usually, at least 5 or at least 6 or at least 7, for example, about 8 to about 10 amino acids in a unique sequence.

A “conformational epitope”, in contrast to a linear epitope, is an epitope wherein the primary sequence of the amino acids comprising the epitope is not the sole defining component of the epitope recognized (e.g., an epitope wherein the primary sequence of amino acids is not necessarily recognized by the binding domain). Typically a conformational epitope comprises an increased number of amino acids relative to a linear epitope. With regard to recognition of conformational epitopes, the binding domain recognizes a three-dimensional structure of the antigen, preferably a peptide or protein or fragment thereof (in the context of the present invention, the antigen for one of the binding domains is comprised within the target cell surface antigen CD33). For example, when a protein molecule folds to form a three-dimensional structure, certain amino acids and/or the polypeptide backbone forming the

conformational epitope become juxtaposed enabling the antibody to recognize the epitope. Methods of determining the conformation of epitopes include, but are not limited to, x-ray crystallography, two-dimensional nuclear magnetic resonance (2D-NMR) spectroscopy and site-directed spin labelling and electron paramagnetic resonance (EPR) spectroscopy.

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The interaction between the binding domain and the epitope or epitope cluster implies that a binding domain exhibits appreciable affinity for the epitope or epitope cluster on a particular protein or antigen (here: the target cell surface antigen CD33 and CD3, respectively) and, generally, does not exhibit significant reactivity with proteins or antigens other than the target cell surface antigen CD33 or CD3.

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“Appreciable affinity” includes binding with an affinity of about 10^{-6} M (KD) or stronger. Preferably, binding is considered specific when the binding affinity is about 10^{-12} to 10^{-8} M, 10^{-12} to 10^{-9} M, 10^{-12} to 10^{-10} M, 10^{-11} to 10^{-8} M, preferably of about 10^{-11} to 10^{-9} M. Whether a binding domain specifically reacts with or binds to a target can be tested readily by, *inter alia*, comparing the reaction of said binding domain with a target protein or antigen with the reaction of said binding domain with proteins or antigens other than the target cell surface antigen CD33 or CD3. Preferably, a binding domain of the invention does not essentially or substantially bind to proteins or antigens other than the target cell surface antigen CD33 or CD3 (*i.e.*, the first binding domain is not capable of binding to proteins other than the target cell surface antigen CD33 and the second binding domain is not capable of binding to proteins other than CD3).

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The term “does not essentially / substantially bind” or “is not capable of binding” means that a binding domain of the present invention does not bind a protein or antigen other than the target cell surface antigen CD33 or CD3, *i.e.*, does not show reactivity of more than 30%, preferably not more than 20%, more preferably not more than 10%, particularly preferably not more than 9%, 8%, 7%, 6% or 5% with proteins or antigens other than the target cell surface antigen CD33 or CD3, whereby binding to the target cell surface antigen CD33 or CD3, respectively, is set to be 100%.

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Specific binding is believed to be effected by specific motifs in the amino acid sequence of the binding domain and the antigen. Thus, binding is achieved as a result of their primary, secondary and/or tertiary structure as well as the result of secondary modifications of said structures. The specific interaction of the antigen-interaction-site with its specific antigen may result in a simple binding of said site to the antigen. Moreover, the specific interaction of the antigen-interaction-site with its specific antigen may alternatively or additionally result in the initiation of a signal, e.g. due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc.

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The term “variable” refers to the portions of the antibody or immunoglobulin domains that exhibit variability in their sequence and that are involved in determining the specificity and binding affinity of

a particular antibody (i.e., the "variable domain(s)"). The pairing of a variable heavy chain (VH) and a variable light chain (VL) together forms a single antigen-binding site.

Variability is not evenly distributed throughout the variable domains of antibodies; it is concentrated in sub-domains of each of the heavy and light chain variable regions. These sub-domains are called "hypervariable regions" or "complementarity determining regions" (CDRs). The more conserved (i.e., non-hypervariable) portions of the variable domains are called the "framework" regions (FRM) and provide a scaffold for the six CDRs in three dimensional space to form an antigen-binding surface. The variable domains of naturally occurring heavy and light chains each comprise four FRM regions (FR1, FR2, FR3, and FR4), largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRM and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site (see Kabat *et al.*, *loc. cit.*).

The terms "CDR", and its plural "CDRs", refer to the complementarity determining region of which three make up the binding character of a light chain variable region (CDR-L1, CDR-L2 and CDR-L3) and three make up the binding character of a heavy chain variable region (CDR-H1, CDR-H2 and CDR-H3). CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen and hence contribute to the functional activity of an antibody molecule: they are the main determinants of antigen specificity.

The exact definitional CDR boundaries and lengths are subject to different classification and numbering systems. CDRs may therefore be referred to by Kabat, Chothia, contact or any other boundary definitions, including the numbering system described herein. Despite differing boundaries, each of these systems has some degree of overlap in what constitutes the so called "hypervariable regions" within the variable sequences. CDR definitions according to these systems may therefore differ in length and boundary areas with respect to the adjacent framework region. See for example Kabat (an approach based on cross-species sequence variability), Chothia (an approach based on crystallographic studies of antigen-antibody complexes), and/or MacCallum (Kabat *et al.*, *loc. cit.*; Chothia *et al.*, J. Mol. Biol., 1987, 196: 901-917; and MacCallum *et al.*, J. Mol. Biol., 1996, 262: 732). Still another standard for characterizing the antigen binding site is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, *e.g.*, Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). To the extent that two residue identification techniques define regions of overlapping, but not identical regions, they can be combined to define a hybrid CDR. However, the numbering in accordance with the so-called Kabat system is preferred.

Typically, CDRs form a loop structure that can be classified as a canonical structure. The term "canonical structure" refers to the main chain conformation that is adopted by the antigen binding (CDR) loops. From comparative structural studies, it has been found that five of the six antigen binding loops have only a limited repertoire of available conformations. Each canonical structure can be characterized by the torsion angles of the polypeptide backbone. Correspondent loops between antibodies may, therefore, have very similar three dimensional structures, despite high amino acid sequence variability in most parts of the loops (Chothia and Lesk, J. Mol. Biol., 1987, 196: 901; Chothia *et al.*, Nature, 1989, 342: 877; Martin and Thornton, J. Mol. Biol, 1996, 263: 800). Furthermore, there is a relationship between the adopted loop structure and the amino acid sequences surrounding it. The conformation of a particular canonical class is determined by the length of the loop and the amino acid residues residing at key positions within the loop, as well as within the conserved framework (*i.e.*, outside of the loop). Assignment to a particular canonical class can therefore be made based on the presence of these key amino acid residues.

The term "canonical structure" may also include considerations as to the linear sequence of the antibody, for example, as catalogued by Kabat (Kabat *et al.*, loc. cit.). The Kabat numbering scheme (system) is a widely adopted standard for numbering the amino acid residues of an antibody variable domain in a consistent manner and is the preferred scheme applied in the present invention as also mentioned elsewhere herein. Additional structural considerations can also be used to determine the canonical structure of an antibody. For example, those differences not fully reflected by Kabat numbering can be described by the numbering system of Chothia *et al* and/or revealed by other techniques, for example, crystallography and two- or three-dimensional computational modeling. Accordingly, a given antibody sequence may be placed into a canonical class which allows for, among other things, identifying appropriate chassis sequences (e.g., based on a desire to include a variety of canonical structures in a library). Kabat numbering of antibody amino acid sequences and structural considerations as described by Chothia *et al.*, loc. cit. and their implications for construing canonical aspects of antibody structure, are described in the literature. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, eds. Harlow *et al.*, 1988.

The CDR3 of the light chain and, particularly, the CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. In some constructs, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. *In vitro* selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody or determine which residues contribute to the binding of an antigen.

Hence, CDR3 is typically the greatest source of molecular diversity within the antibody-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids.

In a classical full-length antibody or immunoglobulin, each light (L) chain is linked to a heavy (H) chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. The CH domain most proximal to VH is usually designated as CH1. The constant ("C") domains are not directly involved in antigen binding, but exhibit various effector functions, such as antibody-dependent, cell-mediated cytotoxicity and complement activation. The Fc region of an antibody is comprised within the heavy chain constant domains and is for example able to interact with cell surface located Fc receptors.

The sequence of antibody genes after assembly and somatic mutation is highly varied, and these varied genes are estimated to encode 10^{10} different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995). Accordingly, the immune system provides a repertoire of immunoglobulins. The term "repertoire" refers to at least one nucleotide sequence derived wholly or partially from at least one sequence encoding at least one immunoglobulin. The sequence(s) may be generated by rearrangement in vivo of the V, D, and J segments of heavy chains, and the V and J segments of light chains. Alternatively, the sequence(s) can be generated from a cell in response to which rearrangement occurs, e.g., *in vitro* stimulation. Alternatively, part or all of the sequence(s) may be obtained by DNA splicing, nucleotide synthesis, mutagenesis, and other methods, see, e.g., U.S. Patent 5,565,332. A repertoire may include only one sequence or may include a plurality of sequences, including ones in a genetically diverse collection.

The term "bispecific" as used herein refers to a construct which is "at least bispecific", i.e., it comprises at least a first binding domain and a second binding domain, wherein the first binding domain binds to one antigen or target, and the second binding domain binds to another antigen or target (here: CD3). Accordingly, bispecific constructs according to the invention comprise specificities for at least two different antigens or targets. The term "bispecific construct" of the invention also encompasses multispecific constructs such as trispecific constructs, the latter ones including three binding domains, or constructs having more than three (e.g. four, five...) specificities. In case the construct used in connection with this invention is an construct, these encompassed corresponding constructs are multispecific constructs such as trispecific constructs, the latter ones including three binding domains, or constructs having more than three (e.g. four, five...) specificities.

Given that the constructs according to the invention are (at least) bispecific, they do not occur naturally and they are markedly different from naturally occurring products. A "bispecific" construct or immunoglobulin is hence an artificial hybrid antibody or immunoglobulin having at least two distinct

binding sites with different specificities. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, Clin. Exp. Immunol. 79:315-321 (1990).

- 5 The at least two binding domains and the variable domains of the construct of the present invention may or may not comprise peptide linkers (spacer peptides). The term “peptide linker” defines in accordance with the present invention an amino acid sequence by which the amino acid sequences of one (variable and/or binding) domain and another (variable and/or binding) domain of the construct of the invention are linked with each other. An essential technical feature of such peptide linker is that said peptide linker
- 10 does not comprise any polymerization activity. Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233 or WO 88/09344. The peptide linkers can also be used to attach other domains or modules or regions (such as half-life extending domains) to the construct of the invention.
- 15 In the event that a linker is used, this linker is preferably of a length and sequence sufficient to ensure that each of the first and second domains can, independently from one another, retain their differential binding specificities. For peptide linkers which connect the at least two binding domains in the construct of the invention (or two variable domains), those peptide linkers are preferred which comprise only a few number of amino acid residues, e.g. 12 amino acid residues or less. Thus, peptide linker of 12, 11,
- 20 10, 9, 8, 7, 6 or 5 amino acid residues are preferred. An envisaged peptide linker with less than 5 amino acids comprises 4, 3, 2 or one amino acid(s) wherein Gly-rich linkers are preferred. A particularly preferred “single” amino acid in context of said “peptide linker” is Gly. Accordingly, said peptide linker may consist of the single amino acid Gly. Another preferred embodiment of a peptide linker is characterized by the amino acid sequence Gly-Gly-Gly-Gly-Ser, i.e. Gly₄Ser, or polymers thereof, i.e.
- 25 (Gly₄Ser)_x, where x is an integer of 1 or greater. The characteristics of said peptide linker, which comprise the absence of the promotion of secondary structures are known in the art and are described *e.g.* in Dall’Acqua et al. (Biochem. (1998) 37, 9266-9273), Cheadle et al. (Mol Immunol (1992) 29, 21-30) and Raag and Whitlow (FASEB (1995) 9(1), 73-80). Peptide linkers which also do not promote any secondary structures are preferred. The linkage of said domains to each other can be provided by, e.g.
- 30 genetic engineering, as described in the examples. Methods for preparing fused and operatively linked bispecific single chain constructs and expressing them in mammalian cells or bacteria are well-known in the art (*e.g.* WO 99/54440 or Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2001).
- 35 Bispecific single chain molecules are known in the art and are described in WO 99/54440, Mack, J. Immunol. (1997), 158, 3965-3970, Mack, PNAS, (1995), 92, 7021-7025, Kufer, Cancer Immunol. Immunother., (1997), 45, 193-197, Löffler, Blood, (2000), 95, 6, 2098-2103, Brühl, Immunol., (2001),

166, 2420-2426, Kipriyanov, J. Mol. Biol., (1999), 293, 41-56. Techniques described for the production of single chain antibodies (see, *inter alia*, US Patent 4,946,778, Kontermann and Dübel (2010), *loc. cit.* and Little (2009), *loc. cit.*) can be adapted to produce single chain constructs specifically recognizing (an) elected target(s).

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Bivalent (also called divalent) or bispecific single-chain variable fragments (bi-scFvs or di-scFvs having the format (scFv)₂) can be engineered by linking two scFv molecules. In case these two scFv molecules have the same binding specificity, the resulting (scFv)₂ molecule will preferably be called bivalent (*i.e.* it has two valences for the same target epitope). In case the two scFv molecules have different binding specificities, the resulting (scFv)₂ molecule will preferably be called bispecific. The linking can be done by producing a single peptide chain with two VH regions and two VL regions, yielding tandem scFvs (see *e.g.* Kufer P. *et al.*, (2004) Trends in Biotechnology 22(5):238-244). Another possibility is the creation of scFv molecules with linker peptides that are too short for the two variable regions to fold together (*e.g.* about five amino acids), forcing the scFvs to dimerize. This type is known as diabodies (see *e.g.* Hollinger, Philipp *et al.*, (July 1993) Proceedings of the National Academy of Sciences of the United States of America 90 (14): 6444-8.).

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Single domain antibodies comprise merely one (monomeric) antibody variable domain which is able to bind selectively to a specific antigen, independently of other V regions or domains. The first single domain antibodies were engineered from heavy chain antibodies found in camelids, and these are called V_HH fragments. Cartilaginous fishes also have heavy chain antibodies (IgNAR) from which single domain antibodies called V_{NAR} fragments can be obtained. An alternative approach is to split the dimeric variable domains from common immunoglobulins *e.g.* from humans or rodents into monomers, hence obtaining VH or VL as a single domain Ab. Although most research into single domain antibodies is currently based on heavy chain variable domains, nanobodies derived from light chains have also been shown to bind specifically to target epitopes. Examples of single domain antibodies are called sdAb, nanobodies or single variable domain antibodies.

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A (single domain mAb)₂ is hence a monoclonal construct composed of (at least) two single domain monoclonal antibodies, which are individually selected from the group comprising VH, VL, VHH and V_{NAR}. The linker is preferably in the form of a peptide linker. Similarly, an "scFv-single domain mAb" is a monoclonal construct composed of at least one single domain antibody as described above and one scFv molecule as described above. Again, the linker is preferably in the form of a peptide linker.

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It is also envisaged that the construct of the invention has, in addition to its function to bind to the target antigen CD33 and CD3, a further function. In this format, the construct is a trifunctional or multifunctional construct by targeting target cells through binding to the target antigen, mediating

cytotoxic T cell activity through CD3 binding and providing a further function such as a label (fluorescent etc.), a therapeutic agent such as a toxin or radionuclide, etc.

Covalent modifications of the constructs are also included within the scope of this invention, and are generally, but not always, done post-translationally. For example, several types of covalent modifications of the construct are introduced into the molecule by reacting specific amino acid residues of the construct with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

Cysteiny l residues most commonly are reacted with α -haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteiny l residues also are derivatized by reaction with bromotrifluoroacetone, α -bromo- β -(5-imidazolyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0. Lysiny l and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysiny l residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimide; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginy l residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ^{125}I or ^{131}I to prepare labeled proteins for use in radioimmunoassay, the chloramine T method described above being suitable.

Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides ($R'-N=C=N-R$), where R and R' are optionally different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide.

Furthermore, aspartyl and glutamyl residues are converted to asparaginyll and glutaminyl residues by reaction with ammonium ions.

Derivatization with bifunctional agents is useful for crosslinking the constructs of the present invention to a water-insoluble support matrix or surface for use in a variety of methods. Commonly used crosslinking agents include, *e.g.*, 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Glutaminyl and asparaginyll residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyll residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, *Proteins: Structure and Molecular Properties*, W. H. Freeman & Co., San Francisco, 1983, pp. 79-86), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the constructs included within the scope of this invention comprises altering the glycosylation pattern of the protein. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (*e.g.*, the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the

recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the construct is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the amino acid sequence of an construct is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the construct is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330, and in Aplin and Wriston, 1981, CRC Crit. Rev. Biochem., pp. 259-306.

Removal of carbohydrate moieties present on the starting construct may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin *et al.*, 1987, *Arch. Biochem. Biophys.* 259:52 and by Edge *et al.*, 1981, *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, 1987, *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin *et al.*, 1982, *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

Other modifications of the construct are contemplated herein. For example, another type of covalent modification of the construct comprises linking the construct to various non-proteinaceous polymers,

including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. In addition, as is known in the art, amino acid substitutions may be made in various positions within the construct, e.g. in order to facilitate the addition of polymers such as PEG.

In some embodiments, the covalent modification of the constructs of the invention comprises the addition of one or more labels. The labelling group may be coupled to the construct *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and can be used in performing the present invention. The term “label” or “labelling group” refers to any detectable label. In general, labels fall into a variety of classes, depending on the assay in which they are to be detected – the following examples include, but are not limited to:

- a) isotopic labels, which may be radioactive or heavy isotopes, such as radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{89}Zr , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I)
- b) magnetic labels (*e.g.*, magnetic particles)
- c) redox active moieties
- d) optical dye (including, but not limited to, chromophores, phosphors and fluorophores) such as fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), chemiluminescent groups, and fluorophores which can be either “small molecule” fluoers or proteinaceous fluoers
- e) enzymatic groups (*e.g.* horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase)
- f) biotinylated groups
- g) predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.)

By “fluorescent label” is meant any molecule that may be detected *via* its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade BlueJ, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, OR), FITC, Rhodamine, and Texas Red (Pierce, Rockford, IL), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, PA). Suitable optical dyes, including fluorophores, are described in Molecular Probes Handbook by Richard P. Haugland.

Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a Renilla, Ptilosarcus, or Aequorea species of GFP (Chalfie *et al.*, 1994, *Science* 263:802-805), EGFP (Clontech Laboratories, Inc., Genbank Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc. 1801 de Maisonneuve Blvd. West, 8th Floor, Montreal, Quebec, Canada H3H 1J9; Stauber, 1998, *Biotechniques* 24:462-471; Heim *et al.*, 1996, *Curr. Biol.* 6:178-182), enhanced yellow fluorescent protein (EYFP, Clontech Laboratories, Inc.), luciferase (Ichiki *et al.*, 1993, *J. Immunol.* 150:5408-5417), β galactosidase (Nolan *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:2603-2607) and Renilla (WO92/15673, WO95/07463, WO98/14605, WO98/26277, WO99/49019, U.S. Patent Nos. 5292658, 5418155, 5683888, 5741668, 5777079, 5804387, 5874304, 5876995, 5925558).

Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz *et al.*, 1988, *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe *et al.*, 1994, *FEBS Letters* 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow *et al.*, 1994, *Semin. Immunol.* 6:267-78. In one approach, recombinant fusion proteins comprising the target antigen antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric target antigen antibody fragments or derivatives that form are recovered from the culture supernatant.

The construct of the invention may also comprise additional domains, which are *e.g.* helpful in the isolation of the molecule or relate to an adapted pharmacokinetic profile of the molecule. Domains helpful for the isolation of an construct may be selected from peptide motives or secondarily introduced moieties, which can be captured in an isolation method, *e.g.* an isolation column. Non-limiting embodiments of such additional domains comprise peptide motives known as Myc-tag, HAT-tag, HA-tag, TAP-tag, GST-tag, chitin binding domain (CBD-tag), maltose binding protein (MBP-tag), Flag-tag, Strep-tag and variants thereof (*e.g.* StrepII-tag) and His-tag. All herein disclosed constructs characterized by the identified CDRs are preferred to comprise a His-tag domain, which is generally known as a repeat of consecutive His residues in the amino acid sequence of a molecule, preferably of six His residues.

T cells or T lymphocytes are a type of lymphocyte (itself a type of white blood cell) that play a central role in cell-mediated immunity. There are several subsets of T cells, each with a distinct function. T cells

can be distinguished from other lymphocytes, such as B cells and NK cells, by the presence of a T cell receptor (TCR) on the cell surface. The TCR is responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules and is composed of two different protein chains. In 95% of the T cells, the TCR consists of an alpha (α) and beta (β) chain. When the TCR engages with antigenic peptide and MHC (peptide / MHC complex), the T lymphocyte is activated through a series of biochemical events mediated by associated enzymes, co-receptors, specialized adaptor molecules, and activated or released transcription factors

The CD3 receptor complex is a protein complex and is composed of four chains. In mammals, the complex contains a CD3 γ (gamma) chain, a CD3 δ (delta) chain, and two CD3 ϵ (epsilon) chains. These chains associate with the T cell receptor (TCR) and the so-called ζ (zeta) chain to form the T cell receptor CD3 complex and to generate an activation signal in T lymphocytes. The CD3 γ (gamma), CD3 δ (delta), and CD3 ϵ (epsilon) chains are highly related cell-surface proteins of the immunoglobulin superfamily containing a single extracellular immunoglobulin domain. The intracellular tails of the CD3 molecules contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or ITAM for short, which is essential for the signaling capacity of the TCR. The CD3 epsilon molecule is a polypeptide which in humans is encoded by the *CD3E* gene which resides on chromosome 11. The sequence of a preferred human CD3 epsilon extracellular domain is shown in SEQ ID NO: 1, and the most preferred CD3 binding epitope corresponding to amino acid residues 1-27 of the human CD3 epsilon extracellular domain is represented in SEQ ID NO: 2.

