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(56) Related Art  
**DAVID C. BUTLER ET AL, "Bifunctional Anti-Huntingtin Proteasome-Directed Intrabodies Mediate Efficient Degradation of Mutant Huntingtin Exon 1 Protein Fragments", PLOS ONE, (2011-12-22), vol. 6, no. 12, page e29199**  
**LECERF J-M ET AL, "Human single-chain Fv intrabodies counteract in situ huntingtin aggregation in cellular models of Huntington's disease", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, US, (2001-04-10), vol. 98, no. 8, pages 4764 - 4769**  
**US 2003/0232052 A1**  
**JAN KO ET AL, "New anti-huntingtin monoclonal antibodies: implications for huntingtin conformation and its binding proteins", BRAIN RESEARCH BULLETIN, ELSEVIER SCIENCE LTD, OXFORD, GB, (2001-10-01), vol. 56, no. 3-4, pages 319 - 329**  
**KHOSHMAN, ET AL, "Effects of intracellular expression of anti-HTT antibodies of various specificities on mutant HTT aggregation and toxicity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, (2002-01-22), vol. 99, no. 2, pages 1002 - 1007**  
**J. LEGLEITER ET AL, "Monoclonal Antibodies Recognize Distinct Conformational Epitopes Formed by Polyglutamine in a Mutant Huntingtin Fragment", JOURNAL OF BIOLOGICAL CHEMISTRY, (2009-08-07), vol. 284, no. 32, pages 21647 - 21658**  
**COLBY D ET AL, "Development of a Human Light Chain Variable Domain (VL) Intracellular Antibody Specific for the Amino Terminus of HTT via Yeast Surface Display", JOURNAL OF MOLECULAR BIOLOGY, (2004-09-17), vol. 342, no. 3, pages 901 - 912**  
**WO 2005/052002 A2**

C. LANDLET ET AL, "Proteolysis of Mutant HTT Produces an Exon 1 Fragment That Accumulates as an Aggregated Protein in Neuronal Nuclei in Huntington Disease", JOURNAL OF BIOLOGICAL CHEMISTRY, (2010-03-19), vol. 285, no. 12, pages 8808 - 8823

WO 2008/081008 A1

SOUTHWELL A L ET AL, "Intrabody Gene Therapy Ameliorates Motor, Cognitive, and Neuropathological Symptoms in Multiple Mouse Models of Huntington's Disease", JOURNAL OF NEUROSCIENCE, (2009-10), vol. 29, no. 43, pages 13589 - 13602

SOUTHWELL AMBER L ET AL, "Intrabodies binding the proline-rich domains of mutant huntingtin increase its turnover and reduce neurotoxicity", JOURNAL OF NEUROSCIENCE, (2008-09), vol. 28, no. 36, ISSN 0270-6474, pages 9013 - 9020

DEHAY BENJAMIN ET AL, "Mapping of the epitope of monoclonal antibody 2B4 to the proline-rich region of human Huntingtin, a region critical for aggregation and toxicity", BIOTECHNOLOGY JOURNAL, (2007-05), vol. 2, no. 5, pages 559 - 564



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(54) Title: HUMAN-DERIVED ANTI-HUNTINGTIN (HTT) ANTIBODIES AND USES THEREOF

(57) Abstract: Provided are novel human-derived anti-huntingtin (HTT) antibodies and biotechnological derivatives thereof, preferably capable of binding mutated and/or aggregated HTT species and or fragments thereof, as well as methods related thereto. The human-derived anti-HTT antibodies and biotechnological derivatives can be used in pharmaceutical and diagnostic compositions for HTT targeted immunotherapy of Huntington Disease and diagnosis thereof.



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## Human-derived anti-Huntingtin (HTT) antibodies and uses thereof

### FIELD OF THE INVENTION

5 The present invention generally relates to antibody-based therapy of Huntington's disease (HD) associated with Huntingtin (HTT). In particular, the present invention relates to novel molecules specifically binding to human HTT and/or antigens thereof, particularly human-derived antibodies as well as HTT-binding fragments, synthetic and biotechnological derivatives thereof, which are useful in the treatment of diseases and conditions induced by  
10 such pathogenic HTT isoforms.

In addition, the present invention relates to pharmaceutical and diagnostic compositions comprising such HTT-binding molecules, antibodies and mimics thereof valuable both as a diagnostic tool to identify diseases and/or disorders associated with HTT aggregation and as a  
15 passive vaccination strategy for treating disorders related to diseases associated with HTT amyloidosis.

### BACKGROUND OF THE INVENTION

Huntington's disease (HD) is an autosomal dominant neurological amyloidogenic disease. 5 to  
20 10 individuals per 100,000 individuals are affected with this autosomal disease. However, the prevalence in the US is much higher, studies have shown that under 200,000 US individuals 50% have the risk of developing HD, in particular 30,000 patients are registered in the US while only 100,000 patients are registered worldwide.

25 HD, as shown in several studies, results from a trinucleotide CAG repeat expansion in the Huntingtin (HTT) gene, in particular in exon 1 of the HTT gene located on chromosome 4 (MacDonald *et al.*, Cell 72, (1993), 971–983), which is translated into a polyglutamine (polyQ) stretch in the HTT protein. HD occurs when the polyQ tract exceeds a threshold of 35-40 glutamine residues in length with a strong inverse correlation between repeat length and age-  
30 of-onset of disease. This polyQ stretch leads to a misfolding and aggregation of HTT in several regions, *e.g.* neurons and glial cells. With increasing age an accumulation of the HTT aggregates takes place leading to degeneration of the striatal GABA-ergic neurons and cortical pyramidal neurons. Symptoms of the HTT misfolding and aggregation include involuntary



movements, lack of motor coordination, depression, cognitive decline such as memory loss and/or dementia.

Since 1993 when the HD mutation was identified the understanding of the pathophysiology and molecular biology of the disease has significantly improved. Medicaments such as *e.g.* Xenazine® (tetraabenazine, Lundbeck) a hexahydro-dimethoxy-benzoquinolizine derivative VMAT2 inhibitor had been designed for symptomatic treatment targeting involuntary muscle movements.

In addition, gene silencing approaches such as RNA interference (RNAi) have been suggested as potential therapies. In particular, the use of siRNA directed against HTT gene in a HD mouse model (R6/2) was shown to inhibit mutant HTT gene expression, see *e.g.* Warby *et al.*, Am. J. Hum Genet. 84 (2009), 351-366 and Olshina *et al.*, Biological Chemistry 285 (2010), 21807-21816. However, one limitation of this method lies in the difficulty to introduce sufficient amount of siRNA into the target cells or tissues as shown by *e.g.* Boudreau *et al.* (Brain Research 1338 (2010), 112-121). Furthermore this approach may face safety liabilities as a continued need for the expression of Huntingtin was suggested by gene deletions studies in animal models and cultured cells (Dragatsis *et al.*, Nat. Genet. 26 (2000), 300-306; Gauthier *et al.*, Cell. 118 (2004), 127-138; Zuccato *et al.*, Nat. Genet. 35 (2003), 76-83).

Therefore, there is a need for novel therapeutic strategies an efficacious and safe therapy of diseases associated with HTT aggregation which preferably directly interfere with amyloid formation by mutant HTT.

This technical problem is solved by the embodiments characterized in the claims and described further below and illustrated in the Examples and Figures.

#### SUMMARY OF THE INVENTION

The present invention provides anti-huntingtin (HTT) antibodies and equivalent HTT-binding molecules for use in the prophylactic or therapeutic treatment of diseases and conditions associated with HTT amyloidosis. More specifically, therapeutically useful human-derived antibodies as well as HTT-binding fragments, synthetic and biotechnological derivatives thereof that recognize mutated and/or aggregated forms of HTT are provided.

In particular, experiments performed in accordance with the present invention were successful in the recombinant cloning and production of human-derived monoclonal HTT-specific antibodies which are specific for mutated and/or aggregated HTT species and/or fragments thereof. The human subjects being the source of the B cells from which the cDNA encoding the variable domain of human-derived monoclonal anti-HTT antibodies, respectively, have been isolated, were healthy donors. However, in another embodiment of the present invention, the source of the B cells from which the human-derived monoclonal anti-HTT antibodies and the cDNA encoding their variable domain, respectively, might be isolated are HD patients carrying trinucleotide CAG repeat expansion in the HTT gene and being either symptom-free or displaying an unusually slow progressing or stable disease course or alternatively displaying typical clinical features of Huntington's disease. Furthermore, as demonstrated in the Examples, the antibodies of the present invention are capable of attenuating dendritic spine loss, improve behavioral performance during task-specific training and enhance sensorimotor ability in a mouse model of HD. Therefore, it is prudent to expect that the human monoclonal anti-HTT antibodies of the present invention and derivatives thereof besides being non-immunogenic also exhibit a therapeutically beneficial effect in human.

As described in the background section, hitherto the pathogenesis of HD has been tried block by intracellular approaches such as RNA interference (RNAi); see also, *e.g.*, Stanek *et al.*, Human Gene Therapy 25 (2014), 461-474 for silencing mutant Huntingtin by Adeno-associated virus-mediated RNA interference. With respect to an immunotherapeutic approach the intracellular expression of single-chain antibody fragments (scFv), *i.e.* intrabodies which are devoid of the constant region of immunoglobulins such as of the IgG class has been explored in the last decade; see, *e.g.*, supra and Butler *et al.*, Prog Neurobiol. 97 (2012), for engineered intracellular scFv and single-domain (dAb; nanobody) antibody therapies to counteract mutant huntingtin and related toxic intracellular proteins.

