Clinical Assessment of M-protein response in Multiple Myeloma

Background

Multiple myeloma (MM) is a hematological cancer that involves the clonal expansion of malignant plasma cells. MM is the most common malignant plasma cell tumor and the second most common hematologic malignancy in the United States. The US age-adjusted incidence rate is 5.5 cases per 100,000 and the annual incidence reaches approximately 6 to 7 per 100,000 in the United Kingdom.

Plasma cells produce immunoglobulins (also called gammaglobulins), which consist of a heavy chain (IgG, IgA, IgM, IgD or IgE) and a light chain (kappa or lambda) linked together. One plasma cell produces one type of immunoglobulin (for instance, IgA kappa or IgG kappa). Normally the body contains a variety of different plasma cells ("polyclonal"), thus the immunoglobulins in the serum also represent a broad spectrum of different formats and specificities (polyclonal). In the case of multiple myeloma, the malignant cells are copies of only one or only a few distinct plasma cell(s) and the Immunoglobulin secreted by this or these cell(s) is considered as monoclonal.

This monoclonal immunoglobulin is called M-protein or paraprotein and may also consist of a heavy chain (most often IgG or IgA but also IgM, IgD or IgE) and a light chain (kappa or lambda) or truncated forms of these immunoglobulins. The increase of M protein in the serum is used to identify B-cell malignancies, such as, MM.

Multiple staging systems are currently used for the diagnosis and monitoring of responses in multiple myeloma: a) the Durie and Salmon Staging System, b) the International Staging System (ISS), and the International Myeloma Working Group (IMWG). The Durie and Salmon staging system involves features that assess tumour cells mass, elevated serum immunoglobulin (Ig)G levels, end-organ damage, and osteolytic bone lesions. The ISS places more emphasis on the disease burden based on β2-microglobulin levels and serum albumin levels. The IMWG takes into account both molecular and cytogenetic abnormalities, specifically, M-protein reduction over time is one of the most important factors and is used to assess the progress of disease and treatment success.

Protein manifestations characteristic of multiple myeloma include increases of monoclonal (M)-protein concentrations (IgG, IgA, IgA, IgD), light chain concentrations (including kappa [κ] and lambda[λ]), abnormal β2-microglobulin, serum albumin, creatinine, and hemoglobin levels, and findings of bone marrow plasma cells (of greater than or equal to 5%). Measurement of the protein manifestations (such as M protein) produced by patients can be achieved by numerous methods. Tests that measure M-proteins are the 24-hour urine collection test, urine protein electrophoresis (UPEP), serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE), and serum free light chain (sFLC) assay.

CD38 is an example of an antigen expressed on malignant plasma cells, and other lymphocytes, and therefore, represents a therapeutic target in the treatment of multiple myeloma and other gammopathies. Functions ascribed to CD38 include both receptor mediation in adhesion and signaling events and (ecto-) enzymatic activity. As an ectoenzyme, CD38 uses NAD+ as substrate for the formation of cyclic ADP-ribose (cADPR) and ADPR, but also of nicotinamide and nicotinic acid-adenine dinucleotide phosphate (NAADP). cADPR and NAADP have been shown to act as second messengers for Ca2+ mobilization. By converting NAD+ to cADPR, CD38 regulates the extracellular NAD+ concentration and hence cell survival by modulation of NAD-induced cell death (NCID). In addition to signaling via Ca2+, CD38 signaling occurs via cross-talk with antigen-receptor complexes on T and B cells or other types of receptor complexes, e.g. MHC molecules, and is in this way involved in several cellular responses, but also in switching and secretion of IgG.

Antibodies specific for CD38 are in development for the treatment of multiple myeloma. Antibodies specific for CD38 are described in WO1999/62526 (Mayo Foundation); WO200206347 (Crucell Holland); US2002164788 (Jonathan Ellis) which is incorporated by reference in its entirety; WO2005/103083 (MorphoSys AG), US serial no. 10/588,568, which is incorporated by reference in its entirety, WO2006/125640 (MorphoSys AG), US serial no. 11/920,830, which is incorporated by reference in its entirety, and WO2007/042309 (MorphoSys AG), US serial no. 12/089,806, which is incorporated by reference in its entirety; WO2006099875 (Genmab), US serial no. 11/886,932, which is incorporated by reference in its entirety; WO2011154453A1 (Genmab), US serial no. 13/702,857, which is incorporated by reference in its entirety; WO08/047242 (Sanofi-Aventis), US serial no. 12/441,466, which is incorporated by reference in its entirety; WO2015066450 (Sanofi), US serial no. 14/529,719, which is incorporated by reference in its entirety; WO2012092616A1, and WO2012092612A1 (Takeda), US serial nos. 13/341,860, and 13/977,207 both of which are incorporated by reference in their entirety, and WO2014178820A1 (Teva).

Anti-CD38 antibody treatment in MM patients can result in partial or complete clearance of the M-protein produced by multiple myeloma cells. Serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) are both essential assays used for identifying and immunotyping monoclonal proteins in patients with multiple myeloma. Recent studies demonstrated that certain therapeutic antibodies in development for the treatment of multiple myeloma are readily detected on serum IFE and can interfere with the detection and monitoring of M protein levels (McCudden et al., Clinical Chemistry, 56:12; 1897-1904 (2010), see also Genzen et al., British Journal of Haematology (2011) 155(1) 123-125). McCudden et al. observed that an incubation with Siltuximab (an anti-IL-6 antibody) with anti-drug antibodies shifted the drug electrophoretic pattern such that the therapeutic antibody Siltuximab could be differentiated from endogenous M-protein. Janssen

also recently published the development of a clinical assay to mitigate Daratumumab's interference with M-protein in IFE using a similar approach, which utilized a mouse anti-daratumumab antibody ideally labeled with biotin or Alexa-fluor tags to shift the complex on IFE. Axel, et al., Development of a Clinical Assay to Mitigate Daratumumab, an IgG1k Monoclonal Antibody, Interference with Serum Immunofixation and Clinical Assessement of M-protein Response in Multiple Myeloma Poster Presented at the 105th Annual Meeting of the American Association for Cancer Research (AACR), April 5-9, 2014, San Diego, California, USA; see also van de Donk et al., Monoclonal antibodies targeting CD38 in hematological malignancies and beyond, Immunological Reviews, 270:95-112 (2016).