The redirected lysis of target cells via the recruitment of T cells by a multispecific, at least bispecific, construct involves cytolytic synapse formation and delivery of perforin and granzymes. The engaged T cells are capable of serial target cell lysis, and are not affected by immune escape mechanisms interfering with peptide antigen processing and presentation, or clonal T cell differentiation; see, for example, WO 2007/042261.

Cytotoxicity mediated by bispecific constructs can be measured in various ways. Effector cells can be e.g. stimulated enriched (human) CD8 positive T cells or unstimulated (human) peripheral blood mononuclear cells (PBMC). If the target cells are of macaque origin or express or are transfected with macaque target cell antigen, the effector cells should also be of macaque origin such as a macaque T cell line, e.g. 4119LnPx. The target cells should express (at least the extracellular domain of) target cell antigen, e.g. human or macaque target cell antigen. Target cells can be a cell line (such as CHO) which is stably or transiently transfected with target cell antigen, e.g. human or macaque target cell antigen. Alternatively, the target cells can be a target cell antigen positive natural expresser cell line, such as a human cancer cell line. Usually EC50 values are expected to be lower with target cell lines expressing higher levels of target cell antigen on the cell surface. The effector to target cell (E:T) ratio is usually

about 10:1, but can also vary. Cytotoxic activity of bispecific constructs can be measured in a ⁵¹chromium release assay (incubation time of about 18 hours) or in a FACS-based cytotoxicity assay (incubation time of about 48 hours). Modifications of the assay incubation time (cytotoxic reaction) are also possible. Other methods of measuring cytotoxicity are well-known to the skilled person and comprise MTT or MTS assays, ATP-based assays including bioluminescent assays, the sulforhodamine B (SRB) assay, WST assay, clonogenic assay and the ECIS technology.

The cytotoxic activity mediated by bispecific constructs of the present invention is preferably measured in a cell-based cytotoxicity assay. It is represented by the EC₅₀ value, which corresponds to the half maximal effective concentration (concentration of the construct which induces a cytotoxic response halfway between the baseline and maximum). Preferably, the EC₅₀ value of the bispecific constructs is ≤20.000 pg/ml, more preferably ≤5000 pg/ml, even more preferably ≤1000 pg/ml, even more preferably ≤500 pg/ml, even more preferably ≤350 pg/ml, even more preferably ≤250 pg/ml, even more preferably ≤100 pg/ml, even more preferably ≤50 pg/ml, even more preferably ≤10 pg/ml, and most preferably ≤5 pg/ml.

Any of the above given EC₅₀ values can be combined with any one of the indicated scenarios of a cell-based cytotoxicity assay, *e.g.* in line with the methods described in the appended example. For example, when (human) CD8 positive T cells or a macaque T cell line are used as effector cells, the EC₅₀ value of the bispecific construct of the invention (*e.g.* a target cell antigen/CD3 bispecific construct) is preferably ≤1000 pg/ml, more preferably ≤500 pg/ml, even more preferably ≤250 pg/ml, even more preferably ≤100 pg/ml, even more preferably ≤50 pg/ml, even more preferably ≤10 pg/ml, and most preferably ≤5 pg/ml. If in this assay the target cells are (human or macaque) cells transfected with the target antigen (*e.g.* the target cell antigen CD33), such as CHO cells, the EC₅₀ value of the bispecific construct is preferably ≤150 pg/ml, more preferably ≤100 pg/ml, even more preferably ≤50 pg/ml, even more preferably ≤30 pg/ml, even more preferably ≤10 pg/ml, and most preferably ≤5 pg/ml. If the target cells are a positive natural expresser cell line (*e.g.* of target cell antigen), then the EC₅₀ value is preferably ≤350 pg/ml, more preferably ≤250 pg/ml, even more preferably ≤200 pg/ml, even more preferably ≤100 pg/ml, even more preferably ≤150 pg/ml, even more preferably ≤100 pg/ml, and most preferably ≤50 pg/ml, or lower. When (human) PBMCs are used as effector cells, the EC₅₀ value of the bispecific construct is preferably ≤1000 pg/ml, more preferably ≤750 pg/ml, more preferably ≤500 pg/ml, even more preferably ≤350 pg/ml, even more preferably ≤250 pg/ml, even more preferably ≤100 pg/ml, and most preferably ≤50 pg/ml, or lower.

Preferably, the bispecific constructs of the present invention do not induce / mediate lysis or do not essentially induce / mediate lysis of target cell antigen negative cells such as CHO cells. The term “do not induce lysis”, “do not essentially induce lysis”, “do not mediate lysis” or “do not essentially mediate

lysis” means that an constructs of the present invention does not induce or mediate lysis of more than 30%, preferably not more than 20%, more preferably not more than 10%, particularly preferably not more than 9%, 8%, 7%, 6% or 5% of target cell antigen negative cells, whereby lysis of a target cell antigen positive cell line is set to be 100%. This usually applies for concentrations of the construct of up to 500 nM. The skilled person knows how to measure cell lysis without further ado. Moreover, the present specification teaches specific instructions how to measure cell lysis.

Preferably, the bispecific construct for the use according to the invention is administered according to a schedule comprising the following steps:

- (a) administration of a first dose of the bispecific construct, followed by
- (b) administration of a second dose of the bispecific construct, wherein said second dose exceeds said first dose, followed by
- (c) administration of a third dose of the bispecific construct, wherein said third dose exceeds said second dose, optionally -depending on the indication- followed by
- (d) administration of a forth, a fifth and a sixth dose of the bispecific construct, wherein said optional forth dose exceeds said third dose, and said optional fifth dose exceeds the optional forth dose and the optional sixth dose exceeds the fifth dose.

In line with the above it is further preferred that the period of administration of the first dose is up to seven days. This period of administration of the first dose may be used during the initial phase/first cycle of administration of the bispecific construct e.g. to reduce the tumor load in a patient (tumor debulking) while avoiding conditions such as cytokine storm and/or cytokine release syndrome which one might expect in case a higher dose is used during the period of administration of the first dose.

While in one embodiment of the invention the period of administration of the first dose is up to seven days, it is also within this preferred embodiment that this first dose is administered for a period of six days, five days, four days, three days, two days or one day. In the case that the tumor load or general condition of the individual patient does require the administration of the limited dose of the bispecific construct in the first limited dose step, this first dose step is understood as a run-in phase/adaptation phase which should avoid or limit side effects resulting from the first contact of the patient with the bispecific construct. A preferred range for a dose in such run-in phase/adaptation phase may be in a range of 1 to 50 µg/d, preferably in a range of 3 to 30 µg/d, further preferably in a range of 4 to 20 µg/d and even more preferably in a range of 5 to 15 µg/d for a canonical BiTE® such as CD33XCD3 BISPECIFIC CONSTRUCT, which is a 54 kDa single chain polypeptide. In a very preferred embodiment, the bispecific construct according to the present invention is administered at a dose of 10 µg/d.

Preferred ranges for a second dose of the bispecific construct are e.g. for a canonical BiTE[®] such as CD33XCD3 BISPECIFIC CONSTRUCT in the range of 10 µg/d to 10 mg/d, more preferably in the range of 25 µg/d to 1 mg/d and even more preferably in the range of 30 µg/d to 500 µg/d. In a very preferred embodiment, the second dose is 30 µg/d or 60 µg/d. In line with the above, the preferred ranges for the third dose of the bispecific construct exceed the respective dose of the second dose. The third dose is typically in the range of 60 µg/d to 500 µg/d and preferably eradicates residual target cells which may have evaded treatment equivalent to the second dose according to the present invention.

It was surprisingly found that when a step dosing comprising at least two dosage steps is applied according to the present invention, then immunologic side effects such as undesired cytokine release, e.g. a cytokine release syndrome, may be effectively prevented. In contrast, if a dose equivalent to the second dosage is given without a prior lower dose equitant to the first dose of the present invention, then side effects, such as undesired cytokine release, e.g. a cytokine release syndrome, may occur. The same applies for the third dosage with respect to the second dosage.

It is also preferred for the present invention that the period of administration of the first and second dose is as short as possible to reach the target dose which addresses leukemic stem cells as soon as possible. This is decisive for therapeutic success with respect to an aggressive and progredient disease such as AML. Hence, it is a major achievement according to the present invention to provide a dosage scheme having a period of administration of the first dosage for only two or three days, preferably two days, and of two to four days for the second dosage. In turn the third dosage or the optional forth dosage, i.e. the target dosage, comprises a prolonged period of administration of preferably at least 21 days combined as described herein.

Also in line with the present invention it is preferred for the bispecific construct used in the treatment of myeloid leukemia that the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100 preferably 94 to 96 and 98 to 100 as described herein.

Moreover, in line with the present invention it is preferred for the bispecific construct used in the treatment of myeloid leukemia that the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 9 to 14, 27 to 32, 45 to 50, 63 to 68, 81 to 86, 99 to 104, 117 to 122, 135 to 140, 153 to 158 and 171 to 176 of WO 2008/119567.

As well as the second binding domain the first (or any further) binding domain(s) of the construct of the invention is/are preferably cross-species specific for members of the mammalian order of primates.

Cross-species specific CD3 binding domains are, for example, described in WO 2008/119567. According to one embodiment, the first and second binding domain, in addition to binding to human CD33 target cell antigen and human CD3, respectively, will also bind to the CD33 target cell antigen / CD3 of primates including (but not limited to) new world primates (such as *Callithrix jacchus*, *Saguinus* 5 *Oedipus* or *Saimiri sciureus*), old world primates (such baboons and macaques), gibbons, and non-human *homininae*. *Callithrix jacchus* and *Saguinus oedipus* are both new world primate belonging to the family of *Callitrichidae*, while *Saimiri sciureus* is a new world primate belonging to the family of *Cebidae*.

10 In a preferred embodiment of the invention the bispecific construct is a bispecific construct. In line with the definitions provided herein above, this embodiment relates to bispecific constructs, which are constructs. In a preferred embodiment of the invention the bispecific construct is a single chain construct. Such bispecific single chain construct may comprise in line with the invention an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 15 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108.

Amino acid sequence modifications of the bispecific constructs described herein are also contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the bispecific construct. Amino acid sequence variants of the bispecific constructs are prepared by 20 introducing appropriate nucleotide changes into the bispecific constructs nucleic acid, or by peptide synthesis. All of the below described amino acid sequence modifications should result in a bispecific construct which still retains the desired biological activity (binding to target cell antigen and to CD3) of the unmodified parental molecule.

25 The term "amino acid" or "amino acid residue" typically refers to an amino acid having its art recognized definition such as an amino acid selected from the group consisting of: alanine (Ala or A); arginine (Arg or R); asparagine (Asn or N); aspartic acid (Asp or D); cysteine (Cys or C); glutamine (Gln or Q); glutamic acid (Glu or E); glycine (Gly or G); histidine (His or H); isoleucine (Ile or I); leucine (Leu or L); lysine (Lys or K); methionine (Met or M); phenylalanine (Phe or F); pro line (Pro or P); serine (Ser 30 or S); threonine (Thr or T); tryptophan (Trp or W); tyrosine (Tyr or Y); and valine (Val or V), although modified, synthetic, or rare amino acids may be used as desired. Generally, amino acids can be grouped as having a nonpolar side chain (e.g., Ala, Cys, Ile, Leu, Met, Phe, Pro, Val); a negatively charged side chain (e.g., Asp, Glu); a positively charged sidechain (e.g., Arg, His, Lys); or an uncharged polar side chain (e.g., Asn, Cys, Gln, Gly, His, Met, Phe, Ser, Thr, Trp, and Tyr).

35 Amino acid modifications include, for example, deletions from, and/or insertions into, and/or substitutions of, residues within the amino acid sequences of the bispecific constructs. Any combination

of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the bispecific constructs, such as changing the number or position of glycosylation sites.

For example, 1, 2, 3, 4, 5, or 6 amino acids may be inserted or deleted in each of the CDRs (of course, dependent on their length), while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be inserted or deleted in each of the FRs. Preferably, amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues to polypeptides containing a hundred or more residues, as well as intra-sequence insertions of single or multiple amino acid residues. An insertional variant of the bispecific construct of the invention includes the fusion to the N-terminus or to the C-terminus of the bispecific construct to an enzyme or a fusion to a polypeptide which increases the serum half-life of the bispecific construct.

An increased half-life is generally useful in *in vivo* applications of immunoglobulins, especially antibodies and most especially antibody fragments of small size. Although such constructs based on antibody fragments (Fvs, disulphide bonded Fvs, Fabs, scFvs, dAbs) are able to rapidly reach most parts of the body, those constructs are likely to suffer from rapid clearance from the body. Strategies described in the art for extending the half-life of constructs such as single-chain diabodies include the conjugation of polyethylene glycol chains (PEGylation), the fusion to the IgG Fc region or to an albumin or albumin-binding domain.

Serum albumin is a protein physiologically produced by the liver; it occurs dissolved in blood plasma and is the most abundant blood protein in mammals. Albumin is essential for maintaining the oncotic pressure needed for proper distribution of body fluids between blood vessels and body tissues. It also acts as a plasma carrier by non-specifically binding several hydrophobic steroid hormones and as a transport protein for hemin and fatty acids. The term “serum albumin” respectively the human variant thereof (“human albumin”) defines in the context of the invented proteins either the parental human serum albumin protein (sequence as described in SEQ ID NO: 109) or any variant (e.g. such as albumin protein as depicted in SEQ ID NOS: 110-138) or fragment thereof preferably expressed as genetic fusion proteins and by chemical crosslinking etc. at least with one therapeutic protein. Variants comprising single or multiple mutations or fragments of albumin provide improved properties such as affinities to FcRn receptor and extended plasma half-life compared to its parent or reference. Variants of human albumin are described e.g. in WO 2014/072481. In line with the invention the serum albumin may be linked to the construct via a peptide linker. It is preferred that the peptide linker has the amino acid sequence (GGGGS)_n (SEQ ID NO: 13)_n wherein “n” is an integer in the range of 1 to 5. Further preferred is that “n” is an integer in the range of 1 to 3, and most preferably “n” is 1 or 2.

The sites of greatest interest for substitutional mutagenesis include the CDRs of the heavy and/or light chain, in particular the hypervariable regions, but FR alterations in the heavy and/or light chain are also

contemplated. The substitutions are preferably conservative substitutions as described herein. Preferably, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids may be substituted in a CDR, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be substituted in the framework regions (FRs), depending on the length of the CDR or FR. For example, if a CDR sequence encompasses 6 amino acids, it is envisaged that one, two or three of these amino acids are substituted. Similarly, if a CDR sequence encompasses 15 amino acids it is envisaged that one, two, three, four, five or six of these amino acids are substituted.

A useful method for identification of certain residues or regions of the bispecific constructs that are preferred locations for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells in *Science*, 244: 1081-1085 (1989). Here, a residue or group of target residues within the bispecific construct is/are identified (e.g. charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the epitope.

Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site or region for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* needs not to be predetermined. For example, to analyze or optimize the performance of a mutation at a given site, alanine scanning or random mutagenesis may be conducted at a target codon or region, and the expressed bispecific construct variants are screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in the DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis. Screening of the mutants is done using assays of target antigen binding activities.

Generally, if amino acids are substituted in one or more or all of the CDRs of the heavy and/or light chain, it is preferred that the then-obtained “substituted” sequence is at least 60%, more preferably 65%, even more preferably 70%, particularly preferably 75%, more particularly preferably 80% identical to the “original” CDR sequence. This means that it is dependent of the length of the CDR to which degree it is identical to the “substituted” sequence. For example, a CDR having 5 amino acids is preferably 80% identical to its substituted sequence in order to have at least one amino acid substituted. Accordingly, the CDRs of the bispecific construct may have different degrees of identity to their substituted sequences, e.g., CDRL1 may have 80%, while CDRL3 may have 90%.

Preferred substitutions (or replacements) are conservative substitutions. However, any substitution (including non-conservative substitution or one or more from the “exemplary substitutions” listed in Table 1, below) is envisaged as long as the bispecific construct retains its capability to bind to target cell

antigen via the first binding domain and to CD3 epsilon via the second binding domain and/or its CDRs have an identity to the then substituted sequence (at least 60%, more preferably 65%, even more preferably 70%, particularly preferably 75%, more particularly preferably 80% identical to the "original" CDR sequence).

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Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened for a desired characteristic.

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Table 1: Amino acid substitutions

Original	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val, leu, ile	val
Arg (R)	lys, gln, asn	lys
Asn (N)	gln, his, asp, lys, arg	gln
Asp (D)	glu, asn	glu
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	leu
Leu (L)	norleucine, ile, val, met, ala	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	leu

Substantial modifications in the biological properties of the bispecific construct of the present invention 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

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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: (1) hydrophobic: norleucine, met, ala, val, leu, ile; (2) neutral hydrophilic: cys, ser, thr, asn, gln; (3) acidic: asp, glu; (4) basic: his, lys, arg; (5) residues that influence chain orientation: gly, pro; and (6) aromatic : trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Any cysteine residue not involved in maintaining the proper conformation of the bispecific construct may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Nat. Acad. Sci. U.S.A.* 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux *et al.*, 1984, *Nucl. Acid Res.* 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc.

An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, 1987, *J. Mol. Evol.* 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, *CABIOS* 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

Another example of a useful algorithm is the BLAST algorithm, described in: Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-410; Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402; and Karin *et al.*, 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5787. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul *et al.*, 1996, *Methods in Enzymology* 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable

parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=II. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

An additional useful algorithm is gapped BLAST as reported by Altschul *et al.*, 1993, *Nucl. Acids Res.* 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; Xu set to 16, and Xg set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

Generally, the amino acid homology, similarity, or identity between individual variant CDRs are at least 60% to the sequences depicted herein, and more typically with preferably increasing homologies or identities of at least 65% or 70%, more preferably at least 75% or 80%, even more preferably at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and almost 100%. In a similar manner, "percent (%) nucleic acid sequence identity" with respect to the nucleic acid sequence of the binding proteins identified herein is defined as the percentage of nucleotide residues in a candidate sequence that are identical with the nucleotide residues in the coding sequence of the bispecific construct. A specific method utilizes the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

Generally, the nucleic acid sequence homology, similarity, or identity between the nucleotide sequences encoding individual variant CDRs and the nucleotide sequences depicted herein are at least 60%, and more typically with preferably increasing homologies or identities of at least 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, and almost 100%. Thus, a "variant CDR" is one with the specified homology, similarity, or identity to the parent CDR of the invention, and shares biological function, including, but not limited to, at least 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the specificity and/or activity of the parent CDR.

In one embodiment the bispecific construct for the use in accordance with this invention is administered in combination with one or more epigenetic factors selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid) and wherein:

- (a) the one or more epigenetic factors are administered prior to the administration of the bispecific construct;
- (b) the one or more epigenetic factors are administered subsequent to the administration of the bispecific construct; or
- 5 (c) the one or more epigenetic factors and the bispecific construct are administered simultaneously.

The term "epigenetic factor" in connection with the present invention defines a compound which is capable of changing the gene expression or cellular phenotype of a cell population upon administration. It is understood that such change refers to one or more functional relevant modifications to the genome without involving a change in the nucleic acid sequence. Examples of such modifications are DNA

10 methylation and histone modification, which are both important for the regulation of gene expression without altering the underlying DNA sequence.

Details for a treatment of myeloid leukemia comprising the administration of the bispecific construct in combination with one or more of the above described epigenetic factors have been provided in PCT/EP2014/069575.

15 In one embodiment of the invention it is preferred that the one or more epigenetic factors are administered up to seven days prior to the administration of the bispecific construct.

Also in one embodiment of the invention it is preferred that the epigenetic factor is hydroxyurea.

20 It is preferred for the present invention that the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, acute megakaryoblastic leukemia, essential

25 thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyeloic leukemia, myeloid sarcoma, and acute biphenotypic leukaemia. More preferably, the myeloid leukemia is an acute myeloid leukemia (AML). The definition of AML inter alia comprises acute myeloblastic leukemia, acute myeloid dendritic cell leukemia, acute myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, acute megakaryoblastic leukemia, acute

30 erythroid leukemia, and acute panmyeloic leukemia

The bispecific construct described in connection with this invention may be formulated for an appropriate administration to a subject in the need thereof in form of a pharmaceutical composition.

Formulations described herein are useful as pharmaceutical compositions in the treatment, amelioration

35 and/or prevention of the pathological medical condition as described herein in a patient in need thereof.

The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Treatment includes the application or administration of the formulation to the body, an isolated tissue,

or cell from a patient who has a disease/disorder, a symptom of a disease/disorder, or a predisposition toward a disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptom of the disease, or the predisposition toward the disease.