For example, Lecerf *et al.*, Proc. Nat. Acad. Sci. 98 (2001), 4764-4769 describe a single-chain variable region fragment (scFv) antibody specific for the 17 N terminal residues of huntingtin, adjacent to the polyglutamine in HD exon 1 selected from a large human phage display. A corresponding scFv antibody, scFv-C4 comprising a lambda variable light (V<sub>L</sub>) chain (Kvam *et al.*, PLoS One 4 (2009), e5727; GenBank accession number ACA53373) is described to have some neuro-protective effect in B6.CgHDR6/1 transgenic mice, a HD mouse model, which however weakened both with severity of disease at time of injection. In order to improve the

steady-level of the intrabody and to direct N-terminal htt exon 1 (httex1) protein fragments bound by scFv-C4 to the proteasome for degradation in order to prevent them from aggregation the PEST signal sequence of Mouse Ornithine Decarboxylase (mODC) mODC has been fused to the scFv-C4 antibody; see Butler and Messer, PLoS One 6 (2011), e29199. No in vivo experiments have been reported yet.

Also the group of Khoshnan *et al.* was aiming at the development of intrabody-based therapeutics for HD and *inter alia* describe anti-huntingtin scFv antibodies derived from mouse monoclonal antibodies binding the epitopes polyglutamine (polyQ), polyproline (polyP), and anti-C terminus and their effects upon intracellular expression on mutant huntingtin aggregation and toxicity; see, *e.g.*, Ko *et al.*, Brain Research 56 (2001), 319-329, Khoshnan *et al.*, Proc. Nat. Acad. Sci 99 (2002), 1002-1007 and Legleiter *et al.*, J. Biol. Chem. 284 (2009), 21647-21658 and their patent application US 2003/0232052 A1. In the US application, also a "human" scFv antibody denoted "hMW9" is described to have been isolated from a human scFvs phage library using recombinant mutant huntingtin protein. However, in contrast to mouse monoclonal derived scFv MW1, MW2, MW7 and MW8 no sequence data are provided for hMW9 which hitherto has also never been reported again.

Colby *et al.*, Proc. Nat. Acad. Sci. 342 (2004), 901-912 describe the development of a human light chain variable domain (V<sub>L</sub>) intracellular antibody specific for the amino terminus of Huntingtin via yeast surface display of a non-immune human antibody library. This single-domain intrabody consisting only of the lambda light chain domain of the original scFv was described to inhibit huntingtin aggregation in a cell-free in vitro assay as well as in a mammalian cell culture model of HD; see also to corresponding international application WO 2005/052002. Again, no in vivo experiments have been reported yet.

Hence, apparently current intrabody based approaches either did not extend over cell-based assays or had not been proven to be successful in animal models of HD yet, at least not in long term experiments. In particular, intrabodies reveal several limitations *in-vivo* such as their potential toxicity due to intracellular/intranuclear accumulation of intrabody-antigen complexes or the limited distribution of for example viral delivery into large brain volumes in humans; see, *e.g.*, Butler *et al.*, Prog. Neurobiol. 97 (2012), 190-204 and Sothwell *et al.*, J. Neurosci. 29 (2009), 13589-13602. Furthermore, a general drawback of intracellular approaches is the problem of addressing the antibody and its encoding vector DNA, respectively, to the desired

cells and, if exogenously applied the inconvenient administration regimen, for example intrastriatal injections; see, *e.g.*, Snyder-Keller *et al.*, Neuropathol. Exp. Neurol. 69 (2010), 1078–1085. In addition, general concerns with respect to gene therapy and the use of viral vectors remain.

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In contrast, the experiments performed in accordance with the present invention demonstrate for the first time that full-length IgG antibodies directed against different epitopes of huntingtin upon systemic administration can be successfully delivered to the brain (Example 24 and Figure 18) and that the antibodies of the present invention are capable of attenuating dendritic spine loss, improve behavioral performance during task-specific training and enhance sensorimotor ability in a mouse model of HD (Example 34 and Figure 34).

Therefore, as illustrated in the Examples, the anti-HTT antibody or an HTT-binding fragment, synthetic or biotechnological derivative thereof is preferably of the IgG class, which as generally known and described herein comprises two identical variable heavy ( $V_H$ ) chain polypeptides and two identical variable light ( $V_L$ ) chain polypeptides, and a constant region and domain, respectively, *i.e.* at least one or all of the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3). Put in other words, in one aspect of the present invention recombinantly expressed bivalent antibodies specific for Huntingtin and aggregated forms, fragments, peptides and derivatives thereof are provided suitable for use in the treatment or in *in vivo* diagnosis of huntingtin and disorders associated therewith, which are characterized by the presence of an immunoglobulin constant region. As described herein further below the immunoglobulin may be of any class such as IgG, IgM, IgA IgG, or IgE and corresponding immunoglobulin subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1. Preferably however, the antibody is of the human IgG subtype.

In addition, as also further explained herein, the human-derived antibodies of the present invention are characterized by comprising at least one or more CDR of human origin, *i.e.* being encoded by a cDNA derived from human memory B cells, and preferably wherein the  $V_H$  and/or  $V_L$  chain are of human memory B cell origin too. The constant region or any domain thereof if human may be of the same or different origin as the CDR(s) and the  $V_H$  and/or  $V_L$  chain, respectively.

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In this context, unless stated otherwise or clear from context reference herein to the antibody of the present invention includes the human-derived antibodies illustrated in the Examples as well as HTT-binding fragments, synthetic and biotechnological derivatives thereof.

5 As can be further noted from the prior art approaches of providing intrabodies derived from human scFvs phage library almost always scFvs were obtained with a variable light chain of V $\lambda$  origin; see Kvam *et al.* and Colby *et al.*, supra. In contrast, more than 90% of the human-derived antibodies of the present invention use a V $\kappa$  light chain, which also applies to antibodies NI-302.31F11 and NI-302.35C1 illustrated in Example 24 to be capable of  
10 penetrating the brain upon systemic administration and in Example 34 (NI-302.35C1) to have beneficial effects on behavioral performance and motor-related tasks of mice in a HD animal model. Therefore, it is tempting to speculate that antibodies having a V $\kappa$  light chain might have superior properties over antibodies having a light chain of V $\lambda$  origin. Therefore, in a preferred embodiment of the antibody of the present invention the variable light chain is of  
15 V $\kappa$  origin.

As illustrated in the Examples and Figures, the anti-HTT-antibody, HTT-binding fragment, synthetic and biotechnological variant thereof binds to different regions of the HTT exon 1 protein which shows the "toxic" alteration as described above, *i.e.* the expanded, unstable  
20 trinucleotide repeat, as shown in the Examples. In particular, the antibody of the present invention recognizes a polyP-region, a polyQ/polyP-region, the P-rich-region, the C terminal-region or the N-terminal region of HTT exon 1 protein. The epitopes of the subject antibodies illustrated in the Examples are summarized in Figure 20. As mentioned in the background section, HD occurs when the polyQ tract exceeds a threshold of 35-40 glutamine residues in  
25 length due to an aggregation of HTT. Accordingly, as shown in Example 3, aggregated and soluble HTT exon 1 proteins with 21, 35 or 49 polyQ repeats were generated and the binding of the identified antibodies tested. In the following these constructs will be denoted HDX with X being the number of Qs, *e.g.* HTT exon 1 with 21 polyQ repeats will be denoted HD21. Therefore, unless specifically indicated otherwise the term HTT means HTT exon1 and the  
30 soluble HTT refers to the corresponding GST-fusion proteins.

In a preferred embodiment of the present invention, the anti-HTT antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof is capable of preferentially binding aggregated or misfolded forms of HTT. As described in *e.g.* Legleiter *et al.*, JBC 285 (19)

(2010), 14777–14790 and demonstrated in the Examples the aggregation of HDX proteins in terms of speed and seize increases with the number of Qs.

In a particularly preferred embodiment of the present invention, the anti-HTT antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof demonstrates the immunological binding characteristics of an antibody characterized by any one of the variable regions  $V_H$  and/or  $V_L$  as set forth in Fig. 1. Preferably, the variable region of the antibody comprises at least one complementarity determining region (CDR) of the  $V_H$  and/or  $V_L$  of the variable regions, *i.e.* pair of  $V_H$  and  $V_L$  chain as set forth in Fig. 1A to 1AU, wherein one or more amino acid substitutions are permitted as long as binding specificity of the resultant antibody compared to the subject antibody comprising the corresponding pair of  $V_H$  and  $V_L$  chain as set forth in Fig. 1A to 1AU as illustrated in the Examples, *e.g.* as summarized in Figure 20 remains unaffected in kind, *i.e.* epitope specificity and  $EC_{50}$  values in the same order of magnitude for the indicated antigen, preferably in the range of at least 50%, more preferably 25% and most preferably at least 10% identical value. Preferably, one, two or all three CDRs of the  $V_H$  and  $V_L$  chain contain at least one amino acid at a corresponding position which is conserved (*i.e.* being the same or a conservative substitute amino acid) in at least about 20%, preferably about 40%, more preferably about 50% and most preferably about 75% in the  $V_H$  and  $V_L$  chain amino acid sequences, respectively, of the subject antibodies which recognize the same type of HTT epitope, *i.e.* poly-P, P-rich, C-terminus or N-terminus. For example, sequence alignment of the subject antibodies reveals the predominant presence of one or two tyrosines (Y) in CDRH1; see Figure 36. Similar conserved amino acid can be identified in the other CDRs as well.