These approaches, however, are not sufficient for every therapeutic antibody. Novel mitigation strategies are needed that are specific for each therapeutic antibody to avoid this potential interference with SPEP and IFE to ensure valid clinical response descriptions that meet the International Myeloma Working Group (IMWG) criteria.

Summary of the Invention

Applicant herein discloses an anti-idiotypic antibody to MOR202, which when fused to human albumin, shifted the antibody in IFE thus mitigating any potential interference of MOR202 with the M-protein based clinical assessment.

The anti-idiotypic antibody, albumin fusion will be integrated into the clinical development design of MOR202 in order to enhance the clinical assessment of the M-protein response.

An aspect is an anti-idiotypic antibody to MOR202. In an aspect the anti-idiotypic antibody is fused to human albumin. In embodiments the anti-idiotypic antibody comprises a variable heavy chain comprising

an HCDR1 of the amino acid sequence YSFSNYWIS (SEQ ID NO: 18),

an HCDR2 of the amino acid sequence WMGIIDPASSKTRYSPSFQG (SEQ ID NO: 19),

an HCDR3 of the amino acid sequence SRGAGMDY (SEQ ID NO: 20), and

a variable light chain comprising

an LCDR1 of the amino acid sequence TGSSSNIGAGYDVH (SEQ ID NO: 21),

an LCDR2 of the amino acid sequence LLIYADNNRPS (SEQ ID NO: 22),

an LCDR3 of the amino acid sequence GSYDESSNSM (SEQ ID NO: 23).

In an embodiment, the anti-idiotypic antibody is a human antibody.

In embodiments, the anti-idiotypic antibody fusion comprises the heavy chain of amino acid sequence

QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGIIDPASSKTRY
SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGAGMDYWGQGTLVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSDIDAHKSEVAHRFKDLGEENFKAL
VLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETY
GEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARR
HPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKF
GERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICEN
QDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGM
FLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQN
CELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDY
LSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADIC
TLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLV
AASQAALGLVNSRHHHHHH (SEQ ID NO: 24).

In embodiments, the anti-idiotypic antibody fusion comprises the light chain of amino acid sequence

DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNNRPSGVPD
RFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSL
TPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 25)

An aspect is a method of evaluating a blood sample obtained from a patient undergoing treatment for multiple myeloma or other gammopathy comprising

a) obtaining a blood sample from said patient,

b) incubating the blood sample with an anti-idiotypic antibody,

c) performing immunofixation electrophoresis (IFE), and

d) reporting the results of the IFE.

In embodiments, the patient is undergoing treatment with MOR202.

In embodiments, the sample is evaluated for total M-protein levels.

An aspect, is a nucleic acid encoding the exemplified anti-idiotypic antibody or exemplified anti-idiotypic antibody albumin fusion.

Description of Drawings

Figure 1 shows the amino acid sequence of MOR202.

Figure 2A-B show the amino acid sequence of MOR09292 (an anti-idiotypic antibody to MOR202) human albumin fusion protein.

Figure 3 shows a typical normal pattern for the distribution of proteins as determined by serum protein electrophoresis.

Figure 4 shows a serum protein electrophoresis distribution of proteins having a homogeneous spike-like peak in a focal region of the gamma-globulin zone common to disorders known as monoclonal gammopathies. This peak represents a single clone of plasma cells that produce a homogeneous M protein.

Figure 5 shows an example of a gel after serum immunofixation electrophoresis of a healthy donor. Lane ELP = total protein staining; Lane G = anti-IgG staining; Lane A = anti-IgA staining; Lane M = anti-IgM staining; Lane K = anti-kappa staining; Lane L = anti-lambda staining.

Figure 6 shows a serum immunofixation electrophoresis of a sample from a drug naïve healthy donor (A and B) and a drug naïve MM patient (C and D). The samples were tested either unspiked or spiked with MOR202 at different concentrations. (Lane 1 = no MOR202 added; Lane 2 = MOR202 added at 200 µg/mL; Lane 3 = MOR202 added at 400 µg/mL; Lane 4 = MOR202 added at 800 µg/mL; Lane 5 = MOR202 added at 1200 µg/mL). Bands encircled with a dotted line become only visible after MOR202 spike and represent the respective molecule. Bands marked with an arrow represent endogenous M-protein.

Figure 7 shows a serum immunofixation electrophoresis of MOR202 +/- preincubation of MOR0929 IgG1 and MOR09292 IgM in saline. MOR202 at a constant concentration of 1200 µg/mL (A and B) or 560 µg/mL (C) in saline was pre-incubated with its idiotypic antibody MOR09292 in different formats and the prepared samples were analyzed via IFE. A) + B): MOR202 and MOR09292 IgG1 (using anti-IgG staining (A) and anti-lambda staining (B) (Lane 1 = MOR202; Lane 2 = MOR09292 IgG1 2400 µg/mL; Lane 3 = MOR202 + MOR09292 IgG1 at 600 µg/mL; Lane 4 = MOR202 + MOR09292 IgG1 at 1200 µg/mL; Lane 5 = MOR202 + MOR09292 IgG1 at 2400 µg/mL). C): MOR202 and MOR09292 IgM using anti-IgG staining (Lane 2-4), anti-lambda staining (Lane 5-7) and anti-IgM staining (Lane 8-

10) (Lane 2/5/8 = MOR202; Lane 3/6/9 = MOR09292 IgM 560 µg/mL; Lane 4/7/10 = MOR202 + MOR09292 IgM 560 µg/mL; Lane 1 = human serum from a healthy donor stained for total protein to evaluate general background signaling in serum samples).

Figure 8 shows a serum immunofixation electrophoresis of MOR202 +/- preincubation of MOR09292-human albumin fusion (MOR09292-hAlb) in saline and human serum. MOR202 at a constant concentration of 1200 µg/mL in saline (Lane 2 - 3) or serum (Lane 4 – 13) was pre-incubated with or without its idiotypic antibody MOR09292-hAlb at different ratios and the prepared samples were analyzed via IFE using anti-IgG staining (Lane 2-8) or anti-lambda staining (Lane 9-13). (Lane 2 = MOR202; Lane 3 = MOR202 + MOR09292-hAlb at 2400 µg/mL; Lane 4 = MOR202; Lane 5 = MOR202 + MOR09292-hAlb at 1200 µg/mL; Lane 6 = MOR202 + MOR09292-hAlb at 1800 µg/mL; Lane 7 = MOR202 + MOR09292-hAlb at 2400 µg/mL; Lane 8 = MOR202 + MOR09292-hAlb at 3600 µg/mL;Lane 9 = MOR202; Lane 10 = MOR202 + MOR09292-hAlb at 1200 µg/mL; Lane 11 = MOR202 + MOR09292-hAlb at 1800 µg/mL; Lane 12 = MOR202 + MOR09292-hAlb at 2400 µg/mL; Lane 13 = MOR202 + MOR09292-hAlb at 3600 µg/mL; Lane 1 = human serum from a healthy donor stained for total protein to evaluate general background signaling).