5 The term “disease” refers to any condition that would benefit from treatment with the bispecific construct or the pharmaceutical composition described herein. This includes chronic and acute disorders or diseases including those pathological conditions that predispose the mammal to the disease in question.

10 The terms “subject in need” or those “in need of treatment” includes those already with the disorder, as well as those in which the disorder is to be prevented. The subject in need or “patient” includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

The bispecific construct of the invention will generally be designed for specific routes and methods of
15 administration, for specific dosages and frequencies of administration, for specific treatments of specific diseases, with ranges of bio-availability and persistence, among other things. The materials of the composition are preferably formulated in concentrations that are acceptable for the site of administration.

20 Formulations and compositions thus may be designed in accordance with the invention for delivery by any suitable route of administration. In the context of the present invention, the routes of administration include, but are not limited to

- topical routes (such as epicutaneous, inhalational, nasal, ophthalmic, auricular / aural, vaginal, mucosal);
- 25 • enteral routes (such as oral, gastrointestinal, sublingual, sublabial, buccal, rectal); and
- parenteral routes (such as intravenous, intraarterial, intraosseous, intramuscular, intracerebral, intracerebroventricular, epidural, intrathecal, subcutaneous, intraperitoneal, extra-amniotic, intraarticular, intracardiac, intradermal, intralesional, intrauterine, intravesical, intravitreal, transdermal, intranasal, transmucosal, intrasynovial, intraluminal).

30 The pharmaceutical compositions and the bispecific construct described in connection with the invention are particularly useful for parenteral administration, e.g., subcutaneous or intravenous delivery, for example by injection such as bolus injection, or by infusion such as continuous infusion. Pharmaceutical compositions may be administered using a medical device. Examples of medical devices
35 for administering pharmaceutical compositions are described in U.S. Patent Nos. 4,475,196; 4,439,196; 4,447,224; 4,447, 233; 4,486,194; 4,487,603; 4,596,556; 4,790,824; 4,941,880; 5,064,413; 5,312,335; 5,312,335; 5,383,851; and 5,399,163.

In particular, the present invention provides for an uninterrupted administration of the suitable composition. As a non-limiting example, uninterrupted or substantially uninterrupted, i.e. continuous administration may be realized by a small pump system worn by the patient for metering the influx of therapeutic agent into the body of the patient. The pharmaceutical composition comprising the bispecific construct described in connection with the invention can be administered by using said pump systems. Such pump systems are generally known in the art, and commonly rely on periodic exchange of cartridges containing the therapeutic agent to be infused. When exchanging the cartridge in such a pump system, a temporary interruption of the otherwise uninterrupted flow of therapeutic agent into the body of the patient may ensue. In such a case, the phase of administration prior to cartridge replacement and the phase of administration following cartridge replacement would still be considered within the meaning of the pharmaceutical means and methods of the invention together make up one “uninterrupted administration” of such therapeutic agent.

The continuous or uninterrupted administration of the bispecific construct described in connection with the invention may be intravenous or subcutaneous by way of a fluid delivery device or small pump system including a fluid driving mechanism for driving fluid out of a reservoir and an actuating mechanism for actuating the driving mechanism. Pump systems for subcutaneous administration may include a needle or a cannula for penetrating the skin of a patient and delivering the suitable composition into the patient’s body. Said pump systems may be directly fixed or attached to the skin of the patient independently of a vein, artery or blood vessel, thereby allowing a direct contact between the pump system and the skin of the patient. The pump system can be attached to the skin of the patient for 24 hours up to several days. The pump system may be of small size with a reservoir for small volumes. As a non-limiting example, the volume of the reservoir for the suitable pharmaceutical composition to be administered can be between 0.1 and 50 ml.

The continuous administration may also be transdermal by way of a patch worn on the skin and replaced at intervals. One of skill in the art is aware of patch systems for drug delivery suitable for this purpose. It is of note that transdermal administration is especially amenable to uninterrupted administration, as exchange of a first exhausted patch can advantageously be accomplished simultaneously with the placement of a new, second patch, for example on the surface of the skin immediately adjacent to the first exhausted patch and immediately prior to removal of the first exhausted patch. Issues of flow interruption or power cell failure do not arise.

If the pharmaceutical composition has been lyophilized, the lyophilized material is first reconstituted in an appropriate liquid prior to administration. The lyophilized material may be reconstituted in, e.g.,

bacteriostatic water for injection (BWFI), physiological saline, phosphate buffered saline (PBS), or the same formulation the protein had been in prior to lyophilization.

The compositions of the present invention can be administered to the subject at a suitable dose which can be determined e.g. by dose escalating studies by administration of increasing doses of the bispecific construct described in connection with the invention exhibiting cross-species specificity described herein to non-chimpanzee primates, for instance macaques. As set forth above, the bispecific construct described in connection with the invention exhibiting cross-species specificity described herein can be advantageously used in identical form in preclinical testing in non-chimpanzee primates and as drug in humans.

The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts or doses effective for this use will depend on the condition to be treated (the indication), the delivered bispecific construct, the therapeutic context and objectives, the severity of the disease, prior therapy, the patient's clinical history and response to the therapeutic agent, the route of administration, the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient, and the general state of the patient's own immune system.

A therapeutic effective amount of a bispecific construct described in connection with the invention preferably results in a decrease in severity of disease symptoms, an increase in frequency or duration of disease symptom-free periods or a prevention of impairment or disability due to the disease affliction. For treating target cell antigen-expressing tumors, a therapeutically effective amount of the bispecific construct described in connection with the invention, e.g. an anti-target cell antigen/anti-CD3 construct, preferably inhibits cell growth or tumor growth by at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% relative to untreated patients. The ability of a compound to inhibit tumor growth may be evaluated in an animal model predictive of efficacy in human tumors.

The pharmaceutical composition can be administered as a sole therapeutic or in combination with additional therapies such as anti-cancer therapies as needed, e.g. other proteinaceous and non-proteinaceous drugs. These drugs may be administered simultaneously with the composition comprising the bispecific construct described in connection with the invention as defined herein or separately before or after administration of said bispecific construct in timely defined intervals and doses.

Further, the present inventors observed that rare side effects, such as immunologic side effects could be prevented or alleviated by means of a glucocorticoid (pre) and/or (co)therapy.

Accordingly, the present invention establishes that glucocorticoids such as dexamethasone mitigate or even prevent adverse effects which might occur in the course of a treatment with CD33/CD3 specific bispecific constructs according to the present invention.

Glucocorticoids (GCs) are still the most widely used immunosuppressive agents for the treatment of inflammatory disorders and autoimmune diseases. Glucocorticoids (GC) are a class of steroid hormones that bind to the glucocorticoid receptor (GR), which is present in almost every vertebrate animal cell, including humans. These compounds are potent anti-inflammatory agents, regardless of the inflammation's cause. Glucocorticoids suppress, inter alia, the cell-mediated immunity by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN- γ .

Cortisone which belongs to the group of GCs is an important therapeutic drug which is used to fight many ailments ranging from Addison's disease to rheumatoid arthritis. Ever since the discovery of its anti-rheumatic properties, which led to its acclaim as a wonder drug, many derivatives of cortisone with enhanced properties to better fight a specific ailment have been produced. Cortisone belongs to a group of steroids known as corticosteroids. These steroids are produced by the adrenal cortex, which is the outer part of the adrenal glands, near the kidneys. The corticosteroids are divided into two main groups: the glucocorticoids (GCs), which control fat, protein, calcium and carbohydrate metabolism, and the mineralocorticoids controlling sodium and potassium levels. Cortisone belongs to the former group, i.e. to the GCs. Cortisone and its many derivatives are used for a variety of diseases. Cortisone also helped to make organ transplants a reality due to its ability to minimize the defense reaction of the body towards foreign proteins present in the implanted organ and thus damage the functionality of the implanted organ. However, despite clinical use during more than 50 years, the specific anti-inflammatory effects of GC on different cellular compartments of the immune system are not yet clear. GCs affect nearly every cell of the immune system, and there is growing evidence for cell type-specific mechanisms.

In one specific embodiment, the present invention relates to a glucocorticoid (GC) for use in the amelioration, treatment or prophylaxis of adverse effects caused by a CD33/CD3 bispecific construct. As outlined above, these unwanted adverse effects may be prevented by a step dosing as described herein. However, for mere precaution, glucocorticoid(s) for use in the amelioration, treatment or prophylaxis of (immunological) adverse effects in a patient may be provided wherein said patient is subject to therapy with a CD33/CD3 bispecific construct. Accordingly, in one further aspect the present invention relates to a glucocorticoid (GC) for use in a method in the amelioration, treatment or

prophylaxis of immunological adverse effects caused by a CD33/CD3 bispecific construct according to the present invention.

Also, the present invention relates to a method of amelioration, treatment or prophylaxis of immunological adverse effects caused by a CD33/CD3 bispecific construct, said method comprising administering to a patient in need thereof IL-6R blocking antibody tocilizumab or a glucocorticoid (GC). The GC is preferably administered in an amount which is sufficient to ameliorate, treat or prevent said immunological adverse effects caused by a CD33/CD3 bispecific construct.

The term “glucocorticoid” means compounds that bind, preferably specifically, to the glucocorticoid receptor. Said term includes compound(s) selected from the group consisting of cortisone, cortisol (hydrocortisone), clobprednol, prednisone, prednisolone, methylprednisolone, deflazacort, fluocortolone, triamcinolone, dexamethasone, betamethasone, cortivazol, paramethasone, and/or fluticasone, including pharmaceutically acceptable derivatives thereof. In the context of the embodiments of the present invention, the mentioned compounds may be used alone or in combination. Dexamethasone is preferred. The present invention is however not limited to the above mentioned specific GCs. It is envisaged that all substances which already are or will be classified as a “glucocorticoid”, may be employed in the context of the present invention as well. Such future glucocorticoids include compounds which specifically bind to and activate the glucocorticoid receptor.

The term “specifically binds to the GC receptor” means in accordance with the present invention that the GC (or a compound which is assumed to act like a GC) associates with (e.g., interacts with) the GC receptor (also known as NR3C1) to a statistically significant degree as compared to association with proteins/receptors generally (i.e., non-specific binding). When the GC receptor binds to glucocorticoids, its primary mechanism of action is the regulation of gene transcription. In the absence of GC, the glucocorticoid receptor (GR) resides in the cytosol complexed with a variety of proteins including heat shock protein 90 (hsp90), the heat shock protein 70 (hsp70) and the protein FKBP52 (FK506-binding protein 52). The binding of the GC to the glucocorticoid receptor (GR) results in release of the heat shock proteins. It is thus envisaged that a future GC, or a pharmaceutically acceptable derivative or salt of a GC is preferably able to bind to the GC receptor and to release the above mentioned heat shock proteins. The activated GR complex up-regulates the expression of anti-inflammatory proteins in the nucleus or represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus).

In a preferred embodiment, said GC is selected from the most clinical used and relevant GCs like dexamethasone, fluticasonepropionate, prednisolone, methylprednisolone, betamethasone, triamcinolonacetone or combinations thereof.

In an even more preferred embodiment, said GC is dexamethasone.

Dexamethasone has the highest glucocorticoid potency of the most commonly used steroids and also has the longest half-life (see Table 2 below). But a person skilled in the field can select one of the other known glucocorticoids, some of which are disclosed herein, and select an appropriate effective dose to ameliorate or prevent immunological adverse events that may result from the treatment of a patient in need thereof.

Table 2: steroid dosing

Agent	Approx. equiv. dose (mg)	Relative anti-inflammatory (glucocorticoid) potency	Relative mineralocorticoid (Na⁺ retaining) potency	Biologic half-life (hrs)
Cortisone	25	0.8	0.8	8-12
Hydrocortisone	20	1	1	8-12
Prednisone	5	4	0.8	18-36
Prednisolone	5	4	0.8	18-36
Methylprednisolone	5	5	0.5	18-36
Dexamethasone	0.75	25	0	36-54

Dexamethasone also possesses a beneficial effect in malignant central nervous system (CNS) disease (e.g. CNS lymphoma or brain metastases) – possibly due to specific penetration to the CNS. It is also preferentially (over other steroids) used to treat brain edema. Although corticosteroids decrease capillary permeability in the tumor itself, it has been found in animal models that dexamethasone may act differently and decrease edema by effects on bulk flow away from the tumor (Molnar, Lapin, & Goothuis, 1995, Neurooncol. 1995;25(1):19-28).

For the clinical trials in connection with the application of a CD33/CD3 bispecific construct, the present inventors had to develop a treatment regime which was efficient and would be well tolerated by most of the patients. To this end, the present inventors applied a step-wise application of a CD33/CD3 bispecific construct as outlined herein. Thereby, adverse effects could be reduced in number, ameliorated and even prevented.

The dose of the GC that is to be used in accordance with the embodiments of the present invention is not limited, i.e. it will depend on the circumstances of the individual patient. GC can be administered intravenously or orally. Preferred dosages of the GC include, however, between 1 to 6 mg (dexamethasone equivalent) at the lower end of dosing to 40 mg (dexamethasone equivalent). Said

dosage can be administered all at once or subdivided into smaller dosages. Preferred is a subdivide dose wherein one dose of GC is given prior to the infusion of the first and/or second dose according to the step dosing as described herein, and the other dose of GC is given prior to the administration of the second or third dose according to the step dosing as described herein. Hence, GC is preferably two times dosed per treatment cycle. Even more preferably, GC is administered one 24 or 8 h or 4 h or 1 h before the beginning of a treatment cycle or the beginning of the administration of the next higher dose within said treatment cycle. In this regard, 1 h is most preferred. The dose is 1 to 40 mg each, preferably 5 to 20 mg, most preferably 8 mg each. "d" denotes one day. Further dosage regimens are derivable from the appended examples. All dosages given in this paragraph refer to dexamethasone equivalents.

The term "effective and non-toxic dose" as used herein refers to a tolerable dose of a bispecific construct which is high enough to cause depletion of pathologic cells, tumor elimination, tumor shrinkage or stabilization of disease without or essentially without major toxic effects. Such effective and non-toxic doses may be determined e.g. by dose escalation studies described in the art and should be below the dose inducing severe adverse side events (dose limiting toxicity, DLT).

Alternatively, tocilizumab may be used in premedication.

The term "toxicity" as used herein refers to the toxic effects of a drug manifested in adverse events or severe adverse events. These side events might refer to a lack of tolerability of the drug in general and/or a lack of local tolerance after administration. Toxicity could also include teratogenic or carcinogenic effects caused by the drug.

The term "safety", "*in vivo* safety" or "tolerability" as used herein defines the administration of a drug without inducing severe adverse events directly after administration (local tolerance) and during a longer period of application of the drug. "Safety", "*in vivo* safety" or "tolerability" can be evaluated e.g. at regular intervals during the treatment and follow-up period. Measurements include clinical evaluation, e.g. organ manifestations, and screening of laboratory abnormalities. Clinical evaluation may be carried out and deviations to normal findings recorded/coded according to NCI-CTC and/or MedDRA standards. Organ manifestations may include criteria such as allergy/immunology, blood/bone marrow, cardiac arrhythmia, coagulation and the like, as set forth e.g. in the Common Terminology Criteria for adverse events v4 (CTCAE). Laboratory parameters which may be tested include for instance hematology, clinical chemistry, coagulation profile and urine analysis and examination of other body fluids such as serum, plasma, lymphoid or spinal fluid, liquor and the like. Safety can thus be assessed e.g. by physical examination, imaging techniques (i.e. ultrasound, x-ray, CT scans, Magnetic Resonance Imaging (MRI), other measures with technical devices (i.e. electrocardiogram), vital signs, by measuring laboratory parameters and recording adverse events. For example, adverse events in non-chimpanzee

primates in the uses and methods according to the invention may be examined by histopathological and/or histochemical methods.

The above terms are also referred to *e.g.* in the Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6; ICH Harmonised Tripartite Guideline; ICH Steering Committee meeting on July 16, 1997.

In a preferred embodiment of the method of the invention only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dose according to step (b), (c) or (d).

It is preferred for the method of the invention that the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100.

Also in line with a preferred embodiment of the method of the invention the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 9 to 14, 27 to 32, 45 to 50, 63 to 68, 81 to 86, 99 to 104, 117 to 122, 135 to 140, 153 to 158 and 171 to 176 of WO 2008/119567.

In a preferred embodiment of the method of the invention the bispecific construct is a bispecific construct.

Moreover, it is preferred for the method of the invention that the bispecific construct is a single chain construct comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108.

In one embodiment of the method of the invention the bispecific construct is administered in combination with one or more epigenetic factors selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid) and wherein:

- (a) the one or more epigenetic factors are administered prior to the administration of the bispecific construct;
- (b) the one or more epigenetic factors are administered subsequent to the administration of the bispecific construct; or
- (c) the one or more epigenetic factors and the bispecific construct are administered simultaneously.

It is preferred for the method of the invention that the one or more epigenetic factors are administered up to seven days prior to the administration of the bispecific construct.

For one embodiment of the method of the invention it is preferred that the epigenetic factor is hydroxyurea

As described herein above, in line with the present invention the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyeloic leukemia, myeloid sarcoma, and acute biphenotypic leukaemia. It is preferred that the myeloid leukemia is an acute myeloid leukemia (AML).

Also in one embodiment the invention provides a use of a bispecific antibody construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 preferably for the preparation of a pharmaceutical composition for the treatment of myeloid leukemia, wherein the bispecific construct is to be administered for more than 14 days followed by a period of at least 14 days without administration of the construct.

It is preferred of the use of the invention that the bispecific construct is to be administered according to a schedule comprising the following steps:

- (a) administration of a first dose of the bispecific construct, followed by
- (b) administration of a second dose of the bispecific construct, wherein said second dose exceeds said first dose, followed by
- (c) administration of a third dose of the bispecific construct, wherein said optional third dose exceeds said second dose, optionally followed by
- (d) administration of a forth dose of the bispecific construct, wherein said optional third dose exceeds said third dose.

In a preferred embodiment of the use of the invention only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dose according to step (b), (c) or (d).

It is preferred for the use of the invention that the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100.

Also in line with a preferred embodiment of the use of the invention the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 9 to 14, 27 to 32, 45 to 50, 63 to 68, 81 to 86, 99 to 104, 117 to 122, 135 to 140, 153 to 158 and 171 to 176 of WO 2008/119567.

In a preferred embodiment of the use of the invention the bispecific construct is a bispecific construct. Moreover, it is preferred for the use of the invention that the bispecific construct is a single chain construct comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108.

In one embodiment of the use of the invention the bispecific construct is administered in combination with one or more epigenetic factors selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid) and wherein:

- (a) the one or more epigenetic factors are administered prior to the administration of the bispecific construct;
- (b) the one or more epigenetic factors are administered subsequent to the administration of the bispecific construct; or
- (c) the one or more epigenetic factors and the bispecific construct are administered simultaneously.

It is preferred for the use of the invention that the one or more epigenetic factors are administered up to seven days prior to the administration of the bispecific construct.

For one embodiment of the use of the invention it is preferred that the epigenetic factor is hydroxyurea. As described herein above, in line with the present invention the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyeloid leukemia, myeloid sarcoma, and acute biphenotypic leukaemia. It is preferred that the myeloid leukemia is an acute myeloid leukemia (AML).

The patient population considered susceptible for the present inventive method is AML as defined by the WHO Classification persisting or recurring following one or more treatment courses except promyelocytic leukemia (APML). The patient population may comprise AML secondary to prior myelodysplastic syndrome. Preferably, the patient population comprises AML as defined by the WHO Classification either persisting/refractory after at least 1 primary induction courses (i.e., no response after at least 1 prior chemotherapy cycles) or recurring after having achieved an initial response to chemotherapy except promyelocytic leukemia (APML) and except AML secondary to prior myelodysplastic syndrome. Further, the preferred patient population is characterized by having more than 1% blasts in bone marrow, preferably more than 5% blasts. Typically, patient population ECOG performance status is less than 2.

General Definitions

It is noted that as used herein, the singular forms “a”, “an”, and “the”, include plural references unless the context clearly indicates otherwise. Thus, for example, reference to “a reagent” includes one or more of such different reagents and reference to “the method” includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

The term "and/or" wherever used herein includes the meaning of "and", "or" and "all or any other combination of the elements connected by said term".

The term "about" or "approximately" as used herein means within $\pm 20\%$, preferably within $\pm 15\%$, more preferably within $\pm 10\%$, and most preferably within $\pm 5\%$ of a given value or range.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. When used herein the term “comprising” can be substituted with the term “containing” or “including” or sometimes when used herein with the term “having”.

When used herein “consisting of” excludes any element, step, or ingredient not specified in the claim element. When used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim.

In each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms.

It should be understood that the inventions herein are not limited to particular methodology, protocols, or reagents, as such can vary. The discussion and examples provided herein are presented for the purpose of describing particular embodiments only and are not intended to limit the scope of the present invention, which is defined solely by the claims.

All publications and patents cited throughout the text of this specification (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material.

Examples:

The following examples are provided for the purpose of illustrating specific embodiments or features of the present invention. These examples should not be construed as to limit the scope of this invention. The examples are included for purposes of illustration, and the present invention is limited only by the claims.