In a further embodiment of the present invention, the anti-HTT antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof is a bispecific antibody. Thus, the antibody of the present invention may be capable of recognizing at least two distinct epitopes either on the same or on different antigens. For example, while a first antigen-binding site, *i.e.* variable domain may be specific for HTT and preferably comprises a variable region of any one of the subject antibodies illustrated in the appended Examples and Figures, the second antigen-binding site may be specific for a different, preferably also neurotoxic protein and comprise a variable region of corresponding antibody. Hence, protein misfolding and aggregation is a major hallmark of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and HD. Tough until recently, the consensus was that each aggregation-prone protein was characteristic of each disorder [ $\alpha$ -synuclein ( $\alpha$ -syn)/PD, mutant huntingtin (HTT)/HD, Tau and amyloid beta peptide/AD], growing evidence indicates that aggregation-

prone proteins can actually co-aggregate and modify each other's behavior and toxicity, suggesting that this process may also contribute to the overlap in clinical symptoms across different diseases; see, *e.g.*, for co-aggregation of  $\alpha$ -syn and mutant HTT Poças *et al.*, Hum. Mol. Genet. 24 (2015), 1898-1907.

Thus, in one embodiment of the present invention the anti-HTT antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof is a bispecific antibody which is capable of binding HTT and a protein associated with a neurodegenerative disorder, in particular in the brain, preferably selected from the group consisting of  $\alpha$ -synuclein, Tau, amyloid beta peptide, SOD1, C9orf72, and TDP-43; see, *e.g.*, Blokhuis *et al.*, Acta Neuropathol. 125 (2013), 777-794. Human-derived monoclonal antibodies against the mentioned proteins are known in the art; see, *e.g.*, international application WO2008/081008 for anti- $\alpha$ -syn antibody, WO2010/069603 for anti- $\alpha$ -synuclein antibody; WO2012/049570 for anti-tau antibody; WO2012/080518 for anti-SOD1 antibody; WO2012/113775 for anti-ankyrin antibody; WO2013/061163 for anti-TDP-43 antibody and European patent application EP 14 187 180.6 and its subsequent international application for C9orf72. Bi- and multispecific antibodies can be generated by methods well known in the art, for example by chemical recombination of monoclonal immunoglobulin G1 fragments as described, *e.g.*, by Brennan *et al.*, Science. 229 (1985), 81-83, or recombinant simultaneously co-expression of the appropriate heavy and light chain and corresponding pairing; see, *e.g.*, Lewis *et al.*, Nature Biotechnology 32 (2014), 191-198; for review see, *e.g.*, Kontermann, mAbs 4 (2012), 182-197 and Kontermann and Brinkmann, Drug Discovery Today 20 (2015), 838-847.

Alternatively, or in addition the bi- or multi-specific antibody comprises at least a first and second antigen-binding site, *i.e.* variable domain specific for two distinct epitopes of HTT, preferably wherein one or both variable regions are derived from any one of the subject antibodies illustrated in the appended Examples and Figures, and as further described herein. Thus, in a preferred embodiment the bispecific antibody of the present invention comprises two binding sites/domains of an antibody which recognizes a polyP-region, a polyQ/polyP-region, the P-rich-region, the C terminal-region, the N-terminal region or a conformational epitope of HTT exon 1 protein. The epitopes of the subject antibodies illustrated in the Examples are summarized in Figure 20. Accordingly, in one embodiment the bispecific antibody of the present invention recognizes at least two different epitopes depicted in Figure 20 and has the combined binding specificities of the cognate subject antibody, respectively.

The antigen-binding fragment of any one the subject antibodies disclosed herein can be a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an F(ab')<sub>2</sub> fragment, or any other antigen-binding fragment. However, as mentioned in a particularly preferred embodiment, the antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof is a human IgG isotype antibody and comprises at least part of the constant region. Alternatively, the antibody is a chimeric human-rodent or rodentized antibody such as murine or murinized, rat

or ratinized antibody, the rodent versions being particularly useful for diagnostic methods and studies in animals.

Furthermore, the present invention relates to compositions comprising the antibody of the present invention or antigen-binding fragment, synthetic or biotechnological derivative thereof and to immunotherapeutic and immunodiagnostic methods using such compositions in the prevention, diagnosis or treatment of diseases and/or disorders associated with HTT amyloidosis, wherein an effective amount of the composition is administered to a patient in need thereof.

The present invention also relates to polynucleotides encoding at least a variable region of an immunoglobulin chain of the antibody of the invention. Preferably, said variable region comprises at least one complementarity determining region (CDR) of the  $V_H$  and/or  $V_L$  of the variable region as set forth in Fig. 1. Preferably, the polynucleotide is a cDNA.

Accordingly, the present invention also encompasses vectors comprising said polynucleotides and host cells transformed therewith as well as their use for the production of an antibody and equivalent binding molecules which are specific for HTT and preferably are capable of binding mutated and/or aggregated HTT species or fragments thereof. Means and methods for the recombinant production of antibodies and mimics thereof as well as methods of screening for competing binding molecules, which may or may not be antibodies, are known in the art. However, as described herein, in particular with respect to therapeutic applications in human the antibody of the present invention is a human antibody in the sense that application of said antibody is substantially free of an immune response directed against such antibody otherwise observed for chimeric and even humanized antibodies. Hence, the present invention also relates to the use of the cDNA, vector and host cell described herein and illustrated in the Examples for the production of an anti-HTT antibody, in particular human-derived anti-HTT antibody or a biotechnological derivative thereof.

Furthermore, disclosed herein are compositions and methods that can be used to identify HTT, in particular mutated and/or aggregated HTT species or fragments *in vitro*, *e.g.* in samples and/or *in vivo*. The disclosed anti-HTT antibodies and binding fragments thereof can be used to screen human blood, plasma, serum, saliva, peritoneal fluid, cerebrospinal fluid ("CSF"), and urine for the presence of HTT and/or mutated and/or aggregated HTT species or fragments thereof in samples, for example, by using ELISA-based or surface adapted assay. In one



embodiment the present invention relates to a method of diagnosing or monitoring the progression of a disease and/or disorder related to mutated and/or aggregated HTT species or fragments thereof in a subject, the method comprising determining the presence of mutated, and/or aggregated HTT species or fragments in a sample from the subject to be diagnosed with  
5 at least one antibody of the present invention or an HTT-binding molecule and/or binding molecules for mutated and/or aggregated HTT species or fragments having substantially the same binding specificities of any one thereof, wherein the presence of mutated and/or aggregated HTT species or fragments is indicative of the disorder.

10 Accordingly, the present invention also relates to a method of preparing a pharmaceutical composition for use in the treatment of a disorder associated with or caused by HTT aggregates, the method comprising:

- (a) expressing the cDNA of the present invention and/or culturing the host cell of the present invention under appropriate culture conditions suitable for the production of the  
15 anti-HTT antibody, in particular human-derived anti-HTT antibody or a biotechnological derivative thereof;
- (b) purifying the antibody, biotechnological derivative or immunoglobulin chain(s) thereof from a reaction mixture and the culture, respectively, to pharmaceutical grade; and
- 20 (c) admixing the antibody or biotechnological derivative thereof with a pharmaceutically acceptable carrier.

Furthermore, in one embodiment of the present invention the anti-HTT antibodies and HTT-binding molecules comprising at least one CDR of an antibody of the present invention are  
25 provided for the preparation of a composition for *in vivo* detection (also called *in vivo* imaging) of or targeting a therapeutic and/or diagnostic agent to HTT, in particular mutated and/or aggregated HTT species or fragments in the human or animal body. The methods and compositions disclosed herein can aid in diseases and/or disorders associated with HTT aggregation or amyloidosis and characterized, *e.g.*, by the occurrence of aggregated forms of  
30 HTT and can be used to monitor disease progression and therapeutic efficacy of the therapy provided to the subject, for example in *in vivo* imaging related diagnostic methods. In one embodiment the *in vivo* detection (imaging) comprises scintigraphy, positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging or magnetic resonance imaging (MRI).

Hence, it is a particular object of the present invention to provide methods for treating, diagnosing or preventing a disease and/or disorder associated with HTT amyloidosis. The methods comprise administering an effective concentration of a preferably human antibody or antibody derivative to the subject where the antibody targets HTT or fragments thereof, preferably mutated and/or aggregated or misfolded HTT species or fragments thereof.

In a further aspect the present invention provides a peptide having an epitope of HTT, preferably of mutated and/or aggregated HTT species or fragments thereof specifically recognized by an antibody of the present invention. Said peptide comprises or consists of an amino acid sequence as indicated below in the detailed description and in the Examples or a modified sequence thereof in which one or more amino acids are substituted, deleted and/or added. Additionally, the present invention provides a method for diagnosing diseases and/or disorders associated with HTT amyloidosis in a subject, comprising a step of determining the presence of an antibody that binds to said peptide in a biological sample of said subject.