Detailed Description of the Invention

Definitions

The term “anti-idiotypic” describes a protein or peptide that binds to the variable regions of an antibody. The anti-idiotypic protein can be an antibody. For example, antibody MOR09292 binds to the variable regions of MOR202.

The term "antibody" includes antibody fragments. Antibodies include monoclonal antibodies of any isotype, e.g., IgG, IgM, IgA, IgD and IgE. An IgG antibody is comprised of two identical heavy chains and two identical light chains that are joined by disulfide bonds. The heavy and light chains of antibodies contain a constant region and a variable region. Each variable region contains three segments called "complementarity-determining regions" ("CDRs") or "hypervariable regions", which are primarily responsible for binding an epitope of an antigen. They are referred to as CDR1, CDR2, and CDR3, numbered sequentially from the N-terminus. The more highly conserved portions of the variable regions outside of the CDRs are called the "framework regions". An “antibody fragment” means an Fv, scFv, dsFv, Fab, Fab' F(ab')2 fragment, or other fragment, which contains at least one variable heavy or variable light chain, each containing CDRs and framework regions.

The "CDRs" herein are defined by either Chothia et al.., Kabat et al. or by an internal numbering convention. See Chothia C, Lesk AM. (1987) Canonical structures for the hypervariable regions of immunoglobulins. J Mol Biol., 196(4):901-17, which is incorporated by reference in its entirety. See Kabat E.A, Wu T.T., Perry H.M., Gottesman K.S. and Foeller C. (1991). Sequences of Proteins of Immunological Interest. 5th edit., NIH Publication no. 91-3242, US Dept. of Health and Human Services, Washington, DC, which is incorporated by reference in its entirety.

"VH" refers to the variable region of an immunoglobulin heavy chain of an antibody, or antibody fragment. "VL" refers to the variable region of the immunoglobulin light chain of an antibody, or antibody fragment.

"Fc region" means the constant region of an antibody, which in humans may be of the IgG1, 2, 3, 4 subclass or others. The sequences of human Fc regions are available at IMGT, Human IGH C-REGIONs, http://www.imgt.org/ligmdb/ (retrieved on 22 February 2016).

A "human antibody" or "human antibody fragment", as used herein, includes antibodies and antibody fragments having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such sequences.

"Specific" describes a protein that recognizes an antigen and is able to discriminate between such antigen and one or more reference antigen(s). This ability can be identified by a standard ELISA assay. Typically, determination of specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

"Evaluating a blood sample" means evaluating the blood or portion of the blood sample most relevant for the method. Currently immunofixation electrophoresis is done on the serum component of blood. If, however, in the future a different blood component is evaluated, the invention is directed to a method evaluating that blood component. Blood components include, for example, plasma, serum, cells, e.g. red and white cells, and platelets. Plasma includes proteins, such as globulins, and clotting factors, and salts, sugars, fat, hormones and vitamins.

Gammopathies are conditions in which serum immunoglobulin levels are greatly increased. They can be classified either as polyclonal (increases in all major immunoglobulin classes) or monoclonal (increases in a single homogeneous immunoglobulin).

Polyclonal gammopathies result from chronic stimulation of the immune system. They can therefore be caused by chronic pyodermas; chronic viral, bacterial, or fungal infections; granulomatous bacterial diseases; abscesses; chronic parasitic infections; chronic rickettsial diseases, such as tropical canine pancytopenia; chronic immunologic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and myositis; or by some neoplasia. In many cases, there is no obvious predisposing cause. In some animals, the gammopathy may

initially be monoclonal because of the predominance of a single immunoglobulin class (usually IgG).

Monoclonal gammopathies are characterized by the production of large amounts of a single immunoglobulin protein. Monoclonal gammopathies are either benign (ie, associated with no underlying disease), or more commonly, associated with immunoglobulin-secreting tumors. Tumors that secrete monoclonal antibodies originate from plasma cells (myelomas). Myelomas can secrete intact proteins of any immunoglobulin class or immunoglobulin subunits or fragments (light chains or heavy chains). Examples of Monoclonal gammopathies include: Hodgkin's disease; variants of multiple myeloma, e.g., Solitary plasmacytoma of bone, Extramedullary plasmacytoma, Plasma cell leukemia, and Non-secretory myeloma, Lymphoproliferative disorders, such as, Waldenström's macroglobulinemia, and Lymphoma; Heavy chain disease (γ, α, μ); and Amyloidosis.

The term "CD38" refers to the protein known as CD38, having the following synonyms: ADP-ribosyl cyclase 1, cADPr hydrolase 1, Cyclic ADP-ribose hydrolase 1, T10.

Human CD38 has the amino acid sequence of:

MANCEFSPVSGDKPCCRLSRRAQLCLGVSILVLILVVVLAVVVPRWRQQWSGPGTT KRFPETVLARCVKYTEIHPEMRHVDCQSVWDAFKGAFISKHPCNITEEDYQPLMKLGTQTV PCNKILLWSRIKDLAHQFTQVQRDMFTLEDTLLGYLADDLTWCGEFNTSKINYQSCPDWRK DCSNNPVSVFWKTVSRRFAEAACDVVHVMLNGSRSKIFDKNSTFGSVEVHNLQPEKVQTL EAWVIHGGREDSRDLCQDPTIKELESIISKRNIQFSCKNIYRPDKFLQCVKNPEDSSCTSEI (SEQ ID NO: 1).

"MOR202" an anti-CD38 antibody whose amino acid sequence is provided in Figure 1. "MOR202" and "MOR03087" are used as synonyms to describe the antibody shown in Figure 1.