Example 1:

The objective of this study was to establish safety and tolerability of an exemplary CD33xCD3 bispecific construct (SEQ ID NO: 104) and identify phase 2 recommended dose

Study design and patients

The present study is a first-in-human, open label, nonrandomized, multicentre, phase 1, sequential dose-escalation study (NCT02520427). Each cycle (2–4 weeks) was followed by an infusion-free interval. Key inclusion criteria were male or female (≥ 18 years old) patients with confirmed relapsed/refractory (R/R) AML diagnosis, $> 5\%$ myeloblasts in bone marrow (BM), Eastern Cooperative Oncology Group performance status score ≤ 2 , and patients with ≥ 1 prior therapies including hematopoietic stem cell transplantation (HSCT) Assessments and Dose-steps

The molecule was evaluated as a cIV infusion using a 3+3 design. Response was assessed per revised International Working Group criteria. Dose steps were tested at 10 μg (1st step; cohorts 6–10), 60 μg and 240 μg (2nd step; cohorts 11–15), and 600 μg (3rd step; cohorts 16–18) (Fig. 1). Dose steps were intermediate doses of the molecule administered with 1–5 day/s interval prior to the target dose.

Statistics: Descriptive statistics was used for demographics, safety, pharmacokinetic, and pharmacodynamic data

Results

Table 3. Demographics and baseline disease characteristics summarized

Characteristics	Patients: N = 60	Characteristics	Patients: N = 60
Median age (years)	58 (18–80)	ECOG PS, n (%)	
Sex, n (%)		0	15 (25)
Male	33 (55)	1	39 (65)
ELN risk classification, n (%)		2	5 (8)
Favourable	4 (7)	Baseline leukemia burden, n (%)	
Intermediate	9 (15)	< 25%	19 (32)
Adverse	37 (62)	25%–50%	17 (28)
Prior lines of therapies, n (%)		> 50%	24 (40)
1	9 (15)	Baseline myelosuppression (≥ Gr 3), n (%)	
2	11 (18)	Thrombocytopenia	45 (75)
3	11 (18)	Leukopenia	35 (58)
≥ 4	29 (48)	Neutropenia	52 (87)
AML type, n (%)		Response to prior therapies, n (%)	44 (73)
AML, NOS	37 (61)	Prior HSCT, n (%)	27 (45)
AML with recurrent genetic abnormalities	16 (27)		
AML with myelodysplasia-related changes	7 (12)		

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; Gr, grade; HSCT, haematopoietic stem cell transplantation; N, total number of patients in the analysis set; n, total number of patients with observed data; NOS, not otherwise specified

Table 4. Key Drug-Related Adverse Events in ≥ 20% Patients

Drug-Related* AEs, N=60	All grades, n (%)	≥ Gr 3, n (%)
Patients with drug-related AEs	54 (90)	33 (55)
Immune disorders		
Cytokine Release Syndrome	40 (67)	9 (15)
Skin disorders	35 (58)	6 (10)
(including rashes, pruritus, urticaria)		
Gastrointestinal disorders	18 (30)	
Nausea	13 (22)	0 (0)
Vomiting	7 (12)	0 (0)
Diarrhea	4 (7)	0 (0)
Elevated liver function tests		
(including ALT, AST, ALP, GGT, bilirubin)	15 (25)	3 (5)
Blood and lymphatic disorders	14 (23)	
Febrile neutropenia	11 (18)**	10 (17)

*As per investigators' assessment; **Database cleaning in progress for 1 AE in grade 2; AE, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; Gr, grade; N, total number of patients in the analysis set; n, total number of patients with observed data

Cytokine Release Syndrome (CRS) was the most frequent (67%) CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) -related adverse event (AE). Other frequent AEs reported in ≥ 40% patients included rashes (58%).

Higher grades of CRS were observed in patients with higher leukemic burden and with higher Effector:Target (E:T) ratio (Fig 3A and 3B). Frequency and severity of CRS was associated with higher levels of cytokines released in response to CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) treatment (Fig 3C).

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Eight patients responded to SEQ ID NO 104 treatment: complete remission (CR; n = 3, cohorts 11, 15, and 16), complete remission with incomplete hematologic recovery (CRi; n = 4, cohorts 8, 9, 12, and 15) and morphologic leukemia-free state (n=1, cohort 2) with 3 responders out of 14 treated patients (21%) in cohorts 15–17 (Fig 2). For patients achieving CR/CRi (n = 7), minimal efficacious dose was established at the 120 µg/day dose level.

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Table 5. Characteristics of the responders

Characteristics	Non-responders ^a at TD $\geq$ 120 µg, N=35; n (%)	Responders ^b at TD $\geq$ 120 µg, N=7; n (%)
ELN risk classification		
Favourable	2 (6)	0
Intermediate	3 (9)	2 (29)
Adverse	22 (63)	4 (57)
Unknown	8 (23)	1 (14)
Lines of prior therapies		
1	5 (14)	1 (14)
2	5 (14)	2 (29)
3	6 (17)	1 (14)
$\geq$ 4	19 (54)	3 (43)
Prior HSCT	14 (40)	4 (57)

^aNon-Responders (CR or CRi) at target dose $\geq$ 120 µg were patients with a best overall response other than CR or CRi on study and in cohort 8 or later cohorts with planned target dose $\geq$ 120 µg; ^bResponders (CR/CRi) at target dose $\geq$ 120 µg were patients with a best overall response of CR/CRi on study and in cohort 8 or later cohorts with planned target dose $\geq$ 120 µg. Css, concentration at steady state; BM, bone marrow; ELN, European LeukemiaNet; HSCT, hematopoietic stem cell transplantation; N, total number of patients in the analysis set; n, total number of patients with observed data; TD, target dose; WBC, white blood cells

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Responders typically showed higher SEQ ID NO 104 Css than non-responders (Fig 4A). Among patients with CR/CRi response (17%), 57% had adverse cytogenetic profile. Lower leukemic burden in bone marrow and peripheral blood was associated with higher likelihood of response to CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) (Fig 4B & 6C). 20% (4/20) of patients with < 4 lines of prior therapies and 14% (3/22) of patients with $\geq$ 4 lines of prior therapies responded to CD33xCD3

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bispecific construct (as exemplified by SEQ ID NO 104) treatment (Table 3). Among responders, 43% received ≥ 4 lines of prior therapies (Table 3)

Conclusion CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) was safe and tolerable in R/R AML patients in the present study with CRS as the most frequent expected mechanism of action-based toxicity, and without unexpected toxicities to date

Optimized schedule of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) administration using dose steps allowed higher Target Dose levels with improved drug exposure. Frequency and severity of CRS was associated with higher levels of cytokines released in response to CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) treatment, and higher CRS grades were observed in patients with higher baseline leukemic burden. A total of seven patients achieved CR/CRi at a minimal efficacious dose of at least 120 $\mu\text{g/day}$ with a 21% response rate for patients in three cohorts 15–17.

Example 2:

The objectives of this study was to characterize the clinical pharmacokinetics, exposure-efficacy and exposure-safety relationships of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) in R/R AML patients using the data from phase I dose-escalation study (NCT02520427) and to evaluate the effect of baseline patient characteristics on efficacy and safety of SEQ ID NO 104.

Methods

A continuous IV infusion of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) was evaluated in a 14–28 days cycle at escalating target doses (range from 0.5 to 720 $\mu\text{g/day}$) using a 3+3 design with patients receiving step dose/s (Figure 2) Pharmacokinetics

Serum concentrations of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) were tested using a validated, GLP compliant, electro-chemiluminescence assay. Non-compartmental and population-based approach using nonlinear mixed effects modeling was used to characterize PK

A one compartment model with interindividual variability (IIV) on clearance and volume of distribution was used to describe the data

Exposure-Response/Safety analyses

Relationships between CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures, baseline patient characteristics with efficacy (IWG responses)/incidence of cytokine release syndrome (CRS) events were explored. Worst grade CRS for each patient was modelled with CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures using a proportional odds logistic regression model. The effect of baseline patient characteristics was tested as a covariate in the logistic regression model.

Data from 55 patients (sex: 33M/22F; median age of 58 [18–80] years) were included in the analyses. 8 responses were reported: CR (n=3, cohorts 11, 15, and 16), CRi (n=4, cohorts 8, 9, 12, and

15) and MLFS (n=1, cohort 2). CRS, an expected on-target toxicity, was the most frequent (67% all grades; 15% Gr $\geq$ 3) CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) -related adverse event.

A one compartment model with linear clearance and IIV on CL and V was used to describe the CD33xCD3 bispecific construct PK (as exemplified by SEQ ID NO 104).

Table 6: PK parameters and variability estimates

Parameter	Estimate (%RSE)	IIV CV % (%RSE)
Clearance (L/day)	180 (24.1)	55.5 (87)
Volume of distribution (L)	28.7 (70)	111.8 (101)
σ_1 (Proportional)	0.38 (25)	
σ_2 (Additive)	0.19 (22.7)	

In Figure 6, Goodness of fit plots are shown (Observed vs Individual predicted concentrations, and Conditional weighted residuals vs Individual predicted concentrations) which were generated to check the model fit Results

Dose dependent increases were observed in CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures.

A trend towards better clinical responses was observed in patients with lower baseline leukemic burden in bone marrow, higher CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures and higher baseline Effector (CD3) : Target (Blasts) cell ratio (see Fig. 7)

Higher grade CRS events were observed in patients at higher baseline leukemic burden and CD33 expression on blast cells (see Fig. 8)

A positive relationship was observed for CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures with probability of CRS occurrence and severity (see Fig. 9).

Conclusions

Dose-related increases in CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures, lack of any major impact of shed target on free CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) exposures & modest trends of exposure-efficacy and exposure-safety relationships were observed

Results from these analyses are being used to identify optimal CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) dosing regimens that minimize the risk for CRS in ongoing and planned clinical investigations.

Example 3:

The objectives of this study was to characterize the clinical efficacy of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) in MRD+ AML patients using the data from phase I dose-escalation study (NCT02520427). Patients were screened for blast percentage at baseline and after the respective treatment cycle and peripheral blood cell counts at baseline and after the respective treatment cycle. Based on blast count, MRD status (“+” or “-”) was determined according to European LeukemiaNet (ELN) recommendations with 0.1% blast threshold (Schoorhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018;131:1275-1291). Subjects were pre-treated with 8 mg IV dexamethasone within 1 hour prior to the initial dose step of the CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104). Then, subjects were treated with a starting dose of 30 µg/d for 2 days, then with a dose of 240 µg/d for 5 days and then with a target dose of 600, 720, 840, 960, and 1600 µg/d for 21 days.

Three subjects completed cycle 1 with a total duration of 28 days being treated at dose of 30 µg/d for 2 days, 240 µg/d for 5 days and 600 µg/d for 21 days. One subject #66003-044 enrolled with MRD+ CRi with 4.2% blasts at baseline; after completion of cycle 1, the number of blasts by morphology was 0%, MRD assessment showed abnormal blasts <0.01% meeting MRD-negative status, peripheral blood counts recovered meeting CR criteria; in summary – patient started with MRD+ CRi and converted to MRD- CR. Another subject #66001-027 enrolled with 4% at baseline and after cycle 1 had 1% blasts; while MRD remained positive, this patient experienced 75% decrease in blast counts and proceeded to transplant. Only one patient #66001-029 in this cohort experienced disease progression.

Hence, applying a two-step dosage regimen comprising three different dosages of at least 30 µg/d as initial dose followed by a dose of at least 240 µg/d followed of a target dose of at least 600 µg/d may effectively convert an AML patient of MRD+ status to MRD- status and, thus, reduce the patients risk of a future disease progression.

Example 4:

The objectives of this study was to characterize the clinical safety of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) in MRD+ AML patients using the data from phase I dose-escalation study (NCT02520427). Patients were screened for at each dosage level of the respective treatment cycle for occurrence of CRS and in case of occurrence the event was graded according to generally accepted standards at the time when the clinical study has started (Lee et al., Blood 2014 Jul 10;124(2):188-95. doi: 10.1182/blood-2014-05-552729.). Subjects were pre-treated with 8 mg IV dexamethasone within 1 hour prior to the initial dose step of the CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104). Then, subjects were treated with a starting dose of 30 µg/d for 2 days, then with a dose of 240 µg/d for 5 days and then with a target dose of 600, 720, 840, 960, and 1600 µg/d for 21 days.

Table 7: Safety in terms of CRS occurrence and grade in subjects treated for MRD AML

Subject	30 mg/day	140 mg/day	600 mg/day
66003-044	G1 ~ 7 hrs	G1 ~ 31 hrs	G2 ~ 13 hrs
66001-027	-	G1 16 hrs	-
66001-029	G1 24 hrs	-	-

As safety result for the present study, Subject 66003-044 completed one CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) cycle with no interruptions and no ICU transfers. The subject experienced the following key AEs: Grade 2 rash at 240 ug/day dose; Grade 1 CRS at 30 ug/day dose and 240 ug/day dose, Grade 2 CRS at 600 ug/day dose

Subject 66001-027 completed one CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) cycle with no interruptions and no ICU transfers. The subject experienced the following key AEs: Grade 1 CRS and Grade 2 rash at 240 ug/day dose

Subject 66001-029 completed one CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) cycle with no interruptions and no ICU transfers. The subject experienced the following key AEs: Grade 1 CRS at 30 ug/day dose, Grade 2 rash at 240 ug/day dose.

In summary, the first dosage is safe as no patient with dose limiting toxicity (DLT) evaluable data has experiences CRS exceeding grade 1. The second dosage, i.e. after the first step, is tolerable as two patients experienced grade 1 CRS but none exceeded grade 1, and the target dose, i.e. after the second step, is considered safe as two patients did not experience CRS at all and one patient had grade 2 CRS below 48 h and had not exceeded grade 2. Hence, the safety of the CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) is considered good for use in the treatment of MRD AML given the surprisingly large second dosage step.

Example 5:

The objectives of this study was to characterize the clinical efficacy of CD33xCD3 bispecific construct (as exemplified by SEQ ID NO 104) in MDS patients using the data from phase I dose-escalation study (NCT02520427). Patients were screened for blast percentage at baseline and after the respective treatment cycle at baseline and after the respective treatment cycle. As a preferred dosage regimen, MSD patients receive cycle 2 after cycle 1 has been completed, i.e. without any infusion-free interval resulting in a duration of treatment of 56 days non-stop. An MDS patient in cohort 1 who had 12% blasts at baseline, showed 10% after cycle 1, i.e. no response, but 0% blasts after cycle 2. Hence, the CD33xCD3 bispecific construct (as exemplified by SEQ ID NO: 104) is effective for use in the treatment of MDS applying a dosage regimen as described herein.

SEQ ID NO.	DESIGNATION	SOURCE	SEQUENCE
1	Human CD3e extracellular domain	Human	QDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDEHLSLKE FSELEQSGYVVCYPRGSKPEDANFYLYLRARVCNCMEMD
2	Human CD3e 1-27	Human	QDGNEEMGGITQTPYKVSISGTTVILT
3	<i>Callithrix jacchus</i> CD3e extracellular domain	<i>Callithrix jacchus</i>	QDGNEEMGDDTTQNPNYKVSISGTTVTLTCPRYDGHEIKWL VNSQNKEGHEDHLLLEDFSEMEQS GYYACLSKETPAEEASHYLYLKARVCNCVEVD
4	<i>Callithrix jacchus</i> CD3e 1-27	<i>Callithrix jacchus</i>	QDGNEEMGDDTTQNPNYKVSISGTTVTLT
5	<i>Saguinus oedipus</i> CD3e extracellular domain	<i>Saguinus oedipus</i>	QDGNEEMGDDTTQNPNYKVSISGTTVTLTCPRYDGHEIKWL VNSQNKEGHEDHLLLEDFSEMEQS GYYACLSKETPAEEASHYLYLKARVCNCVEVD
6	<i>Saguinus oedipus</i> CD3e 1-27	<i>Saguinus oedipus</i>	QDGNEEMGDDTTQNPNYKVSISGTTVTLT
7	<i>Saimiri sciureus</i> CD3e extracellular domain	<i>Saimiri sciureus</i>	QDGNEEIGDDTTQNPNYKVSISGTTVTLTCPRYDGHEIKWL VNDQNKEGHEDHLLLEDFSEMEQS YYACLSKETPTEEASHYLYLKARVCNCVEVD
8	<i>Saimiri sciureus</i> CD3e 1-27	<i>Saimiri sciureus</i>	QDGNEEIGDDTTQNPNYKVSISGTTVTLT
9	CD33 VH of AH3	Artificial	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYA DDFKGRVTMSDDTSTSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWGQGTTVTVSS NYGMN
10	CD33 HCDR1 of AH3	Artificial	WINTYTGEPTYADDFKG
11	CD33 HCDR2 of AH3	Artificial	WSWSDGYVYFDY
12	CD33 HCDR3 of AH3	Artificial	WSWSDGYVYFDY
13	CD33 VL of AH3	Artificial	DIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIP DRFSGSGGTDFLTIDSLQPEDSATYCYQQSAHFPIITFGQTRLEIK
14	CD33 LCDR1 of AH3	Artificial	KSSQSVLDSSKNKNSLA
15	CD33 LCDR2 of AH3	Artificial	WASTRES
16	CD33 LCDR3 of AH3	Artificial	QQSAHFPIIT

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17	CD33 CD33 HL of AH3	Artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNFGMNWVVRQAPGQGLEWMGWINTYTGEPTYA DDFKGRVTMSDDTSTSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWGQGTITVTVSSGG GGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQKPGQPPK LLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPFITFGQGTRLEIK
18	CD33 AH3 HL x H2C HL	Artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNFGMNWVVRQAPGQGLEWMGWINTYTGEPTYA DDFKGRVTMSDDTSTSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWGQGTITVTVSSGG GGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQKPGQPPK LLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPFITFGQGTRLEIKSGGG GSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYAT YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNFGNSYISYWAYWGQGTITV VSSGGGGGGGGGGGSGTQVTVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPGQA PRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTV L
19	CD33 AH3 HL x F12Q HL	Artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNFGMNWVVRQAPGQGLEWMGWINTYTGEPTYA DDFKGRVTMSDDTSTSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWGQGTITVTVSSGG GGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQKPGQPPK LLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPFITFGQGTRLEIKSGGG GSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYAT YYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNFGNSYISYWAYWGQGTITV TVSSGGGGGGGGGGGSGTQVTVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPGQ APRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLT VL
20	CD33 AH3 HL x I2C HL	Artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNFGMNWVVRQAPGQGLEWMGWINTYTGEPTYA DDFKGRVTMSDDTSTSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWGQGTITVTVSSGG GGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQKPGQPPK LLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPFITFGQGTRLEIKSGGG GSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYAT YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNFGNSYISYWAYWGQGTITV VSSGGGGGGGGGGGSGTQVTVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPGQA PRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTV L
21	CD33 VH of AF5	Artificial	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNFGMNWVVRQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS S

22	CD33 HCDR1 of AF5	Artificial	NYGMN	
23	CD33 HCDR2 of AF5	Artificial	WINTYTGPTYADDFKG	
24	CD33 HCDR3 of AF5	artificial	WSWSDGYVYFDY	
25	CD33 VL of AF5	artificial	DIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPGQPPLKLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIK	
26	CD33 LCDR1 of AF5	artificial	KSSQSVLDSSKNKNSLA	
27	CD33 LCDR2 of AF5	artificial	WASTRES	
28	CD33 LCDR3 of AF5	artificial	QQSAHFPIT	
29	CD33HL of AF5	artificial	QVQLVQSGAEVKPGASVKVCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIK	
30	CD33 AF5 HL x H2C HL	artificial	QVQLVQSGAEVKPGASVKVCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIKS GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYISYWAYWGQ TLVTVSSGGGGSGGGSGGTQVVTQEPSTVSPGGTTLTTCGSSTGAVTSGYYPNWWVQQK PGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGT KLTIVL	
31	CD33 AF5 HL x F12Q HL	artificial	QVQLVQSGAEVKPGASVKVCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIKS GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYISYWAYWGQ GTLVTVSSGGGGSGGGSGGTQVVTQEPSTVSPGGTTLTTCGSSTGAVTSGYYPNWWVQQ KPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGG TKLTVL	

32	CD33 AF5 HL x I2C HL	artificial	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWGGTTTIVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQQAHPITFGQGRLEIKS GGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNYSIISYWAYWGQG TLVTVSSGGGGSGGGGGGQTVVTQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQK PGQAPRGLIGGKFLAPGTPARFSGSLLGGKAALTLGVPEDAEYYCVLWYSNRRWVFGGGT KLTVL
33	CD33 VH of AC8	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSDGYVYFDYWGGTTTIVTS S
34	CD33 HCDR1 of AC8	artificial	NYGMIN
35	CD33 HCDR2 of AC8	artificial	WINTYTGEPTYADDFKG
36	CD33 HCDR3 of AC8	artificial	WSWSDGYVYFDY
37	CD33 VL of AC8	artificial	DIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIP DRFSGSGGTDFLTIDSLQPEDSATYYCQQAHPITFGQGRLEIK
38	CD33 LCDR1 of AC8	artificial	KSSQSLDSSKNKNSLA
39	CD33 LCDR2 of AC8	artificial	WASTRES
40	CD33 LCDR3 of AC8	artificial	QQAHPIT
41	CD33 HL of AC8	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSDGYVYFDYWGGTTTIVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQQAHPITFGQGRLEIK
42	CD33 AC8 HL x H2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSDGYVYFDYWGGTTTIVTS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQQAHPITFGQGRLEIKS GGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNYSIISYWAYWGQG TLVTVSSGGGGSGGGGGGQTVVTQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQK

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43	CD33 AC8 HL x F12Q HL	artificial	PGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLSGVQPEDEAEYYCALWYSNRWVFGGGT KLTVL QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSDGYVYFDYWGGQTTVTVS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPITFGQTRLEIKS GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNN YATYYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQ GTLVTVSSGGGGSGGGGSGTQVVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQ KPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLSGVQPEDEAEYYCVLWYSNRWVFGGG TKLTVL
44	CD33 AC8 HL x I2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSDGYVYFDYWGGQTTVTVS SGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPITFGQTRLEIKS GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFENKYAMNWVRQAPGKGLEWVARIRSKYNN YATYYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQ TLVTVSSGGGGSGGGGSGTQVVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQ PGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGT KLTVL
45	CD33 VH of AH11	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISSLRSDDTAVYYCARWSWSDGYVYFDYWGGQTTVTVSS NYGMN
46	CD33 HCDR1 of AH11	artificial	WINTYTGEPTYADDFKG
47	CD33 HCDR2 of AH11	artificial	WSWSDGYVYFDY
48	HCDR3	artificial	
49	CD33 VL of AH11	artificial	DIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIP DRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHPITFGQTRLEIK
50	CD33 LCDR1 of AH11	artificial	KSSQSVLDSSKNKNSLA
51	CD33 LCDR2 of AH11	artificial	WASTRES

52	CD33LCDR3 of AH11	artificial	QQSAHFPT	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTGLEIK
53	CD33 HL of AH11	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTGLEIK
54	CD33 AH11 HL x H2C HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTGLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNY ATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWVGQGT LTVTVSSGGGGSGGGGGSGGTQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGYYPNWWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVALWYSNRWVFGGGTKL TVL
55	CD33 AH11 HL x F12Q HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTGLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNY ATYYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWVGQGT LTVTVSSGGGGSGGGGGSGGTQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGYYPNWWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVALWYSNRWVFGGGTKL LTVL
56	CD33 AH11 HL x I2C HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLKWMGWINTYTGEPTY ADDFKGRVTMTSDTSTSTAYMEISLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTGLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNY ATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWVGQGT LTVTVSSGGGGSGGGGGSGGTQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGYYPNWWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVALWYSNRWVFGGGTKL TVL

57	CD33 VH of B3	artificial	QVQLVQSGAEVKKPGESVKVSKKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNYS ADKFQGRVTFTSDTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS
58	CD33 HCDR1 of B3	artificial	NYGMN
59	CD33 HCDR2 of B3	artificial	WINTYTGETNYADKFQG
60	CD33 HCDR3 of B3	artificial	WSWSDGYVYFDY
61	CD33 VL of B3	artificial	DIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPKLLLSWASTRESGIP DRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGTRLDIK
62	CD33 LCDR1 of B3	artificial	KSSQSVLDSSTNKNSLA
63	CD33 LCDR2 of B3	artificial	WASTRE
64	CD33 LCDR3 of B3	artificial	QQSAHFPIIT
65	CD33 HL of B3	artificial	QVQLVQSGAEVKKPGESVKVSKKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNYS ADKFQGRVTFTSDTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGGGGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGTRLDIK
66	CD33 B3 HL x H2C HL	artificial	QVQLVQSGAEVKKPGESVKVSKKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNYS ADKFQGRVTFTSDTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGGGGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGTRLDIKS GGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNHWVRQAPGKLEWVARIRSKYNN YATYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGNSYISYWAYWGQG TLVTVSSGGGGGGGGGGGSGTQVTVTQEPSTVSPGGTTLTTCGSSTGAVTSGYYPNWVQQK PGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLGSGVQPEDEAEYYCALWYSNRWVFGGGT KLTVL
67	CD33 B3 HL x F12Q HL	artificial	QVQLVQSGAEVKKPGESVKVSKKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNYS ADKFQGRVTFTSDTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGGGGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGTRLDIKS GGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNHWVRQAPGKLEWVARIRSKYNN YATYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGNSYISYWAYWGQG GTLVTVSSGGGGGGGGGGGSGTQVTVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQ

			KPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLSGVQPEDEAEYYCVLWYNSNRWVFGGG TKLTVL
68	CD33 B3 HL x I2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFTSDTSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGSGGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPG QPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPIFGGQTRLDIKS GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGNSYISYWAYWYGGG TLVTVSSGGGGSGGGGGGQTVVTQEPSTVSPGGTTLTTCGSSTGAVTSGNYPNWWVQQK PGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAAALTLSGVQPEDEAEYYCVLWYNSNRWVFGGGT KLTVL
69	CD33 VH of F2	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFTSDTSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS S
70	CD33 HCDR1 of F2	artificial	NYGMN
71	CD33 HCDR2 of F2	artificial	WINTYTGETNYADKFQG
72	CD33 HCDR3 of F2	artificial	WSWSDGYVYFDY
73	CD33 VL of F2	artificial	DIVMTQSPDSLVSLEGGTINCKSSQSVLDSSTNKNSLAWYQQKPGQPKLLLSWASTRESGIP DRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPIFGGQTRLEIK
74	CD33 LCDR1 of F2	artificial	KSSQSVLDSSTNKNSLA
75	CD33 LCDR2 of F2	artificial	WASTRES
76	CD33 LCDR3 of F2	artificial	QQSAHFPIIT
77	CD33 HL of F2	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFTSDTSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGSGGGSDIVMTQSPDSLVSLEGGTINCKSSQSVLDSSTNKNSLAWYQQKPGQ PKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPIFGGQTRLEIK
78	CD33 F2 HL x H2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFTSDTSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGSGGGSDIVMTQSPDSLVSLEGGTINCKSSQSVLDSSTNKNSLAWYQQKPGQ PKLLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPIFGGQTRLEIKSG GGGSEVQLVESGGGLVQPGGSLKSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNY

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			ATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWVGQGT LTVL
79	CD33 F2 HL x F12Q HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGSGGGSDIVMTQSPDSLVSLEGGTINCKSSQSLDSSNKNLSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWRQAPGKGLEWVARIRSKYN ATYYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWVGQGT LTVL
80	CD33 F2 HL x I2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS SGGGSGGGSGGGSDIVMTQSPDSLVSLEGGTINCKSSQSLDSSNKNLSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQAHPITFGQGTTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWRQAPGKGLEWVARIRSKYN ATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWVGQGT LTVL
81	CD33 VH of B10	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNHWVKQAPGQGLEWMGWINTYTGETNY ADKFQGRVTFSTSTAYMELRNKSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVS
82	CD33 HCDR1 of B10	Artificial	NYGMN
83	CD33 HCDR2 of B10	artificial	WINTYTGEPTYADKFQ
84	CD33 HCDR3 of B10	artificial	WSWSDGYVYFDY
85	CD33 VL of B10	artificial	DIVMTQSPDSLVSLEGGTINCKSSQSLDSSNKNLSLAWYQQKPGQPPKLLLSWASTRESGIP DRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQGTTRLEIK
86	CD33 LCDR1 of B10	artificial	KSSQSLDSSNKNLSLA
87	CD33 LCDR2 of B10	artificial	WASTRES

88	CD33 LCDR3 of B10	artificial	QQSAHFPIIT	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQTRLEIK
89	CD33 HL of B10	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRVRAQPGKLEWVARIRSKYNNY ATYYADSVKDRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNGNSYISYWAYWVGQGT LTVSSGGGGGGGGGGGQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKL TVL
90	CD33 B10 HL x H2C HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRVRAQPGKLEWVARIRSKYNNY ATYYADSVKDRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNGNSYISYWAYWVGQGT LTVSSGGGGGGGGGGGQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKL TVL
91	CD33 B10 HL x F12Q HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRVRAQPGKLEWVARIRSKYNNY ATYYADSVKGRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNGNSYISYWAYWVGQGT LTVSSGGGGGGGGGGGQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKL LTVL
92	CD33 B10 HL x I2C HL	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS GGGSGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQQKPGQ PPKLLLSWASTRESGIPDRFSGSGGTDFTLTIDGLQPEDSATYYCQQAHPITFGQTRLEIKSG GGSEVQLVESGGGLVQPGGSLKLSAASGFTFNKYAMNWRVRAQPGKLEWVARIRSKYNNY ATYYADSVKDRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNGNSYISYWAYWVGQGT LTVSSGGGGGGGGGGGQTVVTVQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQQKPG QAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKL TVL
93	CD33 VH of E11	artificial		QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGQGTITVTVSS

94	CD33 HCDR1 of E11	artificial	NYGMN	
95	CD33 HCDR2 of E11	artificial	WINTYTGEPTYADKFQG	
96	CD33 HCDR3 of E11	artificial	WSWSDGYVYFDY	
97	CD33 VL of E11	artificial	DIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPLKLLSWASTRESGIPDRFSGSGGTDFLTIDSPQPEDSATYYCQSAHFPIFGQGRLEIK	
98	CD33 LCDR1 of E11	artificial	KSSQSVLDSSTNKNSLA	
99	CD33 LCDR2 of E11	artificial	WASTRES	
100	CD33 LCDR3 of E11	artificial	QQSAHFPIIT	
101	CD33 HL of E11	artificial	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWGQGTSTVTVSSGGGGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPLKLLSWASTRESGIPDRFSGSGGTDFLTIDSPQPEDSATYYCQSAHFPIFGQGRLEIKSGG	
102	CD33 E11 HL x H2C HL	artificial	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWGQGTSTVTVSSGGGGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPLKLLSWASTRESGIPDRFSGSGGTDFLTIDSPQPEDSATYYCQSAHFPIFGQGRLEIKSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTSLTVSSGGGGGGGGGGSGTQVVTQEPSTVSPGGTTLTLCGSSTGAVTSGYYPNWWVQQKPGQAPRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLT	
103	CD33 E11 HL x F12Q HL	artificial	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWWVKQAPGQGLEWMGWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWGQGTSTVTVSSGGGGGGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPLKLLSWASTRESGIPDRFSGSGGTDFLTIDSPQPEDSATYYCQSAHFPIFGQGRLEIKSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTSLTVSSGGGGGGGGGGSGTQVVTQEPSTVSPGGTTLTLCGSSTGAVTSGYYPNWWVQQKPGQAPRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL	

104	CD33 E11 HL x I2C HL	artificial	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWWVKQAPGGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFYDYWGQGSTVTVSS GGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQP PKLLLSWASTRESGIPDRFSGSGGTDFTLTIDSPQPEDSATYCYCQSAHFPIITFGQTRLEIKSGG GGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNYA TYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGT TVSSGGGGSGGGSGGGGQTAVTQEPSTVSPGGTTLTCSGSTGAVTSGNYPNWWVQQKPGQ APRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLT VL
105	CD33 UD H2C HL x AF5 HL	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNYATY YADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGT SSGGSGGGSGGGSGGGQTAVTQEPSTVSPGGTTLTCSGSTGAVTSGNYPNWWVQQKPGQAP RGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLT SGGGSGVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWWKQAPGQGLKWMGWINTY TGEPTYADDFKGRVTMTSDTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFYDYWGQ TTVTVSSGGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWY QQKPGQPPKLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGT RLEIK
106	CD33 UD F12Q HL x AF5 HL	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNYATY ADSVKGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGT SSGGSGGGSGGGSGGGQTAVTQEPSTVSPGGTTLTCSGSTGAVTSGNYPNWWVQQKPGQAP RGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLT SGGGSGVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWWKQAPGQGLKWMGWINTY TGEPTYADDFKGRVTMTSDTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFYDYWGQ TTVTVSSGGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWY QQKPGQPPKLLSWASTRESGIPDRFSGSGGTDFLTIDSLQPEDSATYCYCQSAHFPIITFGQGT RLEIK
107	CD33 UD I2C HL x AF5 HL	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWWVRQAPGKGLEWVARIRSKYNNYATY YADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGT SSGGSGGGSGGGSGGGQTAVTQEPSTVSPGGTTLTCSGSTGAVTSGNYPNWWVQQKPGQAP RGLIGGTTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLT SGGGSGVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWWKQAPGQGLKWMGWINTY TGEPTYADDFKGRVTMTSDTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFYDYWGQ TTVTVSSGGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSKNKNSLAWY

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108	CD33 E11 HL x I2C HL H6	artificial	QQKPGPPKLLLSWASTRESGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQAHHFPTFGQGT RLEIK QVQLVQSGAEVKKPGESVKVSCKASGYTFTNRYGMNWVKQAPGQGLEWMGWINTYTGEPTYA DKFQGRVTMTTDTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWGQGTSTVTVSS GGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSSTKNKSLAWYQKPGQP PKLLLSWASTRESGIPDRFSGSGSGTDFTLTIDSPQPEDSATYYCQQAHHFPTFGQGTREIKSGG GGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNRYA TYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAYYCVRHGNFNSIYSYWAYWGQGTLV TVSSGGGGSGGGSGGGSQTIVTQEPSLTVSPGGTIVTLCGSSTGAVTSGNYPNWVQQKPGQ APRGLIGGTTKFLAPGTPARFSGSLLGGKAALTLGVPQPEDEAEYYCVLWYSNRWVFGGGTKLT VLHHHHH
109	HALB	human	DAHKSEVAHRFKDGLGEENFKALVLIAFQAQYLQCCPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVLRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTGCCQAADKAACLLPKLDELDEG KASSAKQRLKCSLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECEKPLLEKSHCIAEVENDEMPADPLSLAADFVESKDV KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFQGEYKFNQALLVRYTKKVPQVSTPTLVESRNLGKVGSKCKKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPFCFALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFEKCKCKADDDKTCF AEEGKKLVAAASQAALGL
110	HALB7	artificial	DAHKSEVAHRFKDGLGEENFKALVLIAFQAQYLQCCPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVLRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTGCCQAADKAACLLPKLDELDEG KASSAKQRLKCSLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECEKPLLEKSHCIAEVENDEMPADPLSLAADFVESKDV KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFQGEYKFNQALLVRYTKKVPQVSTPTLVESRNLGKVGSKCKKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPFCFALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFEKCKCKADDDKTCF AEEGKKLVAAASQAALGL
111	HALB098	artificial	DAHKSEVAHRFKDGLGEENFKALVLIAFQAQYLQCCPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVLRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTGCCQAADKAACLLPKLDELDEG KASSAKQRLKCSLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE

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112	HALB114	artificial	CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAAFVEKCKCKADDDKETCF AEEGPKLVAASQAALGL DAHKSEVAHRFKDLGEENFKALVLIJFAQYLQOCPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVMCT AFHDNEETFLKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRPFAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAAFVEKCKCKADDDKETCF AEEGPKLVAASKAALGL
113	HALB254	artificial	DAHKSEVAHRFKDLGEENFKALVLIJFAQYLQOCPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVMCT AFHDNEETFLKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRPFAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLVAASQAALGL DAHKSEVAHRFKDLGEENFKALVLIJFAQYLQOCPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVMCT AFHDNEETFLKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRPFAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLVAASQAALGL
114	HALB253	artificial	DAHKSEVAHRFKDLGEENFKALVLIJFAQYLQOCPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVMCT AFHDNEETFLKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRPFAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLVAASQAALGL DAHKSEVAHRFKDLGEENFKALVLIJFAQYLQOCPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVMCT AFHDNEETFLKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRPFAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEA KDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTLEKCCAAADPHECYAKVDFEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALVRYTKKVPQVSTPTLV EYSRNLGKVGSKCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLVAASQAALGL

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115	HALB131	artificial	TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAEACND KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNNLPRLVRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAFTTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPAEFAEVSCLKVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVDC KNYAEAKDVFLGMFLYFYARRHPDYSVVLLRLAKTYETTLKCCCAAADPHECYAKVDFEFK PLVEEPQNLJKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL
116	HALB135	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAEACND KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNNLPRLVRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAFTTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPAEFAEVSCLKVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVDC KNYAEAKDVFLGMFLYFYARRHPDYSVVLLRLAKTYETTLKCCCAAADPHECYAKVDFEFK PLVEEPQNLJKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL
117	HALB133	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAEACND KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNNLPRLVRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAFTTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPAEFAEVSCLKVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVDC KNYAEAKDVFLGMFLYFYARRHPDYSVVLLRLAKTYETTLKCCCAAADPHECYAKVDFEFK PLVEEPQNLJKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL
118	HALB234	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAEACND KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNNLPRLVRPEVDVMCT AFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAFTTECCQAADKAACLLPKLDELDRDEG

119	HALB C34S	artificial	KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCECKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV/C KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCSELFQGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKCKADDDKETCF AEEGKLV AASKAALGL DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCECKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV/C KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCSELFQGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKCKADDDKETCF AEEGKLV AASKAALGL
120	HALB7 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCECKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV/C KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCSELFQGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKCKADDDKETCF AEEGKLV AASKAALGL
121	HALB098 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTCCQAADKAAACLLPKLDELREDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCECKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV/C KNYAEAKDVFLGMFLYFYARRHPDYVSVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCSELFQGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKCKADDDKETCF AEEGKLV AASKAALGL

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122	HALB114 C34S	artificial	TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDDFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKA AFTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTL EKCCAAADPHECYAKV FDEFK PLVEEPQNLKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALDVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDDFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL
123	HALB254 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKA AFTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTL EKCCAAADPHECYAKV FDEFK PLVEEPQNLKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALGVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL
124	HALB253 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKA AFTECCQAADKAACLLPKLDELDRDEG KASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDILLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDYSV VLLRLAKTYETTL EKCCAAADPHECYAKV FDEFK PLVEEPQNLKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALGVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASQAALGL
125	HALB131 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFQAQYLQQSPFEDHVKL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKA AFTECCQAADKAACLLPKLDELDRDEG

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			KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPHLV AASKAALGL DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQSPFEDHV KLVNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPHLV AASKAALGL
126	HALB135 C34S	artificial	
127	HALB133 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQSPFEDHV KLVNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQSPFEDHV KLVNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL
128	HALB234 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQSPFEDHV KLVNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQSPFEDHV KLVNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLEKCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLV EVSRLNGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL

129	HALB C34A	artificial	TFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEQLKAVMDDFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL DAHKSEVAHRFKDLGEENFKALVLIAFAYQLQQAPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTTECCQAADKAAACLLPKLDELDRDEG KASSAKQRLKCSLQKFGERAFKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEAKDVFLGMFLYEYARRHPDYSVLLRLAKTYETTTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCLEFQEGEYKFNALLVRYTKVPQVSTPTLVEVSRNLGKVGSKCCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEQLKAVMDDFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL
130	HALB7 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAYQLQQAPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTTECCQAADKAAACLLPKLDELDRDEG KASSAKQRLKCSLQKFGERAFKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEAKDVFLGMFLYEYARRHPDYSVLLRLAKTYETTTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCLEFQEGEYKFNALLVRYTKVPQVSTPTLVEVSRNLGKVGSKCCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEQLKAVMDDFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL
131	HALB098 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAYQLQQAPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTTECCQAADKAAACLLPKLDELDRDEG KASSAKQRLKCSLQKFGERAFKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV KNYAEAKDVFLGMFLYEYARRHPDYSVLLRLAKTYETTTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCLEFQEGEYKFNALLVRYTKVPQVSTPTLVEVSRNLGKVGSKCCCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEQLKAVMDDFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL
132	HALB114 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAYQLQQAPFEDHVKL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTTECCQAADKAAACLLPKLDELDRDEG

133	HALB254 C34A	artificial	KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALDVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFEVKCCKADDDKETCF AEEGPKLV AASQAALGL DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQ QAPFEDHV KL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALDVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL
134	HALB253 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQ QAPFEDHV KL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALDVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL
135	HALB131 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQ QAPFEDHV KL VNEVTEFAKTCVADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKKDDNP NLPRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAP ELLFFAKRYKAAFT ECCCQAADKAAACLLPKLDEL RDEG KASSAKQRLKCASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFK PLVEEPQNLKQNCCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRNLGKVGSKCCKHPE AKRMPCAEEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALDVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCCKADDDKETCF AEEGPKLV AASQAALGL

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136	HALB135 C34A	artificial	TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPHLV AASKAALGL DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQA PFEDHV KL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPPELLFFAKRYKAAFTTECCQAADKAACLLPKLDEL RDEG KASSAKQRLK CASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLECCCKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRN LGKV GSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPHLV AASKAALGL
137	HALB133 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQA PFEDHV KL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPPELLFFAKRYKAAFTTECCQAADKAACLLPKLDEL RDEG KASSAKQRLK CASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLECCCKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRN LGKV GSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL
138	HALB234 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQA PFEDHV KL VNEVTEFAKTCV ADESAENCD KSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNL PRLVRPEVDVMCT AFHDNEETFLKKYL YEIARRHPYFYAPPELLFFAKRYKAAFTTECCQAADKAACLLPKLDEL RDEG KASSAKQRLK CASLQKFGERAFAKAWAVARLSQRFPKAEFAEVS KLVTDLTKVHTECCCHGDLLE CADDRADLAKYICENQDSISSKLECCCKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV C KNYAEAKDVFLGMFLY EYARRHPDY SVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFK PLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVESRN LGKV GSKCKCKHPE AKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAE TFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCKCKADDDKETCF AEEGPKLV AASKAALGL
139	Peptide linker	artificial	GGGG