Further embodiments of the present invention will be apparent from the description and Examples that follow.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**Fig. 1:** Amino acid sequences of the variable regions of human antibodies NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302.31F11, NI-302.2A2, NI-302.6N9, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.37C12, NI-302.55D8, NI-302.7A8, NI-302.78H12, NI-302.71F6, NI-302.11H6, NI-302.3D8, NI-302.18A1, NI-302.8F1, NI-302.52C9, NI-302.46C9, NI-302.15E8, NI-302.15D3, NI-302.64E5, NI-302.7D8, NI-302.72F10, NI-302.12H2, NI-302.8M1 and NI-302.4A6. Framework (FR) and complementarity determining regions (CDRs) are indicated with the CDRs being underlined. The Kabat numbering scheme was used (cf. <http://www.bioinf.org.uk/abs/>).

**Fig. 2:** Characterization of Huntingtin (HTT) exon 1 proteins and aggregates. **(A)** Cloning of GST-HttEx1Q21 (GST-HD21), GST-HttEx1Q35 (GST-HD35) and GST-HttEx1Q49 (GST-HD49) expression constructs; **(B)** Coomassie dye staining upon SDS-PAGE of purified GST only (lane 1), GST-HttExon1Q21 (GST-HD21, lane 2), GST-HttExon1Q35 (GST-HD35, lane 3) and GST-HttExon1Q49 (GST-HD49, lane 4)

proteins showing good purity but also some additional bands; **(C)** Characterization of *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation analysis (right) with polyclonal HD-1 antibody as detection antibody. Aggregation reactions of HD35 at 24 hours or HD49 reactions after 3 hours show aggregates larger than the pore size of 0.2  $\mu\text{m}$  detectable by HD-1 in the filter retardation assay analysis; **(D)** Characterization of *in vitro* HD35 and HD49 preparations by electron microscopy. Aggregation reactions of HD35 after 24 hours [A, E] or HD49 reactions after 1 hour [B, F], 3 hours [C, G] or 24 hours [D, H]. Overview pictures [A-D] with 1'000x magnification and detailed structures [E-H] at 66'000x magnification.

**Fig. 3:** Characterization of the binding affinity of anti-polyP domain-binding antibody NI-302.33C11. **(A)** NI-302.33C11 binding affinity for different HTT species determined by direct ELISA; **(B)** NI-302.33C11  $\text{EC}_{50}$  determinations for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1 proteins using direct ELISA. NI-302.33C11 antibody binds with similar  $\text{EC}_{50}$  values to all four species; and **(C)** NI-302.33C11 binding analysis to HTT aggregates on *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation assay (right) with preferential binding to later (aggregated) reactions of HD35 and HD49 in the dot-blot assays and aggregates of HD35 and HD49 in the filter retardation assay.

**Fig. 4:** Determination of NI-302.33C11 antibody binding epitope by scan of overlapping peptides. At the top: pepscan image after NI-302.33C11 antibody hybridization. Below: graphical overviews of peptides sequences bound by NI-302.33C11 antibody. Overlapping amino acids between peptides (putative binding epitope) being recognized by the NI- 302.33C11 antibody are highlighted in bold in the consensus sequences. The HRP-conjugated donkey anti-human IgG Fc $\gamma$  detection antibody alone does not bind any linear huntingtin peptide.

**Fig. 5:** NI-302.33C11 binds to the polyP-domain of HTT.  $\text{EC}_{50}$  determinations for GST-HD49 (●), BSA-coupled P-rich domain peptide (◆), BSA-coupled C-terminal peptide (■) or BSA-coupled polyP peptide (▲) using direct ELISA.

**Fig. 6:** Characterization of the purity and integrity as well as the binding specificity of NI-302.33C11 antibody. SDS-PAGE analysis followed by Coomassie staining of 2 and 10 µg recombinant human NI-302.33C11 anti-polyP domain antibody.

**Fig. 7:** Characterization of binding affinity of anti-proline-rich domain antibody NI302.63F3. **(A)** NI-302.63F3 binding affinity for different HTT species determined by direct ELISA; **(B)** NI-302.63F3 EC<sub>50</sub> determinations for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1 proteins using direct ELISA. NI-302.63F3 antibody has a similar EC<sub>50</sub> values to all four species; **(C)** Characterization of antibody NI-302.63F3 on *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation assay (right) with preferential binding to huntingtin with expanded polyQ tracts (HD49>HD35) in the dot-blot assays and aggregates of HD35 and HD49 in the filter retardation assay.

**Fig. 8:** Determination of NI-302.63F3 antibody binding epitope by scan of overlapping peptides. At the top: pepscan image after NI-302.63F3 antibody hybridization. Below: graphical overviews of peptides sequences bound by NI-302.63F3 antibody. Overlapping amino acids between peptides (putative binding epitope) being recognized by the NI-302.63F3 antibody are highlighted in bold in the consensus sequences. The HRP-conjugated donkey anti-human IgG Fcγ detection antibody alone does not bind any linear huntingtin peptide.

**Fig. 9:** NI-302.63F3 binds to the P-rich domain of HTT. EC<sub>50</sub> determinations for GST-HD49 (●), BSA-coupled P-rich domain peptide (◆), BSA-coupled C-terminal peptide (■) or BSA-coupled polyP peptide (▲) using direct ELISA.

**Fig. 10:** Characterization of the purity and integrity as well as the binding specificity of NI-302.63F3 antibody. SDS-PAGE analysis followed by Coomassie staining of 2 and 10 µg recombinant human NI- 302.63F3 anti-proline-rich domain antibody.

**Fig. 11:** Characterization of the binding affinity of anti-C-terminal domain-binding antibody NI 302.35C1. **(A)** NI-302.35C1 binding affinity for different HTT species determined by direct ELISA; **(B)** NI-302.35C1 EC<sub>50</sub> determinations for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1

proteins using direct ELISA; **(C)** Characterization of antibody NI-302.35C1 on *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation assay (right) with preferential binding to later (aggregated) reactions of HD35 and HD49 in the dot-blot assays and aggregates of HD35 and HD49 in the filter retardation assay.

**Fig. 12:** NI-302.35C1 binds to the BSA-coupled C-terminal domain peptide of HTT. EC<sub>50</sub> determinations for GST-HD49 (●), BSA-coupled P-rich domain peptide (◆), BSA-coupled C-terminal peptide (■) or BSA-coupled polyP peptide (▲) using direct ELISA.

**Fig. 13:** Characterization of the purity and integrity as well as the binding specificity of NI-302.35C1 antibody. SDS-PAGE analysis followed by Coomassie staining of 2 and 10 µg recombinant human NI-302 anti-C-terminal domain antibody.

**Fig. 14:** Characterization of binding affinity of anti-N-terminal domain antibody NI302.15E8. **(A)** NI-302. 15E8 binding affinity for different HTT species determined by direct ELISA; **(B)** NI-302.15E8 EC<sub>50</sub> determinations for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1 proteins using direct ELISA. NI-302. 15E8 antibody has a higher affinity binding EC<sub>50</sub> values to non-aggregated species.

**Fig. 15:** NI-302.15E8 binds to the BSA-coupled N-terminal domain peptide of HTT. EC<sub>50</sub> determinations for GST-HD49 (●), BSA-coupled N-terminal peptide (▼) BSA-coupled P-rich domain peptide (◆), BSA-coupled C-terminal peptide (■) or BSA-coupled polyP peptide (▲) using direct ELISA..

**Fig. 16:** Target specificity analysis by direct ELISA. NI-302 antibodies **(A)** NI-302.33C11, **(B)** NI-302.63F3, and **(C)** NI-302.35C1 and **(D)** NI-302.15E8 do not bind unrelated aggregating protein targets as shown in the binding specificity analysis by direct ELISA.

**Fig. 17:** Spine density is significantly reduced in hippocampal slice cultures of Tg(HDexon1)62Gpb/1J transgenic mice compared to non-transgenic littermates. **(A-**

**D)** Overview of GFP positive hippocampal neurons of non-transgenic littermates (**A**, **C**) vs. Tg(HDexon1)62Gpb/1J mice (**B**, **D**), showing a single dendrite with the individual spines at higher magnification (**C**, **D**). (**E**) Significant reduction of dendritic spine density in transgenic vs. wildtype animals (n=3-7 slices per group from 2 wt or 3 transgenic animals). (**F**) Attenuation of dendritic spine density loss by antibodies NI-302.11F11 and 302.63F3 in slices of transgenic mice. (n=8-13 slices per group from a total of 12 transgenic animals). Data represent the mean  $\pm$  SEM. \*p<0.05 (MWU), #p=0.05.

**Fig. 18:** Penetration of NI-302 antibodies in the brain of R6/1 animal model. (**A**) Mean NI-302.31F11 (●) and NI-302.35C1 (■) plasma and brain drug levels in R6/1 transgenic animals after a single intraperitoneal injection of 50mg/kg. Data represent the mean  $\pm$  SEM. n=3 for each group; (**B**) Plasma and brain drug levels of individual mice after a single dose of 50 mg/kg.

**Fig. 19:** EC<sub>50</sub> determinations of human-derived HTT antibodies for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1 proteins using direct ELISA. Some antibodies (e.g. NI-302.37C12 (**I**), NI-302.55D8 (**J**), NI-302.11A4 (**F**) or NI-302.22H9 (**G**)) seem to have preferred binding to uncut GST-HTT protein suggesting that these antibodies preferentially recognize uncut soluble GST-HD constructs whereas some antibodies (e.g. NI-302.74C11 (**C**) or NI-302.71F6 (**M**)) showed high affinity binding with similar EC-values to all HTT preparation suggesting that they bind to an epitope that is similar exposed in aggregated and uncut HTT exon 1 constructs in the ELISA assay.