The DNA sequence encoding the MOR202 Variable Heavy Domain is:

CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCC TGCGTCTGAGCTGCGCGGCCTCCGGATTTACCTTTTCTTCTTATTATATGAATTGGGTGC GCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGGTATCTCTGGTGATCCTAGCAA TACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGATAATTCGAAAAA CACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA (SEQ ID NO: 2)

The DNA sequence encoding the MOR202 Variable Light Domain is:

GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGC GCGTATCTCGTGTAGCGGCGATAATCTTCGTCATTATTATGTTTATTGGTACCAGCAGAA ACCCGGGCAGGCGCCAGTTCTTGTGATTTATGGTGATTCTAAGCGTCCCTCAGGCATCC CGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCATTAGCGGCAC

TCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTATACTGGTGGTGCTTCTCTTG
TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG (SEQ ID NO: 3)

MOR202 is disclosed in WO2007/042309, US serial no. 12/089,806, which is incorporated by reference in its entirety. In US serial no. 12/089,806, MOR202 is the antibody comprising the variable heavy chain corresponding to SEQ ID NO: 21 and variable light chain corresponding to SEQ ID NO: 51, and the nucleic acids encoding MOR202 are variable heavy chain SEQ ID NO: 6 and variable light chain SEQ ID NO:36.

MOR202 is currently being tested in a phase 1/2a trial in patients with relapsed/refractory myeloma. The study is evaluating the safety and preliminary efficacy of MOR202 as monotherapy and in combination with pomalidomide and lenalidomide plus dexamethasone.

The antibody, MOR09292, is an anti-idiotypic antibody to MOR202 and is encoded by the nucleic acid sequence:

VH:

CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAA
TTAGCTGCAAAGGTTCCGGATATTCCTTTTCTAATTATTGGATTTCTTGGGTGCGCCAGA
TGCCTGGGAAGGGTCTCGAGTGGATGGGCATTATCGATCCGGCTTCTAGCAAGACCCG
TTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAAAAGCATTAGCACCG
CGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT
TCTCGTGGTGCTGGTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 4)

VL:

GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCA
TCTCGTGTACGGGCAGCAGCAGCAACATTGGTGCTGGTTATGATGTGCATTGGTACCAG
CAGTTGCCCGGGACGGCGCCGAAACTTCTGATTTATGCTGATAATAATCGTCCCTCAGG
CGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCGAGCCTTGCGATTACG
GGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCGGTTCTTATGATGAGTCTTCTAA
TTCTATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG (SEQ ID NO: 5)

DNA encoding MOR09292-VH-CH1_HSA_6His (no leader sequence) (MOR09292-hAlb heavy chain):

CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAA
TTAGCTGCAAAGGTTCCGGATATTCCTTTTCTAATTATTGGATTTCTTGGGTGCGCCAGA
TGCCTGGGAAGGGTCTCGAGTGGATGGGCATTATCGATCCGGCTTCTAGCAAGACCCG
TTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAAAAGCATTAGCACCG
CGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT
TCTCGTGGTGCTGGTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAG
CCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG

GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT
GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA
CCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAG
AGTTGAGCCCAAATCTGATATCGACGCCCACAAGAGCGAGGTGGCCCACCGGTTTAAG
GACCTGGGCGAGGAAAACTTCAAGGCCCTGGTGCTGATCGCCTTCGCCCAGTACCTGC
AGCAGTGCCCCTTCGAGGACCACGTGAAGCTCGTGAACGAAGTGACCGAGTTCGCCAA
GACCTGCGTGGCCGATGAGAGCGCCGAGAACTGCGACAAGAGCCTGCACACCCTGTT
CGGCGACAAGCTGTGTACCGTGGCCACCCTGAGAGAAACCTACGGCGAGATGGCCGA
CTGCTGCGCCAAGCAGGAACCCGAGAGGAACGAGTGCTTCCTGCAGCACAAGGACGA
CAACCCCAACCTGCCCAGACTCGTGCGGCCCGAAGTGGACGTGATGTGCACCGCCTTC
CACGACAACGAGGAAACCTTCCTGAAGAAGTACCTGTACGAGATCGCCAGACGGCACC
CCTACTTCTACGCCCCCGAGCTGCTGTTCTTCGCCAAGCGGTACAAGGCCGCCTTCAC
CGAGTGTTGCCAGGCCGCCGATAAGGCCGCTTGCCTGCTGCCTAAGCTGGACGAGCT
GAGGGATGAGGGCAAGGCCAGCTCTGCCAAGCAGAGACTGAAGTGCGCCAGCCTGCA
GAAGTTCGGCGAGCGGGCCTTTAAAGCCTGGGCCGTGGCTAGACTGAGCCAGAGATTC
CCCAAGGCCGAGTTTGCCGAGGTGTCCAAGCTCGTGACCGACCTGACCAAGGTGCACA
CCGAGTGCTGTCACGGCGACCTGCTGGAATGCGCCGACGACAGAGCCGATCTGGCCA
AGTACATCTGCGAGAACCAGGACAGCATCAGCAGCAAGCTGAAAGAGTGCTGCGAGAA
GCCTCTGCTGGAAAAGAGCCACTGTATCGCCGAGGTGGAAAACGACGAGATGCCCGCC
GATCTGCCTTCTCTGGCCGCCGACTTCGTGGAAAGCAAGGACGTGTGCAAGAACTACG
CCGAGGCCAAGGATGTGTTCCTGGGCATGTTTCTGTATGAGTACGCCCGCAGACACCC
CGACTACAGCGTGGTGCTGCTGCTGAGACTGGCCAAAACCTACGAGACAACCCTGGAA
AAGTGCTGTGCCGCCGCTGACCCCCACGAGTGTTACGCCAAGGTGTTCGACGAGTTCA
AGCCACTGGTGGAAGAACCCCAGAACCTGATCAAGCAGAATTGCGAGCTGTTCGAGCA
GCTGGGCGAGTACAAGTTCCAGAACGCCCTGCTCGTGCGGTACACCAAGAAAGTGCCC
CAGGTGTCCACCCCCACCCTGGTGGAAGTGTCCCGGAACCTGGGCAAAGTGGGCAGC
AAGTGCTGCAAGCACCCTGAGGCCAAGAGAATGCCCTGCGCCGAGGACTACCTGTCTG
TGGTGCTGAACCAGCTGTGCGTGCTGCACGAGAAAACCCCCGTGTCCGACAGAGTGAC
CAAGTGCTGTACCGAGAGCCTCGTGAACAGACGGCCCTGCTTCAGCGCCCTGGAAGTG
GATGAGACATACGTGCCCAAAGAGTTCAACGCCGAGACATTCACCTTCCACGCCGACAT
CTGCACCCTGTCCGAGAAAGAGCGGCAGATCAAGAAACAGACCGCTCTGGTGGAACTC
GTGAAGCACAAGCCCAAGGCCACCAAAGAACAGCTGAAGGCCGTGATGGACGACTTCG
CCGCCTTTGTGGAAAAATGCTGCAAGGCCGATGACAAAGAGACATGCTTCGCCGAAGA
GGGCAAGAAACTGGTGGCCGCCTCTCAGGCTGCTCTGGGACTGGTTAACTCTAGACAC
CATCACCATCACCAT (SEQ ID NO: 26).