140	Peptide linker	artificial	GGGS
141	Peptide linker	artificial	GGGQ
142	Peptide linker	artificial	PGGGGS
143	Peptide linker	artificial	PGDGS
144	Peptide linker	artificial	SGGGGS
145	Peptide linker	artificial	GGGSGGGGS
146	Peptide linker	artificial	GGGSGGGGS
147	Peptide linker	artificial	GGGSGGGSGGGGS
148	CDR-L1 of F6A	artificial	GSSTGAVTSGYYPN
149	CDR-L2 of F6A	artificial	GTKFLAP
150	CDR-L3 of F6A	artificial	ALWYSNRWV
151	CDR-H1 of F6A	artificial	IYAMN
152	CDR-H2 of F6A	artificial	RIRSKYNNYATYYADSVKS
153	CDR-H3 of F6A	artificial	HGNFGNSYVSFFAY
154	CDR-L1 of H2C	artificial	GSSTGAVTSGYYPN
155	CDR-L2 of H2C	artificial	GTKFLAP
156	CDR-L3 of H2C	artificial	ALWYSNRWV
157	CDR-H1 of H2C	artificial	KYAMN
158	CDR-H2 of H2C	artificial	RIRSKYNNYATYYADSVKD
159	CDR-H3 of H2C	artificial	HGNFGNSYISYWAY
160	CDR-L1 of H1E	artificial	GSSTGAVTSGYYPN

161	CDR-L2 of H1E	artificial	GTKFLAP
162	CDR-L3 of H1E	artificial	ALWYSNRWV
163	CDR-H1 of H1E	artificial	SYAMN
164	CDR-H2 of H1E	artificial	RIRSKYNNYATYYADSVKG
165	CDR-H3 of H1E	artificial	HGNFGNSYLSFWAY
166	CDR-L1 of G4H	artificial	GSSTGAVTSGYYPN
167	CDR-L2 of G4H	artificial	GTKFLAP
168	CDR-L3 of G4H	artificial	ALWYSNRWV
169	CDR-H1 of G4H	artificial	RYAMN
170	CDR-H2 of G4H	artificial	RIRSKYNNYATYYADSVKG
171	CDR-H3 of G4H	artificial	HGNFGNSYLSYFAY
172	CDR-L1 of A2J	artificial	RSSTGAVTSGYYPN
173	CDR-L2 of A2J	artificial	ATDMRPS
174	CDR-L3 of A2J	artificial	ALWYSNRWV
175	CDR-H1 of A2J	artificial	VYAMN
176	CDR-H2 of A2J	artificial	RIRSKYNNYATYYADSVKK
177	CDR-H3 of A2J	artificial	HGNFGNSYLSWWAY
178	CDR-L1 of E1L	artificial	GSSTGAVTSGYYPN
179	CDR-L2 of E1L	artificial	GTKFLAP
180	CDR-L3 of E1L	artificial	ALWYSNRWV
181	CDR-H1 of E1L	artificial	KYAMN

182	CDR-H2 of E1L	artificial	RIRSKYNNYATYYADSVKS
183	CDR-H3 of E1L	artificial	HGNFGNSYTSYYAY
184	CDR-L1 of E2M	artificial	RSSTGAVTSGYYPN
185	CDR-L2 of E2M	artificial	ATDMRPS
186	CDR-L3 of E2M	artificial	ALWYSNRWV
187	CDR-H1 of E2M	artificial	GYAMN
188	CDR-H2 of E2M	artificial	RIRSKYNNYATYYADSVKE
189	CDR-H3 of E2M	artificial	HRNFGNSYLSWFAY
190	CDR-L1 of F7O	artificial	GSSTGAVTSGYYPN
191	CDR-L2 of F7O	artificial	GTKFLAP
192	CDR-L3 of F7O	artificial	ALWYSNRWV
193	CDR-H1 of F7O	artificial	VYAMN
194	CDR-H2 of F7O	artificial	RIRSKYNNYATYYADSVKK
195	CDR-H3 of F7O	artificial	HGNFGNSYISWAY
196	CDR-L1 of F12Q	artificial	GSSTGAVTSGNYPN
197	CDR-L2 of F12Q	artificial	GTKFLAP
198	CDR-L3 of F12Q	artificial	VLWYSNRWV
199	CDR-H1 of F12Q	artificial	SYAMN
200	CDR-H2 of F12Q	artificial	RIRSKYNNYATYYADSVKG
201	CDR-H3 of F12Q	artificial	HGNFGNSYVSWWAY
202	CDR-L1 of I2C	artificial	GSSTGAVTSGNYPN

203	CDR-L2 of I2C	artificial	GTKFLAP	
204	CDR-L3 of I2C	artificial	VLWYSNRWV	
205	CDR-H1 of I2C	artificial	KYAMN	
206	CDR-H2 of I2C	artificial	RIRSKYNNYATYYADSVKD	
207	CDR-H3 of I2C	artificial	HGNFGNSYISYWAY	
208	I2C – VH		EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVVRQAPGKGLEWVARIRSKYNNYATY YADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLLVTV SS	
209	I2C – VL		QTVVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARF SGSLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL	

Claims

1. A bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 for use in a method for the treatment of (i.) myeloid leukemia selected from relapsed/refractory AML (R/R AML) and AML with minimal residual disease (MRD), or (ii.) myelodysplastic syndrome (MDS), wherein the bispecific construct is administered in one or more treatment cycles, wherein at least one treatment cycle comprises more than 14 days of administration of the bispecific construct in at least three different dosages applying at least two dosage steps, optionally followed by a period without administration of the construct,
wherein the bispecific construct is administered in at least one of the one or more treatment cycles according to a schedule comprising the following steps:
 - (a) administration of a first dosage of the bispecific construct of at least 10 µg per day for use in the treatment of R/R AML or at least 30 µg per day for use in the treatment of MRD or MDS, followed by
 - (b) administration of a second dosage of the bispecific construct, wherein said second dosage is at least 240 µg per day and/or preferably exceeds said first dose at least 10-fold for use in the treatment of R/R AML or at least 8-fold for use in the treatment of MRD or MDS and/or wherein the delta between the first and the second dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, followed by
 - (c) administration of a third dosage of the bispecific construct, wherein said third dosage is at least 600 per day and/or preferably exceeds said second dosage at most three-fold and/or wherein the delta between the second and the third dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day for use in the treatment of R/R AML, and wherein said third dosage is in the range of 600 to 1600 µg/d for use in the treatment of MRD or MDS, preferably followed by
 - (d) administration of a forth dosage of the bispecific construct, preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional forth dose is at least 720 µg per day and/or exceeds said third dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, optionally followed by
 - (e) administration of a fifth dosage of the bispecific construct, preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional fifth dose is at least 960 µg per day and/or exceeds said fourth dosage and/or wherein the delta between the fourth and

- the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day, optionally followed by
- (f) administration of a sixth dosage of the bispecific construct, preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional sixth dose is at least 1200 µg per day and/or exceeds said fifth dosage and/or wherein the delta between the fifth and the sixth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day.
2. The bispecific construct for the use according to claim 1, wherein the time of administering the bispecific construct in one treatment cycle including all steps (a) to (c) or (d) or (e) or (f) is at least 15 days, preferably 15 to 60 days, more preferably 28 to 56 days, most preferably 28 days wherein the bispecific construct is for use in the treatment of R/R AML or MRD AML or 56 days wherein the bispecific construct is for use in the treatment MDS.
3. The bispecific construct for the use according to claim 1 or 2 preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein the first dosage in step (a) is at least 10 µg per day, preferably in the range of 10 to 20 µg per day, preferably 10 µg per day, the second dosage in step (b) is at least 240 µg per day, preferably in the range of 240 to 600 µg per day, the third dosage in step (c) of at least 600 µg per day, preferably in the range of 600 to 1000 µg per day, and preferably the fourth dosage in step (d) of at least 720 µg per day, preferably 720 to 1600 µg per day, more preferably in the range of 960 to 1080 µg per day, more preferably 960 µg per day, optionally the fifth dosage in step (e), of at least 960 µg per day, preferably at least 1200 or 1300 µg per day, and optionally the sixth dosage in step (f), of at least 1200 µg per day, preferably at least 1300 or 1600 µg per day.
4. The bispecific construct for the use according to claim 1, wherein the period of administration of the first dosage in step (a) is 1 to 5 days, preferably 2 or 3 days, the period of administration of the second dosage in step (b) is 2 to 5 days, preferably 2 or 3 days, and the period of administration of the third dosage in step (c) and the optional fourth, fifth and sixth dosage in step (d), (e) and (f), respectively, together is 7 to 52 days, preferably 14 to 52 days, more preferably 22, 23 wherein the bispecific construct is for use in the treatment of R/R AML or MRD AML or 52 days wherein the bispecific construct is for use in the treatment MDS.
5. The bispecific construct for the use according to any one of claims 2 to 4, wherein the treatment comprises two or more treatment cycles, preferably two, three, four, five, six or seven treatment cycles, whereof at least one, two, three, four five, six or seven treatment cycles comprise more than 14 days of bispecific construct administration.

6. The bispecific construct for the use according to any one of claims 2 to 5, wherein at least one treatment cycle is followed by the period without administration of the construct, preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days without treatment.
7. The bispecific construct for the use according to any one of claims 2 to 5, wherein at least one treatment cycle is not followed by the period without administration of the construct, preferably where the bispecific construct is for use in the treatment of MDS.
8. The bispecific construct for the use according to any of claims 5 to 7, wherein only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dose according to step (b).
9. The bispecific construct for the use according to any one of claims 1 to 8, wherein the construct is a single chain bispecific construct.
10. The bispecific construct for the use according to any one of claims 1 to 8, wherein the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100, preferably 94 to 96 and 98 to 100.
11. The bispecific construct for the use according to any one of claims 1 to 8, wherein the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 148-153, 154-159, 160-165, 166-171, 172-177, 178-183, 184-189, 190-195, 196-201 and 202-207, preferably 202-207.
12. The bispecific construct for the use according to any one of claims 1 to 10, wherein the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 94 to 96 or 98 to 100 and the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 202-207.
13. The bispecific construct for the use according to any one of claims 1 to 10, wherein the first binding domain of the bispecific construct comprises a VH of SEQ ID NO 93 and a VL of SEQ ID NO 97, and wherein the second binding domain of the bispecific construct comprises a VH of SEQ ID NO 208 and a VL of SEQ ID NO 209.

14. The bispecific construct for the use according to claims 1 to 13, wherein the bispecific construct is a single chain construct comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108, preferably selected from the group consisting of SEQ ID NOs: 104, 105, 106, 107 and 108, more preferably SEQ ID NO 104.
15. A method for the treatment of (i.) myeloid leukemia selected from relapsed/refractory AML (R/R AML) and AML with minimal residual disease (MRD), or (ii.) myelodysplastic syndrome (MDS) in a patient in need thereof comprising administering a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 in one or more treatment cycles, wherein the at least one treatment cycle comprises more than 14 days of administration of the bispecific construct in at least three different dosages applying at least two dosage steps,
- wherein the bispecific construct is administered in one treatment cycle according to a schedule comprising the following steps:
- (a) administration of a first dosage of the bispecific construct of at least 10 µg per day in the treatment of R/R AML or at least 30 µg per day in the treatment of MRD or MDS, followed by
 - (b) administration of a second dosage of the bispecific construct, wherein said second dosage is at least 240 µg per day and/or preferably exceeds said first dose at least 10-fold in the treatment of R/R AML or at least 8-fold in the treatment of MRD or MDS and/or wherein the delta between the first and the second dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, followed by
 - (c) administration of a third dosage of the bispecific construct, wherein said third dosage is at least 600 µg per day and/or preferably exceeds said second dosage at most three-fold and/or wherein the delta between the second and the third dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day in the treatment of R/R AML, and wherein said third dosage is in the range of 600 to 1600 µg/d used in the treatment of MRD or MDS, preferably followed by
 - (d) administration of a forth dosage of the bispecific construct preferably wherein the bispecific construct used in the treatment of R/R AML, wherein said optional forth dose is at least 720 µg per day and/or exceeds said third dosage and/or wherein the delta between the fourth and the

- fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, optionally followed by
- (e) administration of a fifth dosage of the bispecific construct preferably wherein the bispecific construct used in the treatment of R/R AML, wherein said optional fifth dose is at least 960 µg per day and/or exceeds said fourth dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day, optionally followed by
 - (f) administration of a sixth dosage of the bispecific construct preferably wherein the bispecific construct is used in the treatment of R/R AML, wherein said optional sixth dose is at least 1200 µg per day and/or exceeds said fifth dosage and/or wherein the delta between the fifth and the sixth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day.
16. The method according to claim 15, wherein the time of administering the bispecific construct in one treatment cycle is at least 15 days, preferably 15 to 60 days, more preferably 28 to 56 days, most preferably 28 days wherein the bispecific construct is used in the treatment of R/R AML or MRD AML or 56 days wherein the bispecific construct is used in the treatment MDS..
17. The method according to claim 15 or 17, preferably wherein the bispecific construct is for use in the treatment of R/R AML wherein the first dosage in step (a) is at least 10 µg per day, preferably in the range of 10 to 20 µg per day, preferably 10 µg per day, the second dosage in step (b) is at least 240 µg per day, preferably in the range of 240 to 600 µg per day, the third dosage in step (c) of at least 600 µg per day, preferably in the range of 600 to 1000 µg per day, and preferably the fourth dosage in step (d) of at least 720 µg per day, preferably 720 to 1600 µg per day, more preferably in the range of 960 to 1080 µg per day, more preferably 960 µg per day, optionally the fifth dosage in step (e), of at least 960 µg per day, preferably at least 1200 or 1300 µg per day, and optionally the sixth dosage in step (f), of at least 1200 µg per day, preferably at least 1300 or 1600 µg per day.
18. The method according to any one of claims 15 to 17, wherein the period of administration of the first dosage in step (a) is 1 to 5 days, preferably 1, 2 or 3 days (2 days in particular where used in the treatment of MRD), the period of administration of the second dosage in step (b) is 2 to 5 days, preferably 2 or 3 or 5 days (5 days in particular where used in the treatment of MRD), and the period of administration of the third and the optional fourth dose in step (c) and optional step (d) is 7 to 52 days, preferably 14 to 23 days, more preferably 21, 22 or 23, where used in the treatment of R/R AML or MRD or 52 days where used in the treatment of MDS.

19. The method according to any one of claims 15 to 18, wherein the treatment of the myeloid leukemia or MDS comprises two or more treatment cycles, preferably 2, 3, 4, 5, 6 or 7 treatment cycles, whereof at least 1, 2, 3, 4, 5, 6 or 7 treatment cycles comprise more than 14 days of bispecific construct administration.
20. The method according to any one of claims 15 to 19, wherein the treatment is followed by the period without administration of the bispecific construct, preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days without treatment.
21. The method according to any one of claims 15 to 19, wherein the treatment is followed by the period of at least 14 days without administration of the bispecific construct, preferably where the bispecific construct is for use in the treatment of MDS.
22. The method according to any one of claims 15 to 21, wherein only the first cycle of the treatment comprises the administration according to step (a), whereas the following cycles start with the dose according to step (b).
23. The method according to any one of the preceding claims 15 to 21, wherein the construct is a single chain bispecific construct.
24. The method according to any one of the preceding claims, wherein the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 10 to 12 and 14 to 16, 22 to 24 and 26 to 28, 34 to 36 and 38 to 40, 46 to 48 and 50 to 52, 58 to 60 and 62 to 64, 70 to 72 and 74 to 76, 82 to 84 and 86 to 88, 94 to 96 and 98 to 100, preferably 94 to 96 and 98 to 100.
25. The method according to any one of claims 14 to 23, wherein the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 148-153, 154-159, 160-165, 166-171, 172-177, 178-183, 184-189, 190-195, 196-201 and 202-207, preferably 202-207.
26. The method according to any one of claims 15 to 25, wherein the first binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 94 to 96 or 98 to 100 and the second binding domain of the bispecific construct comprises groups of six CDRs selected from the group consisting of SEQ ID NOs: 202-207.
27. The method according to any one of claims 15 to 26, wherein the first binding domain of the bispecific construct comprises a VH of SEQ ID NO 93 and a VL of SEQ ID NO 97, and wherein the second binding domain of the bispecific construct comprises a VH of SEQ ID NO 208 and a VL of SEQ ID NO 209.

28. The method according to any one of claims 15 to 25, wherein the bispecific construct is a single chain construct comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 19, 20, 30, 31, 32, 42, 43, 44, 54, 55, 56, 66, 67, 68, 78, 79, 80, 90, 91, 92, 102, 103, 104, 105, 106, 107 and 108, preferably selected from the group consisting of SEQ ID NOs: 104, 105, 106, 107 and 108, more preferably SEQ ID NO: 104.
29. Use of a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3 in a method for the treatment of (i.) myeloid leukemia selected from relapsed/refractory AML (R/R AML) or and AML with minimal residual disease (MRD) AML, or AML with(ii.) myelodysplastic syndrome (MDS), wherein the bispecific construct is administered in one or more treatment cycles, wherein at least one treatment cycle comprises more than 14 days of administration of the bispecific construct in at least three different dosages applying at least two dosage steps, optionally followed by a period without administration of the bispecific construct,
- wherein the bispecific construct is administered in at least one of the one or more treatment cycle according to a schedule comprising the following steps:
- (a) administration of a first dosage of the bispecific construct of at least 10 µg per day for use in the treatment of R/R AML or at least 30 µg per day for use in the treatment of MRD or MDS, followed by
 - (b) administration of a second dosage of the bispecific construct, wherein said second dosage is at least 240 µg per day and/or preferably exceeds said first dose at least 10-fold for use in the treatment of R/R AML or at least 8-fold for use in the treatment of MRD or MDS and/or wherein the delta between the first and the second dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, followed by
 - (c) administration of a third dosage of the bispecific construct, wherein said third dosage is at least 600 per day and/or preferably exceeds said second dosage at most three-fold and/or wherein the delta between the second and the third dosage is preferably at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day for use in the treatment of R/R AML, or wherein said third dosage is in the range of 600 to 1600 µg/d for use in the treatment of MRD or MDS, preferably followed by
 - (d) administration of a forth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional forth dose is at least 720 µg per day and/or exceeds said third dosage and/or wherein the delta between the fourth

and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360 or at most 400 µg per day, optionally followed by

- (e) administration of a fifth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional fifth dose is at least 960 µg per day and/or exceeds said fourth dosage and/or wherein the delta between the fourth and the fifth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day, optionally followed by
- (f) administration of a sixth dosage of the bispecific construct preferably wherein the bispecific construct is for use in the treatment of R/R AML, wherein said optional sixth dose is at least 1200 µg per day and/or exceeds said fifth dosage and/or wherein the delta between the fifth and the sixth dosage is at least 50 µg per day, preferably at least 100, 150, 200, 250, 300, 350, 360, or at most 400 µg per day.