**Fig. 20:** Characterization of binding affinity by direct ELISA. Binding affinity to the different HTT proteins of human-derived HTT-specific antibodies

**Fig. 21:** Characterization of antibody NI-302.44D7, NI-302.37C12, NI-302.15F9 and NI-302.71F6 on *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation assay (right) with preferential binding in particular NI-302.15F9 and NI-302.71F6 to later (aggregated) reactions of HD35 and HD49 in the dot-blot assays and SDS stable aggregates of HD35 and HD49 in the filter retardation assay.

**Fig. 22:** Target specificity analysis by direct ELISA. NI-302 antibodies **(A)** NI-302.31F11, **(B)** NI-302.6N9, **(C)** NI-302.46C9, **(D)** NI-302.8F1, **(E)** NI-302.2A2, **(F)** NI-302.74C11, **(G)** NI-302.15F9, **(H)** NI-302.39G12, **(I)** NI-302.11A4, **(J)** NI-302.22H9, **(K)** NI-302.44D7, **(L)** NI-302.55D8, **(M)** NI-302.7A8, **(N)** NI-302.78H12, **(O)** NI-302.71F6, **(P)** NI-302.11H6, and **(Q)** NI-302.3D8 do not bind unrelated aggregating protein targets as shown in the binding specificity analysis by direct ELISA

**Fig. 23:** Determination of NI-302 antibody binding epitope by scan of overlapping peptides. At the top: pepscan image after NI-302 antibody hybridization. Below: graphical overviews of peptides sequences and NI-302 antibody binding score to the single peptides are shown. Overlapping amino acids between peptides (putative binding epitope) being recognized by the NI-302 antibody are highlighted in gray in the consensus sequences. The HRP-conjugated donkey anti-human IgG Fcγ detection antibody alone does not bind any linear huntingtin peptide. **(A)** NI-302.31F11 1 µg/ml on a 21 spot membrane, **(B)** NI-302.74C11 1 µg/ml on a 16 spot membrane, **(C)** NI-302.15F9 1 µg/ml on a 16 spot membrane, **(D)** NI-302.39G12 1 µg/ml on a 16 spot membrane, **(E)** NI-302.11A4 1 µg/ml on a 16 spot membrane, **(F)** NI-302.22H9 1 µg/ml on a 16 spot membrane, **(G)** NI-302.44D7 1 µg/ml on a 16 spot membrane, **(H)** NI-302.37C12 1 µg/ml on a 16 spot membrane, **(I)** NI-302.55D8 1 µg/ml on a 16 spot membrane, **(J)** NI-302.7A8 1 µg/ml on a 21 spot membrane, **(K)** NI-302.78H12 1 µg/ml on a 16 spot membrane, **(L)** NI-302.71F6 1 µg/ml on a 16 spot membrane, **(M)** NI-302.11H6 1 µg/ml on a 21 spot membrane, **(N)** NI-302.18A1 1 µg/ml on a 21 spot membrane, **(O)** NI-302.3D8 1 µg/ml on a 21 spot membrane, **(P)** NI-302.46C9 1 µg/ml on a 21 spot membrane and **(Q)** NI-302.52C9 1 µg/ml on a 21 spot membrane, **(R)** NI-302.2A2 1 µg/ml on a 21 spot membrane, **(S)** NI-302.15E8 1 µg/ml on a 21 spot membrane and **(T)** NI-302.15D3 1 µg/ml on a 21 spot membrane.

**Fig. 24:** Immunohistochemical analysis of NI-302 antibodies reveals prominent staining of neuronal intranuclear inclusions in striatal neurons of late disease stage Tg(HDexon1)62Gpb/1J transgenic animals at 5 nM (74C11, 39C12, 11A4, 22H9, 78H12, 37C12, 7D8, 72F10), or 50nM concentrations (15F9, 71F6, 55D8, 44D7, 7A8, 64E5). Mab5492 is a commercially available N-terminal HTT antibody.

**Fig. 25:** Basic characterization of R6/1 transgenic mouse model Tg(HDexon1)61Gpb/J. **(A)** Survival curve, **(B)** body weight curve and **(C)** total brain wet weight during the disease progression of this animal model. **(D-H)** Characterization of appearance of neuronal intranuclear inclusions with disease progression in the striatum by staining with NI-302.33C11 HTT antibody.

**Fig. 26:** Basic characterization of B6C3-Tg(HD82Gln)81Dbo/J (N171-82Q) transgenic mouse model. **(A)** Survival curve, **(B)** body weight curve during the disease progression and **(C)** total brain wet weight at end stage of this animal model. **(D-F)** Characterization of appearance of neuronal intranuclear inclusions with disease progression in the striatum by staining with Mab5492 HTT antibody.

**Fig. 27:** Immunohistochemical analysis with 50 nM of NI-302.33C11(polyP-epitope) shows staining of neuronal intranuclear inclusions in cortical neurons of four different Huntington Disease patients **(A-D)** and in striatal neurons of 270 day old, late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals at 1 **(E)** and 5 nM **(F)** concentration. No staining is detected in non-transgenic littermates **(G)**, if primary antibody is omitted during the staining **(H)** or if tissue of non-Huntington Disease controls is stained with 50 nM of NI-302.33C11.

**Fig. 28:** Immunohistochemical analysis with 50 nM of NI-302.63F3 (P-rich domain epitope) shows staining of neuronal intranuclear inclusions **(A-C)** and staining of some neurites **(D)** of cortical neurons of four different Huntington Disease patients **(A-D)** and in striatal neurons of 270 day old, late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals at 1 **(E)** and 50 nM **(F)** concentration. No staining is detected in non-transgenic littermates **(G)**, if primary antibody is omitted during the staining **(H)** or if tissue of non-Huntington Disease controls is stained with 50nM of NI-302.63F3.

**Fig. 29:** Immunohistochemical analysis with 100 nM of NI-302.35C1 (end Exon 1 epitope) shows staining of neuronal intranuclear inclusions **(A-C)** and staining of some neurites **(D)** of cortical neurons of four different Huntington Disease patients **(A-D)** and in striatal neurons of 270 day old, late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals at 1 **(E)** and 50 nM **(F)** concentration. No staining is detected in



non-transgenic littermates (**G**), if primary antibody is omitted during the staining (**H**) or if tissue of non-Huntington Disease controls is stained with 100nM of NI-302.35C1.

**Fig. 30:** Immunohistochemical analysis with commercially available anti-polyQ antibody Mab1574 (1:2000, Chemicon) shows staining of neuronal intranuclear and cytoplasmic inclusions and staining of some neurites (**A, D**) of cortical neurons of four different Huntington Disease patients (**A-D**) and in striatal neurons of presymptomatic, 150 day old (**E**) and 270 day old (**F**), late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals. No staining is detected in non-transgenic littermates (**G**), if primary antibody is omitted during the staining (**H**) or if tissue of non-Huntington Disease controls is stained with Mab 1574.

**Fig. 31:** EC<sub>50</sub> determinations of human-derived HTT antibodies for aggregated HD49 (●), aggregated HD21 (■), soluble GST-HD49 (▲) and GST-HD21 (▼) Htt Exon 1 proteins using direct ELISA. Some antibodies (e.g. NI-302.64E5 (**A**) or NI-302.7D8 (**B**)) seem to have preferred binding to uncut GST-HD49 protein suggesting that these antibodies preferentially recognize uncut soluble GST-HD constructs containing longer polyQ repeats. Antibody NI-302.72F10 (**C**) shows preference to HD21 constructs and some antibodies (e.g. NI-302.4A6 (**D**), NI-302.12H2 (**E**) or NI-302.8M1 (**F**)) showed high affinity binding with similar EC-values to all HTT preparation suggesting that they bind to an epitope that is similar exposed in aggregated and uncut HTT exon 1 constructs in the ELISA assay.

**Fig. 32:** Characterization of antibody (**A**) NI-302.64E5, (**B**) NI-302.7D8, (**C**) NI-302.72F10, (**D**) NI-302.4A6, (**E**) NI-302.12H2, (**F**) NI-302.8M1 and (**G**) NI-302.33C11 (as control) on *in vitro* HD21, HD35 and HD49 time-resolved *in vitro* aggregation reactions by dot-blot (left) and filter retardation assay (right) with preferential binding in particular of NI-302.64E5 and NI-302.72F10 to later (aggregated) reactions of HD35 and/or HD49 in the dot-blot assays and SDS stable aggregates of HD35 and HD49 in the filter retardation assay.

**Fig. 33:** Target specificity analysis by direct ELISA. NI-302 antibodies (**A**) NI-302.64E5, (**B**) NI-302.7D8, (**C**) NI-302.72F10, (**E**) NI-302.12H2 and (**F**) NI-302.8M1 do not bind

unrelated aggregating protein targets as shown in the binding specificity analysis by direct ELISA, except **(D)** NI-302.4A6 which shows some binding to p53.