DNA encoding MOR09292-VL-lambda (no leader sequence) (MOR09292-hAlb light chain):

GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCA
TCTCGTGTACGGGCAGCAGCAGCAACATTGGTGCTGGTTATGATGTGCATTGGTACCAG
CAGTTGCCCGGGACGGCGCCGAAACTTCTGATTTATGCTGATAATAATCGTCCCTCAGG
CGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCGAGCCTTGCGATTACG
GGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCGGTTCTTATGATGAGTCTTCTAA
TTCTATGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCC
CCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACAC
TGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGA
TAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC

AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAA GCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTA CAGAATGTTCA (SEQ ID NO: 27).

Human albumin has the following amino acid sequence (including the signal sequence):

MKWVTFISLLFLFSSAYSRGVFRRDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPF EDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP ERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLF FAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAV ARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLK ECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYAR RHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFE QLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVV LNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTL SEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLV AASQAALGL (SEQ ID NO: 6)

The International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma are as follows:

Response	*IMWG criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by

	≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,5 a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive Disease	Increase of ≥ 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)6 Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%7 Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as

	something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 mol/L or more]

Electrophoresis is a method of separating proteins based on their biochemical properties. Serum is placed on a specific medium, and a charge is applied. The net charge (positive or negative) and the size and shape of the protein commonly are used in differentiating various serum proteins.

Several subsets of serum protein electrophoresis are available. The names of these subsets are based on the method that is used to separate and differentiate the various serum components. In zone electrophoresis, for example, different protein subtypes which are placed in separate physical locations on a gel made from agar, cellulose, or other plant material. The proteins are stained, and their densities are calculated electronically to provide graphical data on the absolute and relative amounts of the various proteins. Further separation of protein subtypes is achieved by staining with an immunologically active agent, which results in immunofixation and/or immunofluorescence.

The pattern of serum protein electrophoresis results depends on the fractions of two major types of proteins: albumin and globulins. Albumin, the major protein component of serum, is produced by the liver under normal physiologic conditions. Globulins comprise a smaller fraction of the total serum protein content. The subsets of these proteins and their relative quantity are mostly the primary focus of the interpretation of serum protein electrophoresis.

Albumin, the largest peak observed in serum protein electrophoresis, is located closest to the positive electrode. The next five components (globulins) are labeled alpha1, alpha2, beta1, beta2, and gamma. The peaks for these components appear toward the negative electrode, with the gamma peak being closest to that electrode.

Figure 3 shows a typical normal pattern for the distribution of proteins as determined by serum protein electrophoresis.

The albumin band represents the largest protein component of human serum. The albumin level is decreased under circumstances in which there is less production of the protein by the liver or in which there is increased loss or degradation of this protein. Malnutrition, significant liver disease, renal loss (e.g., in nephrotic syndrome), hormone therapy, and pregnancy may account for a low albumin level. Burns also may result in a low albumin level. Levels of albumin are increased for example in patients with a relative reduction in serum water (e.g., dehydration).

Moving toward the negative portion of the gel (i.e., the negative electrode), the next peaks involve the alpha1 and alpha2 components. The alpha1-protein fraction is comprised of alpha1-antitrypsin, thyroid-binding globulin, and transcortin. Malignancy and acute inflammation (resulting from acute-phase reactants) can increase the alpha1-protein band. A decreased alpha1-protein band may occur because of alpha1-antitrypsin deficiency or decreased production of the globulin as a result of liver disease. Ceruloplasmin, alpha2-macroglobulin, and haptoglobin contribute to the alpha2-protein band. The alpha2 component is increased as an acute-phase reactant.

The beta fraction has two peaks labeled beta1 and beta2. Beta1 is composed mostly of transferrin, and beta2 contains beta-lipoprotein. IgA, IgM, and sometimes IgG, along with complement proteins, also can be identified in the beta fraction.

Much of the clinical interest is focused on the gamma region of the serum protein spectrum because immunoglobulins migrate to this region. It should be noted that immunoglobulins often can be found throughout the electrophoretic spectrum. C-reactive protein (CRP) is located in the area between the beta and gamma components.

Although many conditions can cause an increase in the gamma region, several disease states cause a homogeneous spike-like peak in a focal region of the gamma-globulin zone (Figure 4). These so-called “monoclonal gammopathies” constitute a group of disorders that are characterized by proliferation of a single or very few clone(s) of plasma cells each producing a homogeneous M protein, such as MM.

Immunofixation electrophoresis (IFE) is a technique that allows a protein to be anchored after electrophoresis by forming an insoluble complex with a monoclonal or polyclonal detection antibody reagent added. It is performed in the following four steps:

1) Separation of proteins by electrophoresis.
2) Immunofixation (immunoprecipitation) of the electrophoresed proteins - the appropriate electrophoretic migration tracks are overlaid with individual antisera. The antisera diffuse into the gel and precipitate the corresponding antigens when present. The proteins in the reference track are fixed with a fixative agent.

3) The unprecipitated, soluble proteins are removed from the gel by blotting and washing. Precipitation of the antigen-antibody complex is trapped within the gel matrix.
4) The precipitated proteins are visualized by staining (e.g. acid violet stain).

To detect and identify the suspected monoclonal component, the sample is simultaneously electrophoresed in several tracks in parallel (see Figure). After the electrophoresis, the ELP track serves as a reference (containing the total protein fixation) providing a complete electrophoretic pattern of the serum sample's proteins. The remaining tracks allow characterization of the monoclonal component from its reaction, or lack of, usually with antisera against human IgG, IgA and IgM heavy chains, and against free and bound kappa and lambda light chains. Other anti-sera (e.g. anti-IgD, etc.) are also possible. The immunofixed bands are then compared with the suspect bands in the reference pattern - the corresponding band should have the same migration position.