Fig. 1

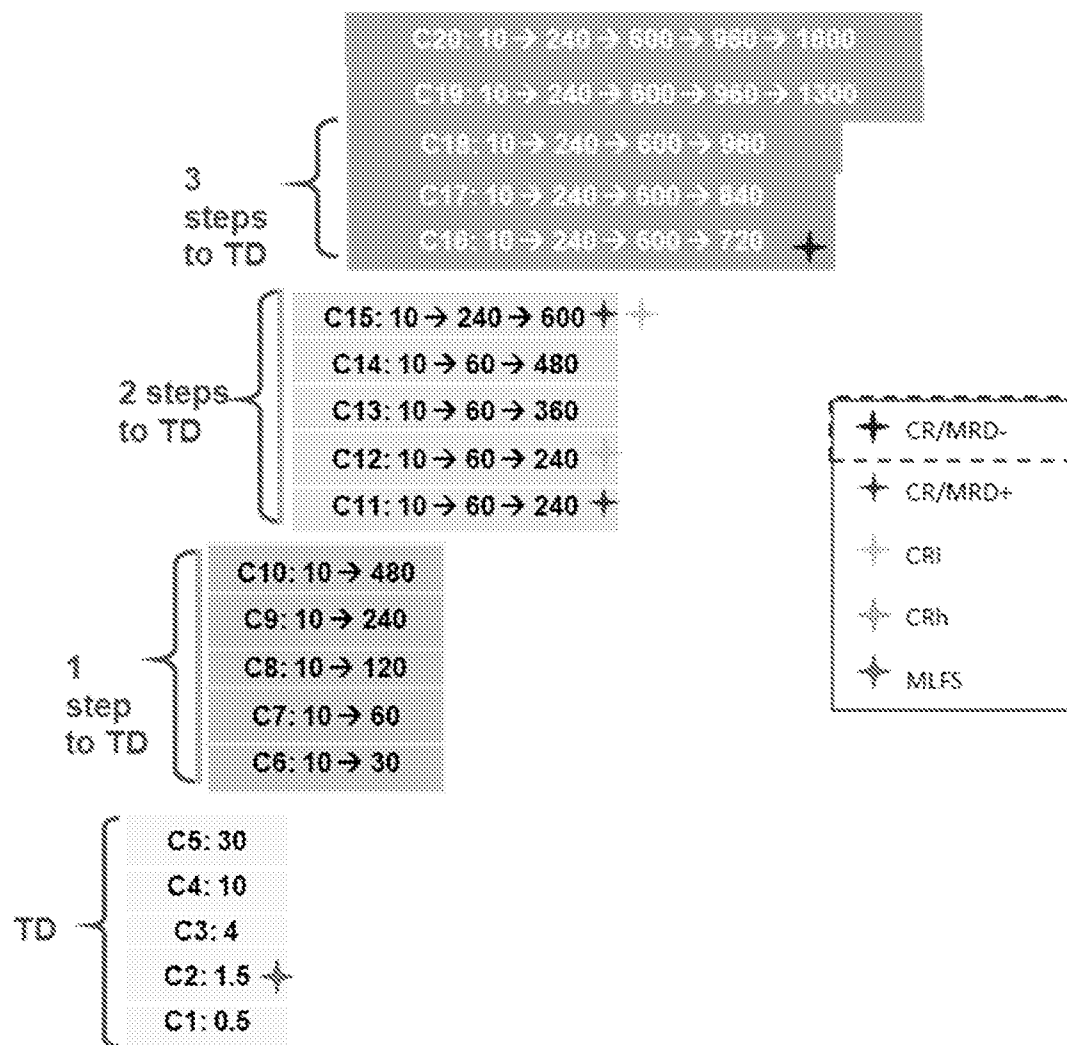
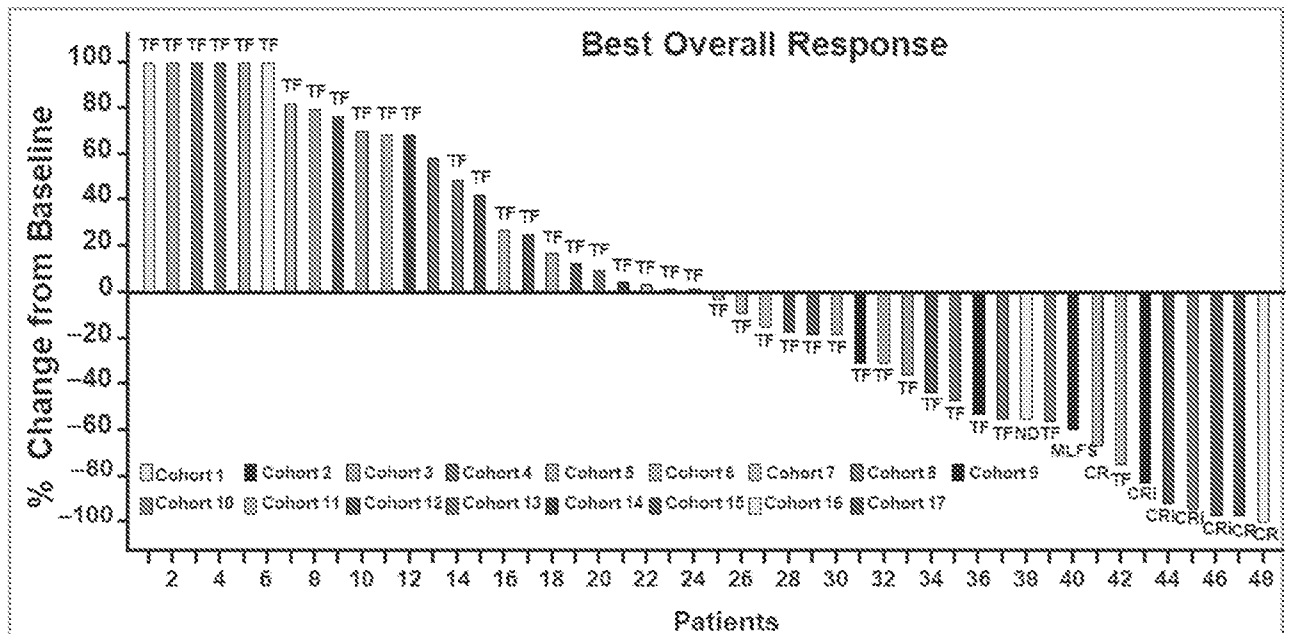


Fig. 2

(A)



(B)

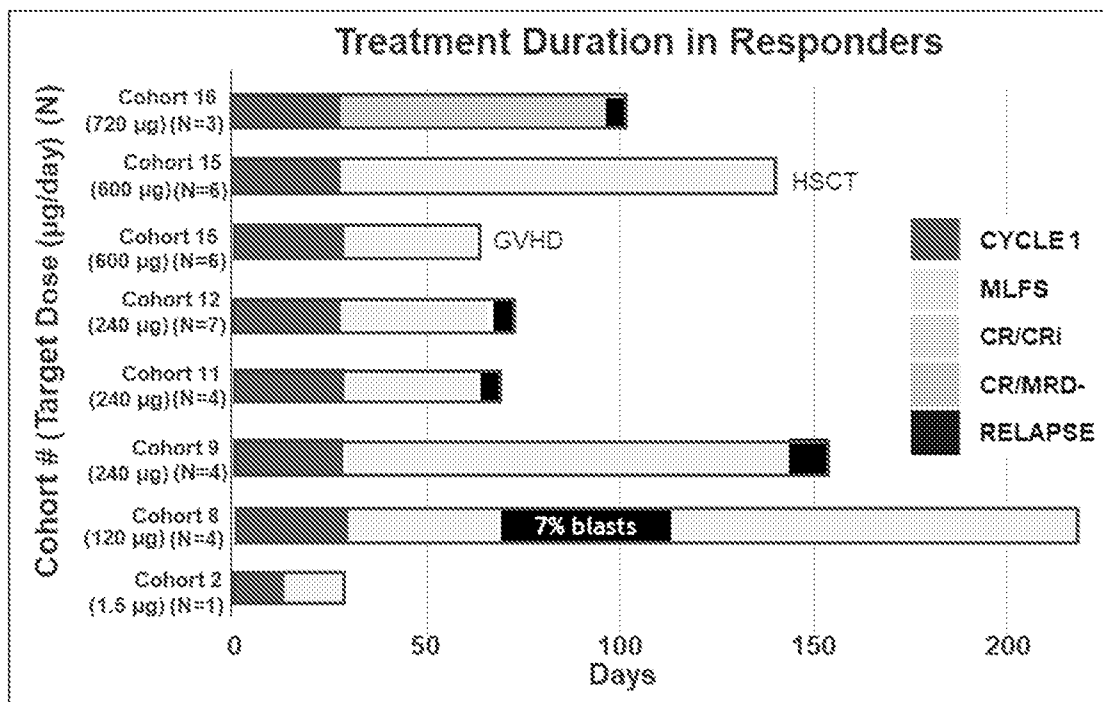
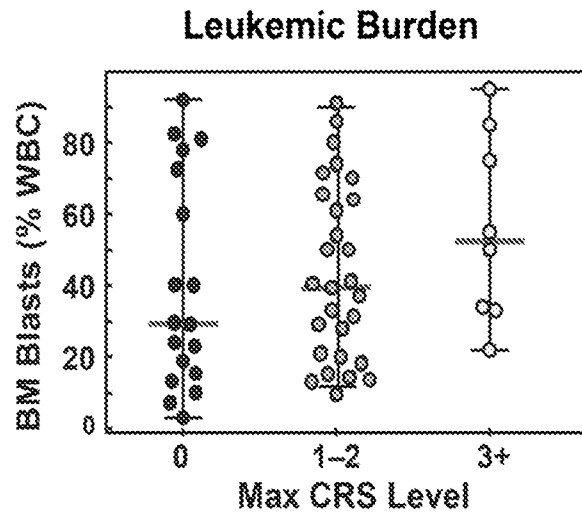
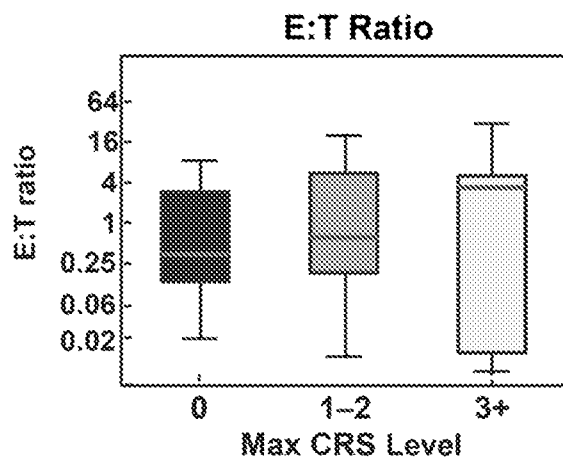


Fig. 3

(A)



(B)



(C)

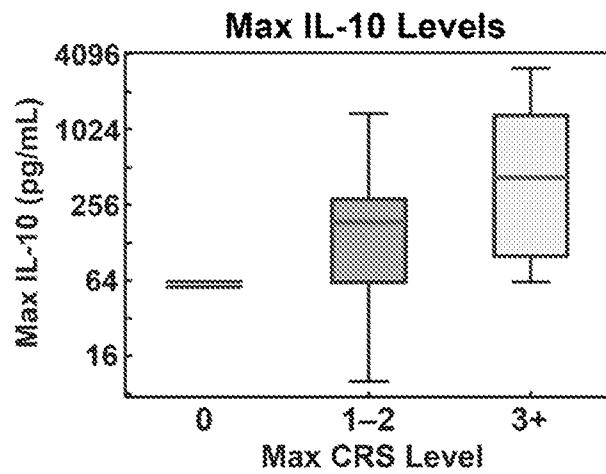


Fig. 4

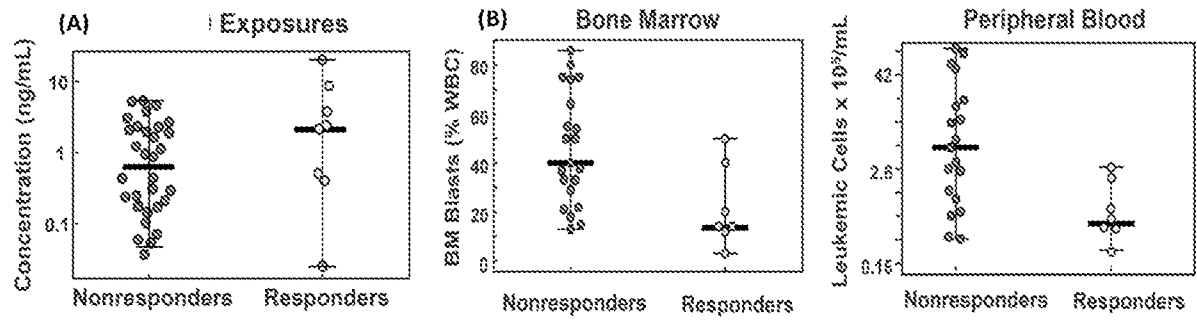
Fig 6. Correlation of CR/CRi response with AMG 330 exposures and leukemic burden

Fig. 5

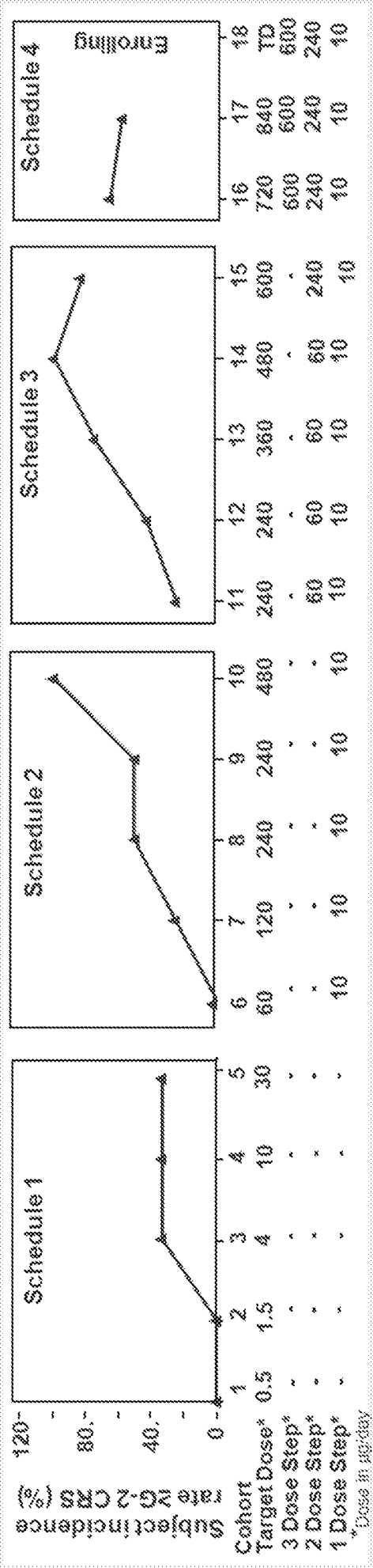
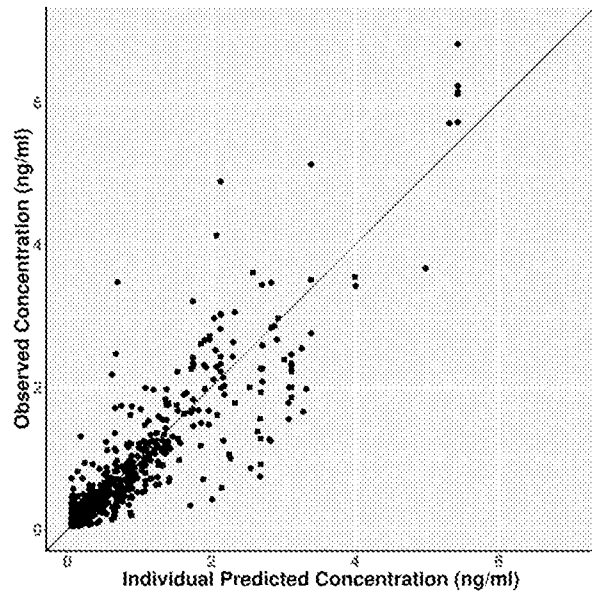


Fig. 6

(A)



(B)

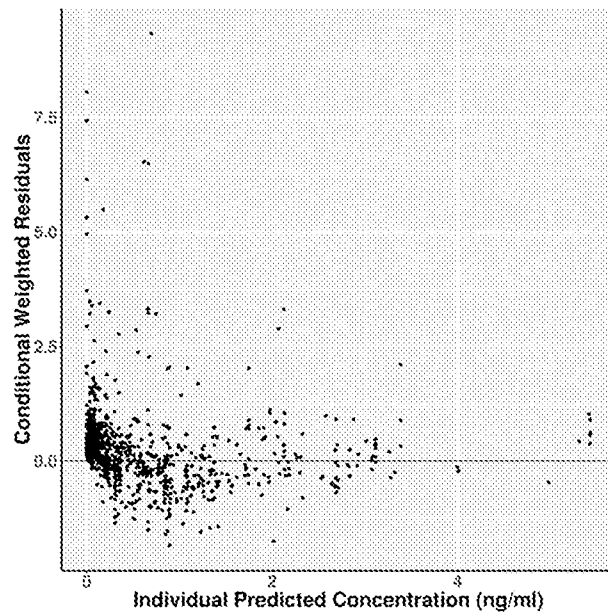
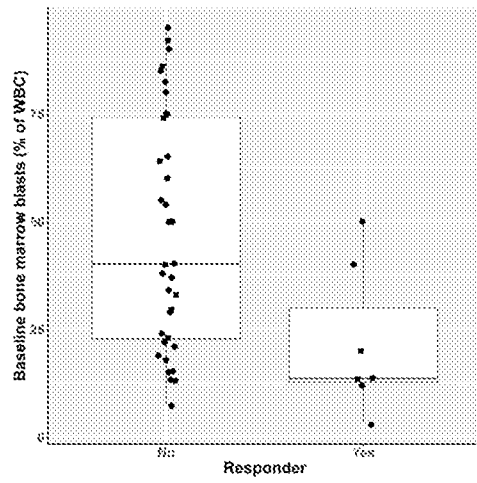
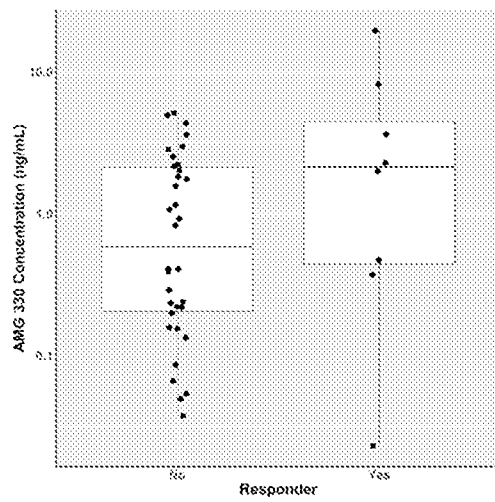


Fig. 7

(A)



(B)



(C)

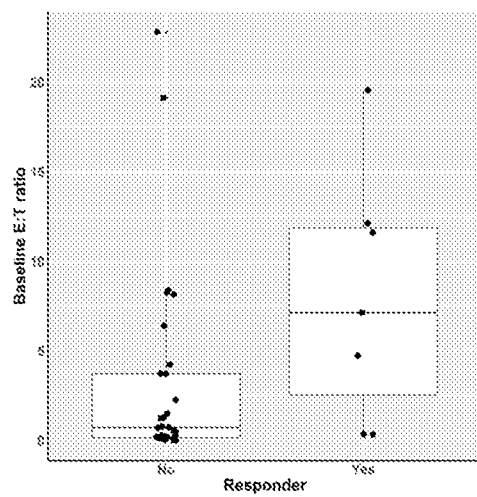
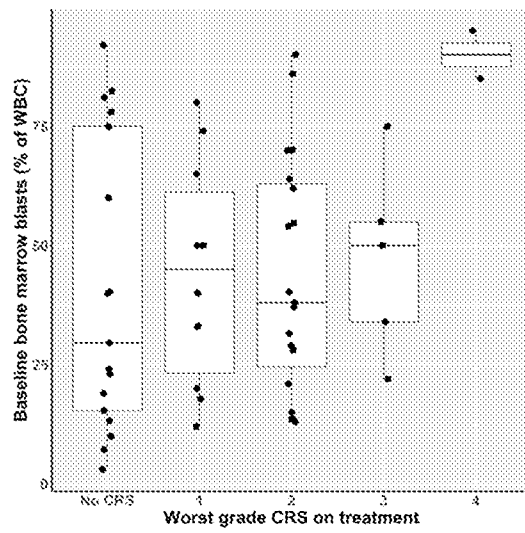
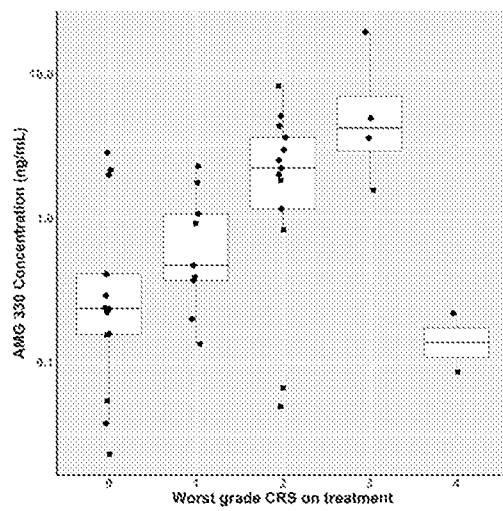


Fig. 8

(A)



(B)



(C)

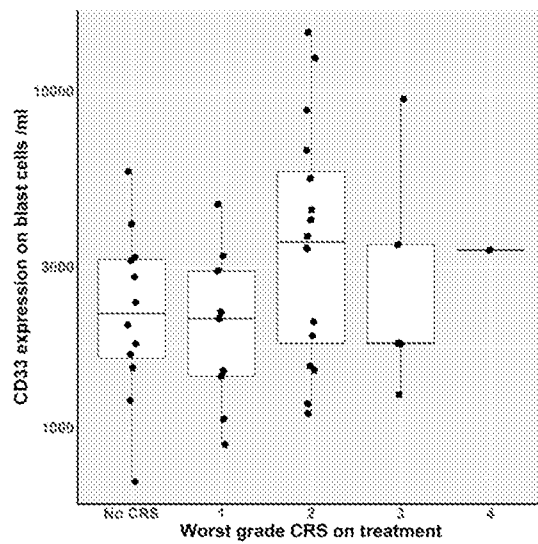
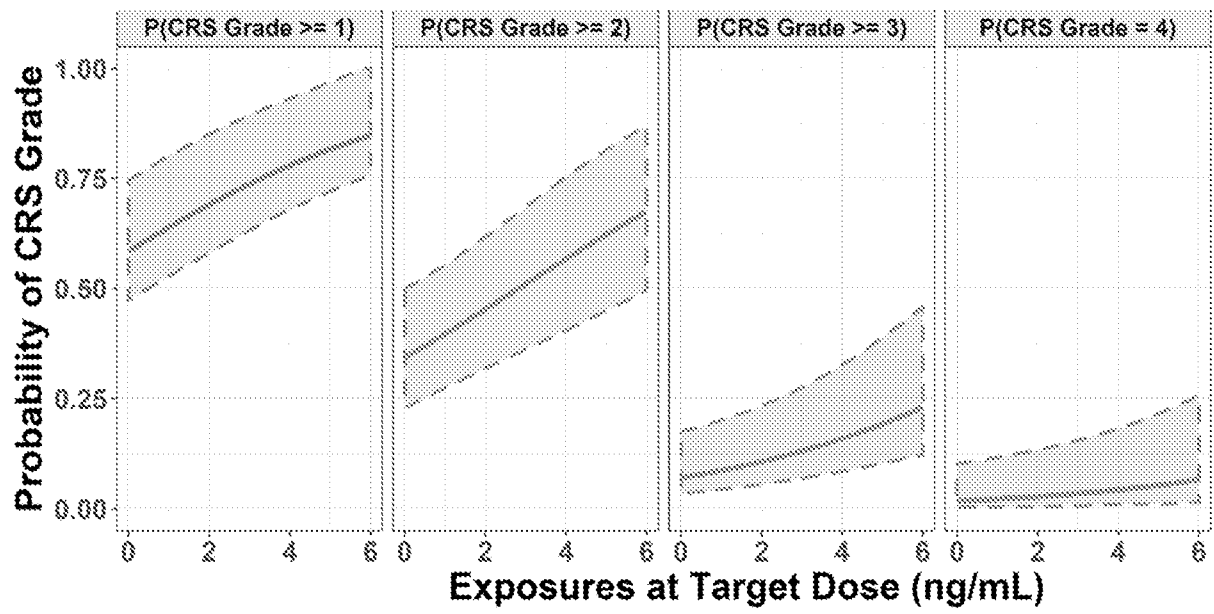