**Fig. 34:** Study of C-terminal domain-binding antibody NI 302.35C1 on behavioral performance during task-specific training and sensorimotor ability in a mice model of HD. **(A)** The plus-maze analysis was used to investigate the level of anxiety in the R6/1 mice. At 6 months of age, NI-302.35C1 treated R6/1 animals spend less time in the open arms, entered the open arms less frequently and did less unprotected head dips on the open arm compared to vehicle treated R6/1 animals. Hence the NI-302.35C1 treated R6/1 mice displayed a more anxious phenotype, comparable to the non-transgenic littermates. **(B)** NI-302.35C1 treated R6/1 animal showed an improved performance in the pole test compared to vehicle treated R6/1 animals reaching levels similar to non-transgenic animals.

**Fig. 35** Determination of NI-302 antibody binding epitope by scan of overlapping peptides. At the top: pepscan image after NI-302 antibody hybridization. Below: graphical overviews of peptides sequences are shown. Overlapping amino acids between peptides (putative binding epitope) being recognized by the NI-302 antibody are shown in the consensus sequence below. The HRP-conjugated donkey anti-human IgG Fcγ detection antibody alone does not bind any linear huntingtin peptide. **(A)** NI-302.64E5, **(B)** NI-302.7D8, **(C)** NI-302.72F10, **(D)** NI-302.4A6, **(E)** NI-302.12H2, **(F)** NI-302.8M1 all antibodies at 1 µg/ml on the 21 spot membrane.

**Fig. 36** Amino acid sequence alignment of the CDRs in the V<sub>H</sub> and V<sub>L</sub> or V<sub>K</sub> chains of NI-302 antibodies. Each sequence was checked in terms of conserved amino acids, segments, or other motifs revealing an accumulation of tyrosines in the CDRs.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention generally relates to immunotherapy and non-invasive methods for the detection of diseases and/or disorders as well as conditions associated with the presence of pathologic, often mutant and/or aggregated forms of huntingtin (HTT). More specifically, the present invention relates to recombinant human-derived monoclonal antibodies and HTT-binding fragments, synthetic and biotechnological derivatives thereof, which have been generated based on sequence information obtained from selected human donor populations and

are capable of binding to such HTT isoforms and antigens thereof. The recombinant human-derived monoclonal antibody of the present invention is advantageously characterized by specifically binding to mutated and/or aggregated HTT species and/or fragments thereof allowing a targeting for treatment and/or diagnosis of pathological altered HTT species. Due to  
5 their human derivation, the resulting recombinant antibodies of the present invention can be reasonably expected to be efficacious and safe as therapeutic agent, and highly specific as a diagnostic reagent for the detection of pathological HTT without giving false positives.

In addition, the present invention relates to the human monoclonal antibody and any derivatives  
10 thereof described herein for use in the treatment of patients either alone or with other agents utilized for symptoms associated with HTT amyloidosis, wherein the antibody of the present invention and any of its derivatives is designed to be administered concomitantly with the agent suppressing side effects or sequentially before or after administration of the same. In this context, the anti-HTT antibody and HTT-binding fragment of the present invention are  
15 preferably substantially non-immunogenic in human. In one embodiment of the present invention, pharmaceutical compositions are provided comprising both a human monoclonal antibody of the present invention or any derivatives thereof and one or more drug utilized for symptoms associated with HTT amyloidosis.

## 20 I. Definitions

Unless otherwise stated, a term as used herein is given the definition as provided in the Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, 1997, revised 2000 and reprinted 2003, ISBN 0 19 850673 2.

25 It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "an antibody," is understood to represent one or more antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

Huntingtin (HTT), also known as IT15 is a disease gene linked to Huntington's disease (HD), a  
30 neurodegenerative disorder characterized by loss of striatal neurons. It is thought that HD is caused by an expanded, unstable trinucleotide repeat in the HTT gene, which translates as a polyglutamine repeat in the protein product. A fairly broad range in the number of trinucleotide repeats has been identified in normal controls, and repeat numbers in excess of 35-40 have been

described as pathological. The HTT locus (NG\_009378.1; 4830 to 174286; NCBI RefSeqGene) is large, spanning 180 kb and consisting of 67 exons.

In this context, it has been demonstrated that an N-terminal fragment of mutant HTT, *i.e.* exon 1 protein of the HTT gene, with an expanded CAG repeat represents the "toxic" species of HTT which is sufficient to cause aggregation and a progressive neurological phenotype in transgenic mice; see, *e.g.*, Mangiarini *et al.*, Cell 87 (1996), 493–506 and Ross *et al.*, Lancet Neurol. 10 (2011), 83–98, DiFiglia *et al.*, Science 277 (1997), 1990–1993, Gutekunst *et al.*, J Neurosci 19(7) (1999), 2522–2534.

Unless stated otherwise, by "specifically recognizing HTT", "antibody specific to/for HTT" and "anti-HTT antibody" antibodies are meant which specifically, generally, and collectively bind to HTT, wherein HTT refer to different forms the HTT including but not limited to the native form of HTT as well as other forms of HTT, *e.g.* pathologically altered HTT, such as mutated, misfolded and/or aggregated HTT. Provided herein are human-derived antibodies selective for full-length and/or fragments and/or mutated, misfolded and/or aggregated forms of HTT.

If not specifically indicated otherwise, the term "HTT", is used interchangeably to specifically refer to the different forms of huntingtin (HTT). The term "HTT" is also used to generally identify other conformers of HTT, for example, pathologically altered forms of HTT such as misfolded and/or aggregated forms of HTT. Furthermore, unless specifically indicated otherwise the term HTT in particular means HTT exon1 and the soluble HTT refers to the corresponding GST-fusion proteins. The term "HTT" is also used to refer collectively to all types and forms of HTT, such as mutated HTT. Added letters in front of the terms, *e.g.* HTT, are used to indicate the organism the particular ortholog is originating from, *e.g.* hHTT for human HTT or mHTT for murine origin.

The anti-HTT antibodies disclosed herein specifically bind HTT and epitopes thereof and to various conformations of HTT and epitopes thereof. For example, disclosed herein are antibodies that specifically bind pathologically altered HTT species or fragments thereof, such as mutated, misfolded, and/or aggregated forms of HTT or fragments thereof. The term (pathologically) mutated, misfolded, and/or aggregated/aggregates of HTT is used interchangeable to specifically refer to the aforementioned forms. The term (pathological) "aggregated forms" or "aggregates" as used herein describes the products of an accumulation

or cluster formation due to HTT erroneous/pathological interaction with one another. These aggregates, accumulations or cluster forms may be, substantially consist or consist of both HTT and/or HTT fragments and of non-fibrillar oligomers and/or fibrillar oligomers and fibrils thereof. As used herein, reference to an antibody that "specifically binds", "selectively binds", or "preferentially binds" HTT refers to an antibody that does not bind other unrelated proteins. In one example, a HTT antibody disclosed herein can bind HTT or an epitope thereof and show no binding above about 2 times background for other proteins. In a preferred embodiment, the antibody of the present invention does not substantially recognize unrelated amyloid-forming proteins selected from the group consisting of paired helical filament (PHF)-tau, TAU, alpha-synuclein, transactive response DNA binding protein 43 (TDP43), islet amyloid polypeptide (IAPP), transthyretin (TTR), serum amyloid A (SAA); see Examples 8, 13, 18 and 31. An antibody that "specifically binds" or "selectively binds" a HTT conformer refers to an antibody that does not bind all conformations of HTT, *i.e.*, does not bind at least one other HTT conformer. For example, disclosed herein are antibodies that can preferentially bind to mutated and/or aggregated forms of HTT both *in vitro* and in tissues obtained from patients with diseases and/or disorders associated with HTT amyloidosis or with a risk to develop diseases and/or disorders associated with HTT amyloidosis. In another embodiment of the present invention the antibodies of the present invention specifically targets different regions of the HTT exon 1; see, *e.g.*, Figs. 5, 9, 12, 14, 15. Since the anti-HTT antibodies of the present invention have been isolated from human subjects, they may also be called "human auto-antibodies" or "human-derived antibodies" in order to emphasize that those antibodies were indeed expressed initially by the subjects and are not synthetic constructs generated, for example, by means of human immunoglobulin expressing phage libraries or xenogeneic antibodies generated in a transgenic animal expressing part of the human immunoglobulin repertoire which hitherto represented one common method for trying to provide human-like antibodies. On the other hand, the human-derived antibody of the present invention may be denoted synthetic, recombinant, and/or biotechnological in order distinguish it from human serum antibodies *per se*, which may be purified via protein A or affinity column.

However, a particular advantage of the therapeutic approach of the present invention lies in the fact that the antibodies of the present invention are derived from B cells or B memory cells from healthy human subjects with no signs of a disease showing the occurrence of, or related to misfolded/aggregated HTT and thus are, with a certain probability, capable of preventing a clinically manifest disease related to misfolded/aggregated HTT, or of diminishing the risk of

the occurrence of the clinically manifest disease, or of delaying the onset or progression of the clinically manifest disease. Typically, the antibodies of the present invention also have already successfully gone through somatic maturation, *i.e.* the optimization with respect to selectivity and effectiveness in the high affinity binding to the target HTT molecules by means of somatic variation of the variable regions of the antibody. The knowledge that such cells *in vivo*, *e.g.* in a human, have not been activated by means of related or other physiological proteins or cell structures in the sense of an autoimmuneological or allergic reaction is also of great medical importance since this signifies a considerably increased chance of successfully living through the clinical test phases. So to speak, efficiency, acceptability and tolerability have already been demonstrated before the preclinical and clinical development of the prophylactic or therapeutic antibody in at least one human subject. It can thus be expected that the human anti-HTT antibodies of the present invention, both its target structure-specific efficiency as therapeutic agent and its decreased probability of side effects significantly increase its clinical probability of success.