Figure 5 shows an example of a gel after serum immunofixation electrophoresis. A serum sample from a healthy donor was separated via gel electrophoresis 6 times in parallel whereas each lane was stained with a different reagent. After staining non complexed proteins were removed by blotting and washing. Lane ELP = total protein staining; Lane G = anti-IgG staining; Lane A = anti-IgA staining; Lane M = anti-IgM staining; Lane K = anti-kappa staining; Lane L = anti-lambda staining

Working Examples

Materials and Method IFE

Immunofixation was performed using Sebia's semi-automated agarose gel electrophoresis systems Hydrasys and Hydrasys2 and using Sebia's Maxikit Hydragel 9IF. The kits are designed for detection of Immunoglobulins in human serum by immunofixation electrophoresis and contain all needed reagents and materials i.e. agarose gels, buffered strips, diluent, acid violet stain, antisera (e.g. IgG, IgA, IgM, Kappa and Lambda), fixative solution and applicators.

In order to evaluate the impact of MOR202 on M-protein analysis, serum samples from healthy donors and MM patients were spiked with MOR202 at different concentrations and incubated for at least 15 min at room temperature (RT). Afterwards the samples were analyzed either spiked or unspiked with MOR202 using IFE and gels were stained with anti-IgG or anti-lambda antisera (both staining reagents are able to bind to MOR202). In both stainings MOR202 was detected already at the lowest concertation tested at 200 µg/mL suggesting IFE interference at or even below this drug serum level (Figure 6).

In order to differentiate between MOR202 related assay signals in IFE vs. endogenous M-protein spikes a method was tested pre-incubating a MOR202 containing sample with an MOR202 specific anti-idiotypic antibody (MOR09292). The objective of this method was to demonstrate that the MOR202 related IFE assay signal can be migrated comparing samples with or without pre-incubation of MOR09292 and therefore clearly identifying MOR202 related assay signals. For evaluating if the migration distance is large enough to be detected samples containing MOR202 in saline were prepared and pre-incubated with or without MOR09292. The anti-idiotypic antibody was produced and tested in an IgG1as well as in IgM antibody format. Test samples were prepared at a constant concentration of 1200 µg/mL MOR202 and pre-incubated without or with various concentrations of the two MOR09292 variants for 60 min. Afterwards, the samples were analyzed and IFE gels were stained with anti-IgG or anti-lambda antisera. The results were that no acceptable migration distance of the MOR202 drug spike suitable for clinical sample assessment could be observed when the test samples were pre-incubated with the various forms of MOR09292 (Figure 7). The surprising finding demonstrate that even when increasing the size of the drug/antibody complex compared to the drug antibody alone approximately 3-fold (MOR09292-IgG) or 7-fold (MOR09292-IgM) the change in molecular weight of the complex does not lead to a relevant shift in assay signals (i.e. changed migration pattern).

Based on these results a further variant of the idiotypic antibody was generated genetically fusing MOR09292-Fab fragment to human albumin (MOR09292-hAlb). The new variant increased the size of the drug-antibody complex compared to the drug antibody alone up to 2.6-fold. More important the incorporation of human serum albumin lowered the overall net-charge of the complex. Sample preparation and testing was performed as described above. As a result a clear shift of the MOR202/MOR09292-huAlb complex could be observed when compared to the assay signal of MOR202 alone, see Figure 8.

The modified IFE assay using MOR09292-hAlb for sample pre-treatment was incorporated into the clinical development of MOR202. Therefore, the assay was validated at the central laboratory responsible for M-protein analysis and introduced into the testing strategy as "Immunofixation (IFE) Reflex Assay". In order to discriminate between MOR202 and M-protein related signals the IFE Reflex Assay was performed in addition to the regular Serum IFE and Serum Protein Electrophoresis (SPE) for example when the following 2 conditions are fulfilled:

a) reduction in serum M-protein levels at least ≥ 40% compared to the M-protein concentration pre-treatment, and
b) at least one of the M-protein spikes left is identical to the characteristics of the drug antibody MOR202 (i.e. IgG / lambda positive staining in IFE).

Case study for the use and results of the IFE Reflex Assay within clinical study MOR202C101

Within the first clinical study treating multiple myeloma patients with MOR202 (MOR202C101) the IFE Reflex Assay was applied for patient 19007 after a reduction of ≥ 86% in serum M-protein levels was observed. For this patient, the M-protein spike identified was described by IFE as IgG / lambda positive, the same molecular properties as known for MOR202. Performing SPE a remaining concentration of potential M-proteins at 1 or 2 g/L was detected on Jan 12, 2106 and Feb 19, 2016. The IFE Reflex Assay could demonstrate that this assay signal was solely caused by MOR202 interference and therefore not M-protein related (see summary laboratory results Table 1). The results demonstrate how the newly established IFE Reflex Assay could clearly discriminate between M-protein and therefore disease related assay signals versus MOR202 treatment related assay signals.

Table 1 IFE Reflex Assay result negative

Sample reception date	19 Feb 2016	11 JAN 2016	14 DEC 2015	16 NOV 2015	26 OCT 2015	21 SEP 2015	07 SEP 2015	24 AUG 2015	10 AUG 2015	27 JUL 2015	17 JUL 2015
Visit	CYCLE 8 / DAY 1	CYCLE 7 / DAY 1	CYCLE 6 / DAY 1	CYCLE 5 / DAY 1	CYCLE 4 / DAY 8	CYCLE 3 / DAY 1	CYCLE 2 / DAY 15	CYCLE 2 / DAY 1	CYCLE 1 / DAY 15	CYCLE 1 / DAY 1	SCREENING
SERUM PROTEIN ELECTROPHORESIS											
Monoclonal peak 1 [Abs]	2	1	2	2	2	3	4	6	9	16	15
Unit	g/L	g/L	g/L	g/L	g/L	g/L	g/L	g/L	g/L	g/L	g/L
SERUM PROTEIN IMMUNOFIXATION											
Monoclonal peak 1	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l	IgG/l
Immunofix. Reflex Assay											
Monoclonal peak 1	Negative	Negative	Positive								

Table 1: Case study for the clinical use of the modified IFE assay applying a MOR09292-hAlb sample pre-treatment step – summary laboratory report patient 19007

Before starting treatment with MOR202 patient 19007 was tested positive for serum M-protein (16 g/L for sample received July 27, 2016 - positive staining for IgG / lambda in IFE). After a ≥ 86% reduction in serum M-protein levels was observed (14-Dec 2015) the IFE Reflex assay was performed in addition to IFE and SPE. On January 12, 2016 and February 19, 2016 it was shown that the remaining M-protein concentration of 1 or 2 g/L, respectively,

was only caused by MOR202 assay interference (i.e. Immunofixation Reflex Assay result "Negative" for M-proteins).