Fig. 9



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<130> 32243/55712

<150> US 63/032,302

<151> 2020-05-29

<150> US 63/044,833

<151> 2020-06-26

<160> 209

<170> PatentIn version 3.5

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<212> PRT

<213> Homo sapiens

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Val	Ser	Ile	Ser	Gly	Thr	Thr	Val	Ile	Leu	Thr	Cys	Pro	Gln	Tyr	Pro
			20					25					30		

Gly	Ser	Glu	Ile	Leu	Trp	Gln	His	Asn	Asp	Lys	Asn	Ile	Gly	Gly	Asp
		35					40					45			

Glu	Asp	Asp	Lys	Asn	Ile	Gly	Ser	Asp	Glu	Asp	His	Leu	Ser	Leu	Lys
	50					55					60				

Glu	Phe	Ser	Glu	Leu	Glu	Gln	Ser	Gly	Tyr	Tyr	Val	Cys	Tyr	Pro	Arg
65					70				75						80

Gly	Ser	Lys	Pro	Glu	Asp	Ala	Asn	Phe	Tyr	Leu	Tyr	Leu	Arg	Ala	Arg
			85						90					95	

Val	Cys	Glu	Asn	Cys	Met	Glu	Met	Asp
			100					105

<210> 2
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<212> PRT
<213> Homo sapiens

<400> 2

Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
20 25

<210> 3
<211> 96
<212> PRT
<213> Callithrix jacchus

<400> 3

Gln Asp Gly Asn Glu Glu Met Gly Asp Thr Thr Gln Asn Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr Cys Pro Arg Tyr Asp
20 25 30

Gly His Glu Ile Lys Trp Leu Val Asn Ser Gln Asn Lys Glu Gly His
35 40 45

Glu Asp His Leu Leu Leu Glu Asp Phe Ser Glu Met Glu Gln Ser Gly
50 55 60

Tyr Tyr Ala Cys Leu Ser Lys Glu Thr Pro Ala Glu Glu Ala Ser His
65 70 75 80

Tyr Leu Tyr Leu Lys Ala Arg Val Cys Glu Asn Cys Val Glu Val Asp
85 90 95

<210> 4
<211> 27
<212> PRT
<213> Callithrix jacchus

<400> 4

Gln Asp Gly Asn Glu Glu Met Gly Asp Thr Thr Gln Asn Pro Tyr Lys

1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr
20 25

<210> 5
<211> 96
<212> PRT
<213> Saguinus oedipus

<400> 5

Gln Asp Gly Asn Glu Glu Met Gly Asp Thr Thr Gln Asn Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr Cys Pro Arg Tyr Asp
20 25 30

Gly His Glu Ile Lys Trp Leu Val Asn Ser Gln Asn Lys Glu Gly His
35 40 45

Glu Asp His Leu Leu Leu Glu Asp Phe Ser Glu Met Glu Gln Ser Gly
50 55 60

Tyr Tyr Ala Cys Leu Ser Lys Glu Thr Pro Ala Glu Glu Ala Ser His
65 70 75 80

Tyr Leu Tyr Leu Lys Ala Arg Val Cys Glu Asn Cys Val Glu Val Asp
85 90 95

<210> 6
<211> 27
<212> PRT
<213> Saguinus oedipus

<400> 6

Gln Asp Gly Asn Glu Glu Met Gly Asp Thr Thr Gln Asn Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr
20 25

<210> 7

<211> 96
<212> PRT
<213> Saimiri sciureus

<400> 7

Gln Asp Gly Asn Glu Glu Ile Gly Asp Thr Thr Gln Asn Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr Cys Pro Arg Tyr Asp
20 25 30

Gly Gln Glu Ile Lys Trp Leu Val Asn Asp Gln Asn Lys Glu Gly His
35 40 45

Glu Asp His Leu Leu Leu Glu Asp Phe Ser Glu Met Glu Gln Ser Gly
50 55 60

Tyr Tyr Ala Cys Leu Ser Lys Glu Thr Pro Thr Glu Glu Ala Ser His
65 70 75 80

Tyr Leu Tyr Leu Lys Ala Arg Val Cys Glu Asn Cys Val Glu Val Asp
85 90 95

<210> 8
<211> 27
<212> PRT
<213> Saimiri sciureus

<400> 8

Gln Asp Gly Asn Glu Glu Ile Gly Asp Thr Thr Gln Asn Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Thr Leu Thr
20 25

<210> 9
<211> 122
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 9

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Ser Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Ile Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 10
<211> 5
<212> PRT
<213> Artificial

<220>
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<400> 10

Asn Tyr Gly Met Asn
1 5

<210> 11
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 11

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 12

<211> 13

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 12

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 13

<211> 113

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 13

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 14
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 14

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 15
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 15

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 16
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 16

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 17
<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 17

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Ser Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Ile Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
245 250

<210> 18
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 18

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1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Ser Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Ile Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

290

295

300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 19
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 19

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Ser Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Ile Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val

385 390 395 400
 Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415
 Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
 420 425 430
 Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445
 Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460
 Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480
 Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495
 Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

 <210> 20
 <211> 505
 <212> PRT
 <213> Artificial

 <220>
 <223> Synthetic peptide

 <400> 20

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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

 Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe

50

55

60

Lys Gly Arg Val Thr Met Ser Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Ile Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe

485

490

495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 21
<211> 122
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<213> Artificial

<220>
<223> Synthetic peptide

<400> 21

Gln 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 Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 22
<211> 5
<212> PRT
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<220>

<223> Synthetic peptide

<400> 22

Asn Tyr Gly Met Asn
1 5

<210> 23

<211> 17

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 23

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 24

<211> 13

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 24

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 25

<211> 113

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 25

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 26
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 26

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 27
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 27

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 28

<211> 9

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 28

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 29

<211> 250

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 29

Gln 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 Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
245 250

<210> 30
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 30

Gln 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 Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr

225		230		235		240									
Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser
				245					250					255	
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
			260					265					270		
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr
		275					280					285			
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	290					295					300				
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
305					310					315					320
Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
				325					330					335	
Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
			340					345					350		
Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp
		355					360					365			
Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
	370					375					380				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val
385					390					395					400
Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu
				405					410					415	
Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn
			420					425					430		
Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
		435					440					445			

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 31
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 31

Gln 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 Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr

325

330

335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 32

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 32

Gln 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 Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn

420

425

430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 33
 <211> 122
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 33

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys

85

90

95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 34
 <211> 5
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 34

Asn Tyr Gly Met Asn
 1 5

<210> 35
 <211> 17
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 35

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
 1 5 10 15

Gly

<210> 36
 <211> 13
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 36

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr

1

5

10

<210> 37
 <211> 113
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 37

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
 20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
 85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
 100 105 110

Lys

<210> 38
 <211> 17
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 38

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 39
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 39

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 40
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 40

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 41
<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 41

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys

245

250

<210> 42
 <211> 505
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 42

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu

165

170

175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 43
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 43

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

260

265

270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 44
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 44

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp

355

360

365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 45
<211> 122
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 45

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr

20

25

30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 46
 <211> 5
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 46

Asn Tyr Gly Met Asn
 1 5

<210> 47
 <211> 17
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 47

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
 1 5 10 15

Gly

<210> 48
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 48

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 49
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 49

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile

100

105

110

Lys

<210> 50

<211> 17

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 50

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 51

<211> 7

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 51

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 52

<211> 9

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 52

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 53

<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 53

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser

180

185

190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 245 250

<210> 54
 <211> 505
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 54

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp

100	105	110																			
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly						
		115					120					125									
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser						
	130					135					140										
Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys						
145					150					155					160						
Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu						
				165					170					175							
Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser						
			180					185					190								
Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser						
		195					200					205									
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu						
	210					215					220										
Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr						
225					230					235					240						
Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser						
				245					250					255							
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly						
			260					265					270								
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr						
		275					280					285									
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val						
						295					300										
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp						
305					310					315					320						

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 55
<211> 505
<212> PRT
<213> Artificial

<220>

<223> Synthetic peptide

<400> 55

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser

195

200

205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 56

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 56

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

290

295

300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 57
<211> 122
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 57

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 58
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 58

Asn Tyr Gly Met Asn

1

5

<210> 59
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 59

Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe Gln
1 5 10 15

Gly

<210> 60
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 60

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 61
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 61

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

Ser Thr Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln

35

40

45

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
 85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Asp Ile
 100 105 110

Lys

<210> 62
 <211> 17
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 62

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 1 5 10 15

Ala

<210> 63
 <211> 6
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 63

Trp Ala Ser Thr Arg Glu
 1 5

<210> 64
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 64

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 65
<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 65

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly

115

120

125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

Pro Asp Ser Met Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys
 245 250

<210> 66
 <211> 505
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 66

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35

40

45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
 50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

Pro Asp Ser Met Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp

465											470											475											480
Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe																		
				485					490					495																			
Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu																									
			500				505																										
<210> 67																																	
<211> 505																																	
<212> PRT																																	
<213> Artificial																																	
<220>																																	
<223> Synthetic peptide																																	
<400> 67																																	
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu																		
1				5				10				15																					
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr																		
			20				25				30																						
Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met																		
		35			40			45																									
Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Thr	Asn	Tyr	Ala	Asp	Lys	Phe																		
		50				55				60																							
Gln	Gly	Arg	Val	Thr	Phe	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr																		
65					70					75					80																		
Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys																		
				85					90					95																			
Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp																		
			100				105				110																						
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly																		
		115				120				125																							
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser																		

130

135

140

Pro Asp Ser Met Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 68

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 68

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Met Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr

225		230		235		240									
Phe	Gly	Gln	Gly	Thr	Arg	Leu	Asp	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser
				245					250					255	
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
			260					265					270		
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr
		275					280					285			
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	290					295					300				
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
305					310					315					320
Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
				325					330					335	
Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
			340					345					350		
Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp
		355					360					365			
Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
	370					375					380				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val
385					390					395					400
Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu
				405					410					415	
Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn
			420					425					430		
Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
		435					440					445			

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 69

<211> 122

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 69

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 70
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 70

Asn Tyr Gly Met Asn
1 5

<210> 71
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 71

Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe Gln
1 5 10 15

Gly

<210> 72
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 72

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 73
<211> 113
<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 73

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 74

<211> 17

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 74

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 75
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 75

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 76
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 76

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 77
<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 77

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe

50

55

60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ser Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
245 250

<210> 78

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 78

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ser Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu

405

410

415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 79

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 79

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
 50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr

65		70		75		80									
Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85				90					95		
Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp
			100					105					110		
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser
	130					135					140				
Pro	Asp	Ser	Leu	Ser	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys
145					150					155					160
Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Thr	Asn	Lys	Asn	Ser	Leu
			165						170					175	
Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser
			180					185					190		
Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser
	195						200					205			
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu
	210					215					220				
Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr
225					230					235					240
Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser
				245					250					255	
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
			260					265					270		
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr
		275					280					285			

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu

500

505

<210> 80
 <211> 505
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 80

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
 50 55 60

Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

Pro Asp Ser Leu Ser Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu

165

170

175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 81
<211> 122
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 81

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 82
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 82

Asn Tyr Gly Met Asn
1 5

<210> 83
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 83

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe Gln
1 5 10 15

Gly

<210> 84

<211> 13
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 84

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
1 5 10

<210> 85
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 85

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

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
20 25 30

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

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Gly Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 86
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 86

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Asn Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 87
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 87

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 88
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 88

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 89
<211> 250
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 89

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Asn Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Gly Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
245 250

<210> 90
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 90

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Asn Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Gly Leu Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr

340

345

350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 91
 <211> 505
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic peptide

<400> 91

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

1		5		10		15													
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr				
		20						25					30						
Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met				
		35					40					45							
Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Lys	Phe				
	50					55					60								
Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr				
65					70					75					80				
Met	Glu	Ile	Arg	Asn	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
				85					90					95					
Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp				
			100					105					110						
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly				
		115					120					125							
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser				
	130					135					140								
Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys				
145					150					155					160				
Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Asn	Asn	Lys	Asn	Ser	Leu				
			165						170					175					
Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser				
			180					185					190						
Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser				
	195						200					205							
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Gly	Leu	Gln	Pro	Glu				
	210					215					220								

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly

435

440

445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

<210> 92

<211> 505

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 92

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp

100	105	110																			
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly						
		115					120					125									
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser						
	130					135					140										
Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys						
145					150					155					160						
Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Asn	Asn	Lys	Asn	Ser	Leu						
				165					170					175							
Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser						
			180					185					190								
Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser						
		195					200					205									
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Gly	Leu	Gln	Pro	Glu						
	210					215					220										
Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr						
225					230					235					240						
Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser						
				245					250					255							
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly						
			260					265					270								
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr						
		275					280					285									
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val						
	290					295					300										
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp						
305					310					315					320						

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 93
<211> 122
<212> PRT
<213> Artificial

<220>

<223> Synthetic peptide

<400> 93

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 94

<211> 5

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 94

Asn Tyr Gly Met Asn
1 5

<210> 95

<211> 17

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 95

Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 96

<211> 13

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 96

Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr
1				5					10			

<210> 97

<211> 113

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 97

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

Glu	Arg	Thr	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser
			20					25					30		

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

Pro	Pro	Lys	Leu	Leu	Leu	Ser	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile
	50					55					60				

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asp Ser Pro Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 98
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 98

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
1 5 10 15

Ala

<210> 99
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 99

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 100
<211> 9
<212> PRT
<213> Artificial

<220>

<223> Synthetic peptide

<400> 100

Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

<210> 101

<211> 250

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 101

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Pro Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
245 250

<210> 102
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 102

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Pro Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr

275

280

285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
 385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
 405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
 420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 103
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 103

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Pro Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly

370

375

380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

<210> 104
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 104

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35

40

45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Pro Gln Pro Glu
 210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
 225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
 245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp

465 470 475 480
 Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495
 Gly Gly Gly Thr Lys Leu Thr Val Leu
 500 505

 <210> 105
 <211> 505
 <212> PRT
 <213> Artificial

 <220>
 <223> Synthetic peptide

 <400> 105
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 100 105 110
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val

130

135

140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
180 185 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Gln
245 250 255

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
260 265 270

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
275 280 285

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
290 295 300

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
305 310 315 320

Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr Leu
325 330 335

Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
340 345 350

Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp Gly
355 360 365

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380

Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro
385 390 395 400

Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys Lys
405 410 415

Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu Ala
420 425 430

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser Trp
435 440 445

Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly
450 455 460

Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu Asp
465 470 475 480

Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr Phe
485 490 495

Gly Gln Gly Thr Arg Leu Glu Ile Lys
500 505

<210> 106
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 106

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
180 185 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe

225		230		235		240
Gly Gly Gly Thr	Lys 245	Leu Thr Val	Leu Ser 250	Gly Gly Gly Gly	Ser 255	Gln
Val Gln Leu	Val 260	Gln Ser Gly	Ala 265	Glu Val Lys Lys	Pro Gly 270	Ala Ser
Val Lys Val	Ser 275	Cys Lys Ala	Ser 280	Gly Tyr Thr Phe	Thr 285	Asn Tyr Gly
Met Asn Trp	Val 290	Lys Gln Ala	Pro 295	Gly Gln Gly	Leu Lys 300	Trp Met Gly
Trp Ile Asn	Thr 305	Tyr Thr Gly	Glu 310	Pro Thr Tyr	Ala 315	Asp Asp Phe Lys 320
Gly Arg Val	Thr 325	Met Thr Ser	Asp 330	Thr Ser Thr	Ala 335	Tyr Leu
Glu Leu His	Asn 340	Leu Arg Ser	Asp 345	Asp Thr Ala	Val Tyr 350	Tyr Cys Ala
Arg Trp Ser	Trp 355	Ser Asp Gly	Tyr 360	Tyr Val Tyr	Phe 365	Asp Tyr Trp Gly
Gln Gly Thr	Thr 370	Val Thr Val	Ser 375	Ser Gly Gly	Gly 380	Gly Ser Gly Gly
Gly Gly Ser	Gly 385	Gly Gly Gly	Ser 390	Asp Ile Val	Met 395	Thr Gln Ser Pro 400
Asp Ser Leu	Thr 405	Val Ser Leu	Gly 410	Glu Arg Thr	Thr 415	Ile Asn Cys Lys
Ser Ser Gln	Ser 420	Val Leu Asp	Ser 425	Ser Lys Asn	Lys 430	Asn Ser Leu Ala
Trp Tyr Gln	Gln 435	Lys Pro Gly	Gln 440	Pro Pro Lys	Leu 445	Leu Leu Ser Trp

Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly
450 455 460

Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu Asp
465 470 475 480

Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr Phe
485 490 495

Gly Gln Gly Thr Arg Leu Glu Ile Lys
500 505

<210> 107
<211> 505
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 107

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
180 185 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Gln
245 250 255

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
260 265 270

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
275 280 285

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
290 295 300

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
305 310 315 320

Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr Leu

325

330

335

Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
 340 345 350

Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp Gly
 355 360 365

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 370 375 380

Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro
 385 390 395 400

Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys Lys
 405 410 415

Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu Ala
 420 425 430

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser Trp
 435 440 445

Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly
 450 455 460

Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu Asp
 465 470 475 480

Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr Phe
 485 490 495

Gly Gln Gly Thr Arg Leu Glu Ile Lys
 500 505

<210> 108

<211> 511

<212> PRT

<213> Artificial

<220>

<223> Synthetic peptide

<400> 108

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Pro Gln Pro Glu
210 215 220

Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
275 280 285

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
290 295 300

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
305 310 315 320

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn

420

425

430

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
 435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
 450 455 460

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
 465 470 475 480

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
 485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu His His His His His His
 500 505 510

<210> 109
 <211> 585
 <212> PRT
 <213> Homo sapiens

<400> 109

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
 1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
 20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 110
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 110

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Gly Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Ala Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 111
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 111

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 112
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 112

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 113
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 113

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Gly Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 114
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 114

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 115
<211> 585
<212> PRT
<213> Artificial

<220>

<223> Synthetic peptide

<400> 115

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 116
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 116

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 117
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 117

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 118
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 118

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 119
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 119

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 120
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 120

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Gly Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Ala Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 121
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 121

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 122
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 122

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 123
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 123

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Gly Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 124
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 124

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 125
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 125

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 126
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 126

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 127
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 127

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 128

<211> 585

<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 128

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 129
<211> 585
<212> PRT
<213> Artificial

<220>

<223> Synthetic peptide

<400> 129

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 130
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 130

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Gly Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Ala Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 131
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 131

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 132
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 132

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 133
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 133

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Gly Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 134
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 134

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 135
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 135

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 136
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 136

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro His Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 137
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 137

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Lys Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 138
<211> 585
<212> PRT
<213> Artificial

<220>
<223> Synthetic peptide

<400> 138

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Asp Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
580 585

<210> 139
<211> 4
<212> PRT
<213> Artificial

<220>
<223> Peptide linker

<400> 139

Gly Gly Gly Gly
1

<210> 140
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Peptide linker

<400> 140

Gly Gly Gly Gly Ser
1 5

<210> 141
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Peptide linker

<400> 141

Gly Gly Gly Gly Gln
1 5

<210> 142
<211> 6
<212> PRT
<213> Artificial

<220>

<223> Peptide linker

<400> 142

Pro Gly Gly Gly Gly Ser
1 5

<210> 143

<211> 6

<212> PRT

<213> Artificial

<220>

<223> Peptide linker

<400> 143

Pro Gly Gly Asp Gly Ser
1 5

<210> 144

<211> 6

<212> PRT

<213> Artificial

<220>

<223> Peptide linker

<400> 144

Ser Gly Gly Gly Gly Ser
1 5

<210> 145

<211> 9

<212> PRT

<213> Artificial

<220>

<223> Peptide linker

<400> 145

Gly Gly Gly Gly Ser Gly Gly Gly Ser
1 5

<210> 146

<211> 10

<212> PRT
<213> Artificial

<220>
<223> Peptide linker

<400> 146

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 147
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Peptide linker

<400> 147

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 148
<211> 14
<212> PRT
<213> Artificial

<220>
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<400> 148

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Val Lys Ser

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Gly Tyr Ala Met Asn
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Val Lys Glu

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Ser Tyr Ala Met Asn
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Val Lys Gly

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Val Lys Asp

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20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
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Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
20 25 30

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
85 90 95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105