In contrast, antibodies derived from cDNA library's or phage displays are artificial molecules such as a humanized antibody which is still of murine origin and thus foreign to the human body. Therefore the clinical utility and efficacy of the therapeutic antibodies can be limited by the production of anti-drug antibodies (ADAs), which can influence the efficacy and pharmacokinetics of the antibodies and sometimes lead to serious side effects, see *e.g.* Igawa *et al.*, MAbs. 3 (2011), 243-252. In particular, humanized antibodies or antibodies generated with recent human-antibody-generation technologies are in contrast to the human-derived antibodies such as those of the present invention prone to induce an antibody response and these human-like antibodies derived from *e.g.* phage display such as adalimumab have been reported to induce ADA production, see, *e.g.*, Mansour, Br. J. Ophthalmol 91 (2007), 274-276 and Igawa *et al.*, MAbs. 3 (2011), 243-252. Therefore, human-derived antibodies which are not prone to undesired immune response are more beneficial for the patient than artificial molecules derived from libraries or displays.

The term "peptide" is understood to include the terms "polypeptide" and "protein" (which, at times, may be used interchangeably herein) within its meaning. Similarly, fragments of proteins and polypeptides are also contemplated and may be referred to herein as "peptides". Nevertheless, the term "peptide" preferably denotes an amino acid polymer including at least 5 contiguous amino acids, preferably at least 10 contiguous amino acids, more preferably at least

15 contiguous amino acids, still more preferably at least 20 contiguous amino acids, and particularly preferred at least 25 contiguous amino acids. In addition, the peptide in accordance with present invention typically has no more than 100 contiguous amino acids, preferably less than 80 contiguous amino acids and more preferably less than 50 contiguous amino acids.

5

Polypeptides:

As used herein, the term "polypeptide" is intended to encompass a singular "polypeptide" as well as plural "polypeptides," and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term "polypeptide" refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, "peptides," "dipeptides," "tripeptides," "oligopeptides," "protein," "amino acid chain," or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of "polypeptide," and the term "polypeptide" may be used instead of, or interchangeably with any of these terms.

15

The term "polypeptide" is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation and derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non-naturally occurring amino acids. A polypeptide may be derived from a natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis.

A polypeptide of the invention may be of a size of about 3 or more, 5 or more, 10 or more, 20 or more, 25 or more, 50 or more, 75 or more, 100 or more, 200 or more, 500 or more, 1,000 or more, or 2,000 or more amino acids. Polypeptides may have a defined three-dimensional structure, although they do not necessarily have such structure. Polypeptides with a defined three-dimensional structure are referred to as folded, and polypeptides which do not possess a defined three-dimensional structure, but rather can adopt a large number of different conformations, and are referred to as unfolded. As used herein, the term glycoprotein refers to a protein coupled to at least one carbohydrate moiety that is attached to the protein via an oxygen-containing or a nitrogen-containing side chain of an amino acid residue, *e.g.*, a serine residue or an asparagine residue.

30

By an "isolated" polypeptide or a fragment, variant, or derivative thereof is intended a polypeptide that is not in its natural milieu. No particular level of purification is required. For example, an isolated polypeptide can be removed from its native or natural environment. Recombinantly produced polypeptides and proteins expressed in host cells are considered  
5 isolated for purposes of the invention, as are native or recombinant polypeptides which have been separated, fractionated, or partially or substantially purified by any suitable technique.

"Recombinant peptides, polypeptides or proteins" refer to peptides, polypeptides or proteins produced by recombinant DNA techniques, *i.e.* produced from cells, microbial or mammalian,  
10 transformed by an exogenous recombinant DNA expression construct encoding the fusion protein including the desired peptide. Proteins or peptides expressed in most bacterial cultures will typically be free of glycan. Proteins or polypeptides expressed in yeast may have a glycosylation pattern different from that expressed in mammalian cells.

15 Included as polypeptides of the present invention are fragments, derivatives, analogs or variants of the foregoing polypeptides and any combinations thereof as well. The terms "fragment," "variant," "derivative", and "analog" include peptides and polypeptides having an amino acid sequence sufficiently similar to the amino acid sequence of the natural peptide. The term "sufficiently similar" means a first amino acid sequence that contains a sufficient or minimum  
20 number of identical or equivalent amino acid residues relative to a second amino acid sequence such that the first and second amino acid sequences have a common structural domain and/or common functional activity. For example, amino acid sequences that comprise a common structural domain that is at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at  
25 least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100%, identical are defined herein as sufficiently similar. Preferably, variants will be sufficiently similar to the amino acid sequence of the preferred peptides of the present invention, in particular to HTT, variants, derivatives or analogs  
30 of either of them. Such variants generally retain the functional activity of the peptides of the present invention. Variants include peptides that differ in amino acid sequence from the native and wt peptide, respectively, by way of one or more amino acid deletion(s), addition(s), and/or substitution(s). These may be naturally occurring variants as well as artificially designed ones.



Furthermore, the terms "fragment," "variant," "derivative", and "analog" when referring to antibodies or antibody polypeptides of the present invention include any polypeptides which retain at least some of the antigen-binding properties of the corresponding native binding molecule, antibody, or polypeptide. Fragments of polypeptides of the present invention include proteolytic fragments, as well as deletion fragments, in addition to specific antibody fragments discussed elsewhere herein. Variants of antibodies and antibody polypeptides of the present invention include fragments as described above, and also polypeptides with altered amino acid sequences due to amino acid substitutions, deletions, or insertions. Variants may occur naturally or be non-naturally occurring. Non-naturally occurring variants may be produced using art-known mutagenesis techniques. Variant polypeptides may comprise conservative or non-conservative amino acid substitutions, deletions or additions. Derivatives of HTT specific binding molecules, *e.g.*, antibodies and antibody polypeptides of the present invention, are polypeptides which have been altered so as to exhibit additional features not found on the native polypeptide. Examples include fusion proteins. Variant polypeptides may also be referred to herein as "polypeptide analogs". As used herein a "derivative" of a binding molecule or fragment thereof, an antibody, or an antibody polypeptide refers to a subject polypeptide having one or more residues chemically derivatized by reaction of a functional side group. Also included as "derivatives" are those peptides which contain one or more naturally occurring amino acid derivatives of the twenty standard amino acids. For example, 4-hydroxyproline may be substituted for proline; 5-hydroxylysine may be substituted for lysine; 3-methylhistidine may be substituted for histidine; homoserine may be substituted for serine; and ornithine may be substituted for lysine.

Determination of similarity and/or identity of molecules:

"Similarity" between two peptides is determined by comparing the amino acid sequence of one peptide to the sequence of a second peptide; see Example 35 as well as Fig. 36. An amino acid of one peptide is similar to the corresponding amino acid of a second peptide if it is identical or a conservative amino acid substitution. Conservative substitutions include those described in Dayhoff, M.O., ed., *The Atlas of Protein Sequence and Structure* 5, National Biomedical Research Foundation, Washington, D.C. (1978), and in Argos, *EMBO J.* 8 (1989), 779-785. For example, amino acids belonging to one of the following groups represent conservative changes or substitutions: -Ala, Pro, Gly, Gln, Asn, Ser, Thr; -Cys, Ser, Tyr, Thr; -Val, Ile, Leu, Met, Ala, Phe; -Lys, Arg, His; -Phe, Tyr, Trp, His; and -Asp, Glu.

"Similarity" between two polynucleotides is determined by comparing the nucleic acid sequence of one polynucleotide to the sequence of a polynucleotide. A nucleic acid of one polynucleotide is similar to the corresponding nucleic acid of a second polynucleotide if it is identical or, if the nucleic acid is part of a coding sequence, the respective triplet comprising the nucleic acid encodes for the same amino acid or for a conservative amino acid substitution.

The determination of percent identity or similarity between two sequences is preferably accomplished using the mathematical algorithm of Karlin and Altschul (1993) Proc. Natl. Acad. Sci USA 90: 5873-5877. Such an algorithm is incorporated into the BLASTn and BLASTp programs of Altschul *et al.* (1990) J. Mol. Biol. 215: 403-410 available at NCBI (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>).

The determination of percent identity or similarity is performed with the standard parameters of the BLASTn programs for BLAST polynucleotide searches and BLASTp programs for BLAST protein search, as recommended on the NCBI webpage and in the "BLAST Program Selection Guide" in respect of sequences of a specific length and composition.

BLAST polynucleotide searches are performed with the BLASTn program.

For the general parameters, the "Max Target Sequences" box may be set to 100, the "Short queries" box may be ticked, the "Expect threshold" box may be set to 1000 and the "Word Size" box may be set to 7 as recommended for short sequences (less than 20 bases) on the NCBI webpage. For longer sequences the "Expect threshold" box may be set to 10 and the "Word Size" box may be set to 11. For the scoring parameters the "Match/mismatch Scores" may be set to 1,-2 and the "Gap Costs" box may be set to linear. For the Filters and Masking parameters, the "Low complexity regions" box may not be ticked, the "Species-specific repeats" box may not be ticked, the "Mask for lookup table only" box may be ticked, the "DUST Filter Settings" may be ticked and the "Mask lower case letters" box may not be ticked. In general the "Search for short nearly exact matches" may be used in this respect, which provides most of the above indicated settings. Further information in this respect may be found in the "BLAST Program Selection Guide" published on the NCBI webpage.