Embodiments

An aspect is an anti-idiotypic antibody fused to albumin. In an embodiment, albumin is human albumin having the amino acid sequence of SEQ ID NO: 6. In an embodiment, the human albumin is a fragment of human albumin or partial sequence of human albumin.

In an embodiment, albumin is a functional fragment of albumin. In another embodiment, human albumin is a functional fragment of human albumin. In this context the term "functional fragment" of albumin or human albumin refers to albumin which is a fragment or a variant of native albumin or human albumin, but which still is functional active in a sense that it is still able to fulfill the physiological role of albumin.

An embodiment, is an anti-idiotypic antibody that is specific for an antibody having a variable heavy domain comprising the amino acid sequence QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGISGDPSNTY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS (SEQ ID NO: 7), and

a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRPSGIPERFS GSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLGQ (SEQ ID NO: 8). An aspect, is an anti-idiotypic antibody that is specific for an antibody having a variable heavy domain comprising the amino acid sequence QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGISGDPSNTY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS (SEQ ID NO: 7), and

a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRPSGIPERFS GSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLGQ (SEQ ID NO: 8). In an embodiment the anti-idiotypic antibody is fused to albumin. In an embodiment, albumin is human albumin having the amino acid sequence of SEQ ID NO: 6. In an embodiment, the human albumin is a fragment of human albumin or partial sequence of human albumin. In an

embodiment, the human albumin is a functional fragment of human albumin or partial sequence of human albumin.

In embodiments, the anti-idiotypic antibody comprises a variable heavy chain comprising

an HCDR1 of amino acid sequence YSFSNYWIS (SEQ ID NO: 18),

an HCDR2 of amino acid sequence WMGIIDPASSKTRYSPSFQG (SEQ ID NO: 19),

an HCDR3 of amino acid sequence SRGAGMDY (SEQ ID NO: 20), and

a variable light chain comprising

an LCDR1 of amino acid sequence TGSSSNIGAGYDVH (SEQ ID NO: 21),

an LCDR2 of amino acid sequence LLIYADNNRPS (SEQ ID NO: 22),

an LCDR3 of amino acid sequence GSYDESSNSM (SEQ ID NO: 23).

In an embodiment, the anti-idiotypic antibody is a human antibody.

In embodiments, the anti-idiotypic antibody comprises the variable heavy chain of amino acid sequence

QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGIIDP
ASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGAGMDY
WGQGTLVTVSS (SEQ ID NO: 16), and

the variable light chain of amino acid sequence

DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN
RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL
TVLGQ (SEQ ID NO: 17).

In embodiments, the anti-idiotypic antibody albumin fusion comprises the heavy chain amino acid sequence

QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGII
DPASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGA
GMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKRVEPKSDIDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPF
EDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA
DCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL
YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKA
SSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVH
TECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLL
RLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLG
EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAE

DYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEF
NAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFV
EKCCKADDKETCFAEEGKKLVAASQAALGLVNSRHHHHHH (SEQ ID NO:
24).

In embodiments, the anti-idiotypic antibody albumin fusion comprises the light chain amino acid sequence

DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN
RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL
TVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE
CS (SEQ ID NO: 25)

An aspect is a method of evaluating a blood sample obtained from a patient undergoing treatment for multiple myeloma or other gammopathy comprising

e) obtaining a blood sample from said patient,
f) incubating the blood sample with an anti-idiotypic antibody,
g) performing immunofixation electrophoresis (IFE), and
h) reporting the results of the IFE.

In embodiments of the method, the patient is undergoing treatment with the antibody having a variable heavy domain comprising the amino acid sequence QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGISGDPSNTY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS (SEQ ID NO: 7), and

a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRPSGIPERFS GSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLGQ (SEQ ID NO: 8).

In an embodiment of the method, the anti-idiotypic antibody is fused to albumin. In an embodiment of the method, albumin is human albumin having the amino acid sequence of SEQ ID NO: 6. In an embodiment of the method, the human albumin is a fragment of human albumin or partial sequence of human albumin.

The exemplified anti-idiotypic antibody MOR09292 is specific for MOR202. The anti-idiotypic antibody to MOR202, when fused to human albumin, shifted the antibody in IFE thus mitigating any potential interference of MOR202 with the M-protein based clinical assessment. It is expected that the fusion of other anti-idiotypic antibody that our specific for other antibodies that are used for therapy in multiple myeloma or other gammopathy would

have a similar result. Meaning that other anti-idiotypic antibody albumin fusions would be useful in shifting the antibody in IFE thus mitigating any potential interference of that antibody with the M-protein based clinical assessment.

In embodiments of the method, the anti-idiotypic antibody comprises a variable heavy chain comprising

an HCDR1 of amino acid sequence YSFSNYWIS (SEQ ID NO: 18),

an HCDR2 of amino acid sequence WMGIIDPASSKTRYSPSFQG (SEQ ID NO: 19),

an HCDR3 of amino acid sequence SRGAGMDY (SEQ ID NO: 20), and

a variable light chain comprising

an LCDR1 of amino acid sequence TGSSSNIGAGYDVH (SEQ ID NO: 21),

an LCDR2 of amino acid sequence LLIYADNNRPS (SEQ ID NO: 22),

an LCDR3 of amino acid sequence GSYDESSNSM (SEQ ID NO: 23).

In embodiments of the method, the anti-idiotypic antibody is a human antibody.

In embodiments of the method, the anti-idiotypic antibody comprises the variable heavy chain of amino acid sequence

QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGIIDP
ASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGAGMDY
WGQGTLVTVSS (SEQ ID NO: 16), and

the variable light chain of amino acid sequence

DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN
RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL
TVLGQ (SEQ ID NO: 17).

In embodiments of the method, the anti-idiotypic antibody albumin fusion comprises the heavy chain amino acid sequence

QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGII
DPASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGA
GMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKRVEPKSDIDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPF
EDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA
DCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL
YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKA
SSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVH
TECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN

DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLL
RLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLG
EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAE
DYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEF
NAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFV
EKCCKADDKETCFAEEGKKLVAASQAALGLVNSRHHHHHH (SEQ ID NO:
24).

In embodiments of the method, the anti-idiotypic antibody albumin fusion comprises the light chain amino acid sequence

DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN
RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL
TVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE
CS (SEQ ID NO: 25)

In embodiments of the method, the sample is obtained from a patient undergoing treatment for multiple myeloma or other gammopathy. In further embodiments, the gammopathy is a monoclonal gammopathy. In further embodiments, the monoclonal gammopathies include: Hodgkin's disease; variants of multiple myeloma, e.g., Solitary plasmacytoma of bone, Extramedullary plasmacytoma, Plasma cell leukemia, and Non-secretory myeloma, Lymphoproliferative disorders, such as, Waldenström's macroglobulinemia, and Lymphoma; Heavy chain disease (γ, α, μ); and Amyloidosis.

In embodiments of the method, the sample is evaluated for total M-protein levels.

An aspect, is a nucleic acid encoding the exemplified anti-idiotypic antibody or anti-idiotypic antibody albumin fusion. In an embodiment, the anti-idiotypic antibody is MOR09292. In an embodiment the anti-idiotypic antibody is encoded by nucleic acid sequences encoding the amino acid sequences shown in Figures 2A-B.

In an embodiment the anti-idiotypic antibody is encoded by nucleic acid sequences SEQ ID NO: 26 (VH) and SEQ ID NO: 27 (VL).

Claims:

1. An anti-idiotypic antibody fused to albumin or a functional fragment thereof.

2. The anti-idiotypic antibody according to claim 1, wherein the anti-idiotypic antibody is specific for an antibody having a variable heavy domain comprising the amino acid sequence
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGIS GDPSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTG FAYWGQGTLVTVSS (SEQ ID NO: 7), and
a variable light chain domain comprising the amino acid sequence
DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRP SGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLG Q (SEQ ID NO: 8)

3. The anti-idiotypic antibody according to any one of the preceding claims, wherein said anti-idiotypic antibody comprises a variable heavy chain comprising
an HCDR1 of the amino acid sequence YSFSNYWIS (SEQ ID NO: 18),
an HCDR2 of the amino acid sequence WMGIIDPASSKTRYSPSFQG (SEQ ID NO: 19),
an HCDR3 of the amino acid sequence SRGAGMDY (SEQ ID NO: 20), and
a variable light chain comprising
an LCDR1 of the amino acid sequence TGSSSNIGAGYDVH (SEQ ID NO: 21),
an LCDR2 of the amino acid sequence LLIYADNNRPS (SEQ ID NO: 22),
an LCDR3 of the amino acid sequence GSYDESSNSM (SEQ ID NO: 23).

4. The anti-idiotypic antibody according to any one of the preceding claims, wherein said anti-idiotypic antibody comprises the variable heavy chain of the amino acid sequence
QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGIIDP ASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGAGMDY WGQGTLVTVSS (SEQ ID NO: 16), and
the variable light chain of the amino acid sequence
DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL TVLGQ (SEQ ID NO: 17).

5. The anti-idiotypic antibody albumin fusion according any one of the preceding claims, wherein the heavy chain comprises the amino acid sequence
QVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWISWVRQMPGKGLEWMGII
DPASSKTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRGA
GMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKRVEPKSDIDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPF
EDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA
DCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL
YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKA
SSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVH
TECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLL
RLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLG
EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAE
DYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEF
NAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFV
EKCCKADDKETCFAEEGKKLVAASQAALGLVNSRHHHHHH (SEQ ID NO:
24).

6. The anti-idiotypic antibody albumin fusion according any one of the preceding claims, wherein the light chain comprises the amino acid sequence
DIVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADNN
RPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCGSYDESSNSMVFGGGTKL
TVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE
CS (SEQ ID NO: 25)

7. The anti-idiotypic antibody albumin fusion according any one of the preceding claims for use in evaluating a blood sample.

8. A nucleic acid encoding the anti-idiotypic antibody according to any one of the preceding claims.

9. A method of evaluating a blood sample obtained from a patient undergoing treatment for multiple myeloma or other gammopathy comprising

a) obtaining a blood sample from said patient,
b) incubating the blood sample with an anti-idiotypic antibody according to any one of claims 1-7,
c) performing immunofixation electrophoresis (IFE), and
d) reporting the results of the IFE.

10. A method according to claim 9, wherein the patient is undergoing treatment with the antibody having a variable heavy domain comprising the amino acid sequence QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGIS GDPSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTG FAYWGQGTLVTVSS (SEQ ID NO: 7), and
a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRP SGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLG Q (SEQ ID NO: 8).

11. The method according to claim 9, where the sample is evaluated for total M-protein levels.

12. An anti-idiotypic antibody that is specific for an antibody having a variable heavy domain comprising the amino acid sequence QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGIS GDPSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTG FAYWGQGTLVTVSS (SEQ ID NO: 7), and
a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRP SGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLG Q (SEQ ID NO: 8)

13. A method of evaluating a blood sample obtained from a patient undergoing treatment for multiple myeloma or other gammopathy comprising
a) obtaining a blood sample from said patient,
b) incubating the blood sample with an anti-idiotypic antibody,
c) performing immunofixation electrophoresis (IFE), and
d) reporting the results of the IFE,
wherein the patient is undergoing treatment with the antibody having a variable heavy domain comprising the amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGIS GDPSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTG FAYWGQGTLVTVSS (SEQ ID NO: 7), and

a variable light chain domain comprising the amino acid sequence DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRP SGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLG Q (SEQ ID NO: 8).

14. The antibody according to claim 12 or method according to claim 13, wherein said anti-idiotypic antibody comprises a variable heavy chain comprising

an HCDR1 of the amino acid sequence YSFSNYWIS (SEQ ID NO: 18),

an HCDR2 of the amino acid sequence WMGIIDPASSKTRYSPSFQG (SEQ ID NO: 19),

an HCDR3 of the amino acid sequence SRGAGMDY (SEQ ID NO: 20), and

a variable light chain comprising

an LCDR1 of the amino acid sequence TGSSSNIGAGYDVH (SEQ ID NO: 21),

an LCDR2 of the amino acid sequence LLIYADNNRPS (SEQ ID NO: 22),

an LCDR3 of the amino acid sequence GSYDESSNSM (SEQ ID NO: 23).