BLAST protein searches are performed with the BLASTp program. For the general parameters, the "Max Target Sequences" box may be set to 100, the "Short queries" box may be ticked, the

"Expect threshold" box may be set to 10 and the "Word Size" box may be set to "3". For the scoring parameters the "Matrix" box may be set to "BLOSUM62", the "Gap Costs" Box may be set to "Existence: 11 Extension: 1", the "Compositional adjustments" box may be set to "Conditional compositional score matrix adjustment". For the Filters and Masking parameters the "Low complexity regions" box may not be ticked, the "Mask for lookup table only" box may not be ticked and the "Mask lower case letters" box may not be ticked.

Modifications of both programs, *e.g.*, in respect of the length of the searched sequences, are performed according to the recommendations in the "BLAST Program Selection Guide" published in a HTML and a PDF version on the NCBI webpage.

#### Polynucleotides:

The term "polynucleotide" is intended to encompass a singular nucleic acid as well as plural nucleic acids, and refers to an isolated nucleic acid molecule or construct, *e.g.*, messenger RNA (mRNA) or plasmid DNA (pDNA). A polynucleotide may comprise a conventional phosphodiester bond or a non-conventional bond (*e.g.*, an amide bond, such as found in peptide nucleic acids (PNA)). The term "nucleic acid" refers to any one or more nucleic acid segments, *e.g.*, DNA or RNA fragments, present in a polynucleotide. By "isolated" nucleic acid or polynucleotide is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, a recombinant polynucleotide encoding an antibody contained in a vector is considered isolated for the purposes of the present invention. Further examples of an isolated polynucleotide include recombinant polynucleotides maintained in heterologous host cells or purified (partially or substantially) polynucleotides in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of polynucleotides of the present invention. Isolated polynucleotides or nucleic acids according to the present invention further include such molecules produced synthetically. In addition, polynucleotide or a nucleic acid may be or may include a regulatory element such as a promoter, ribosome binding site, or a transcription terminator.

As used herein, a "coding region" is a portion of nucleic acid which consists of codons translated into amino acids. Although a "stop codon" (TAG, TGA, or TAA) is not translated into an amino acid, it may be considered to be part of a coding region, but any flanking sequences, for example promoters, ribosome binding sites, transcriptional terminators, introns, and the like, are not part of a coding region. Two or more coding regions of the present invention can be present in a single polynucleotide construct, *e.g.*, on a single vector, or in separate polynucleotide

constructs, *e.g.*, on separate (different) vectors. Furthermore, any vector may contain a single coding region, or may comprise two or more coding regions, *e.g.*, a single vector may separately encode an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region. In addition, a vector, polynucleotide, or nucleic acid of the invention may  
5 encode heterologous coding regions, either fused or unfused to a nucleic acid encoding a binding molecule, an antibody, or fragment, variant, or derivative thereof. Heterologous coding regions include without limitation specialized elements or motifs, such as a secretory signal peptide or a heterologous functional domain.

10 In certain embodiments, the polynucleotide or nucleic acid is DNA. In the case of DNA, a polynucleotide comprising a nucleic acid which encodes a polypeptide normally may include a promoter and/or other transcription or translation control elements operable associated with one or more coding regions. An operable association is when a coding region for a gene product, *e.g.*, a polypeptide, is associated with one or more regulatory sequences in such a way as to  
15 place expression of the gene product under the influence or control of the regulatory sequence(s). Two DNA fragments (such as a polypeptide coding region and a promoter associated therewith) are "operable associated" or "operable linked" if induction of promoter function results in the transcription of mRNA encoding the desired gene product and if the nature of the linkage between the two DNA fragments does not interfere with the ability of the  
20 expression regulatory sequences to direct the expression of the gene product or interfere with the ability of the DNA template to be transcribed. Thus, a promoter region would be operable associated with a nucleic acid encoding a polypeptide if the promoter was capable of effecting transcription of that nucleic acid. The promoter may be a cell-specific promoter that directs substantial transcription of the DNA only in predetermined cells. Other transcription control  
25 elements, besides a promoter, for example enhancers, operators, repressors, and transcription termination signals, can be operable associated with the polynucleotide to direct cell-specific transcription. Suitable promoters and other transcription control regions are disclosed herein.

30 A variety of transcription control regions are known to those skilled in the art. These include, without limitation, transcription control regions which function in vertebrate cells, such as, but not limited to, promoter and enhancer segments from cytomegaloviruses (the immediate early promoter, in conjunction with intron-A), simian virus 40 (the early promoter), and retroviruses (such as Rous sarcoma virus). Other transcription control regions include those derived from vertebrate genes such as actin, heat shock protein, bovine growth hormone and rabbit  $\beta$ -globin,

as well as other sequences capable of controlling gene expression in eukaryotic cells. Additional suitable transcription control regions include tissue-specific promoters and enhancers as well as lymphokine-inducible promoters (*e.g.*, promoters inducible by interferons or interleukins).

5 Similarly, a variety of translation control elements are known to those of ordinary skill in the art. These include, but are not limited to ribosome binding sites, translation initiation and termination codons, and elements derived from picornaviruses (particularly an internal ribosome entry site, or IRES, also referred to as a CITE sequence).

10 In other embodiments, a polynucleotide of the present invention is RNA, for example, in the form of messenger RNA (mRNA).

Polynucleotide and nucleic acid coding regions of the present invention may be associated with additional coding regions which encode secretory or signal peptides, which direct the secretion  
15 of a polypeptide encoded by a polynucleotide of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal peptide or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Those of ordinary skill in the art are aware that polypeptides secreted by vertebrate cells generally have a signal peptide fused to the  
20 N-terminus of the polypeptide, which is cleaved from the complete or "full-length" polypeptide to produce a secreted or "mature" form of the polypeptide. In certain embodiments, the native signal peptide, *e.g.*, an immunoglobulin heavy chain or light chain signal peptide is used, or a functional derivative of that sequence that retains the ability to direct the secretion of the polypeptide that is operable associated with it. Alternatively, a heterologous mammalian signal  
25 peptide, or a functional derivative thereof, may be used. For example, the wild-type leader sequence may be substituted with the leader sequence of human tissue plasminogen activator (TPA) or mouse  $\beta$ -glucuronidase.

A "binding molecule" as used in the context of the present invention relates primarily to  
30 antibodies, and fragments thereof, but may also refer to other non-antibody molecules that bind to HTT including but not limited to hormones, receptors, ligands, ankyrins, major histocompatibility complex (MHC) molecules, chaperones such as heat shock proteins (HSPs) as well as cell-cell adhesion molecules such as members of the cadherin, integrin, C-type lectin and immunoglobulin (Ig) superfamilies. Thus, for the sake of clarity only and without

restricting the scope of the present invention most of the following embodiments are discussed with respect to antibodies and antibody-like molecules which represent the preferred binding molecules for the development of therapeutic and diagnostic agents.

5 Antibodies:

The terms "antibody" and "immunoglobulin" are used interchangeably herein. An antibody or immunoglobulin is a binding molecule which comprises at least the variable domain of a heavy chain, and normally comprises at least the variable domains of a heavy chain and a light chain. Basic immunoglobulin structures in vertebrate systems are relatively well understood; see, *e.g.*,  
10 Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988).

As will be discussed in more detail below, the term "immunoglobulin" comprises various broad classes of polypeptides that can be distinguished biochemically. Those skilled in the art will  
15 appreciate that heavy chains are classified as gamma, mu, alpha, delta, or epsilon, ( $\gamma$ ,  $\mu$ ,  $\alpha$ ,  $\delta$ ,  $\epsilon$ ) with some subclasses among them (*e.g.*,  $\gamma 1$ - $\gamma 4$ ). It is the nature of this chain that determines the "class" of the antibody as IgG, IgM, IgA, IgG, or IgE, respectively. The immunoglobulin subclasses (isotypes) *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, etc. are well characterized and are known to confer functional specialization. Modified versions of each of these classes and  
20 isotypes are readily discernible to the skilled artisan in view of the instant disclosure and, accordingly, are within the scope of the instant invention. All immunoglobulin classes are clearly within the scope of the present invention, the following discussion will generally be directed to the IgG class of immunoglobulin molecules. With regard to IgG, a standard immunoglobulin molecule comprises two identical light chain polypeptides of molecular  
25 weight approximately 23,000 Daltons, and two identical heavy chain polypeptides of molecular weight 53,000-70,000. The four chains are typically joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" and continuing through the variable region.

30 Light chains are classified as either kappa or lambda ( $\kappa$ ,  $\lambda$ ). Each heavy chain class may be bound with either a kappa or lambda light chain. In general, the light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated either by hybridomas, B cells or genetically engineered host cells. In the heavy

chain, the amino acid sequences run from an N-terminus at the forked ends of the Y configuration to the C-terminus at the bottom of each chain.

Both the light and heavy chains are divided into regions of structural and functional homology.

5 The terms "constant" and "variable" are used functionally. In this regard, it will be appreciated that the variable domains of both the light ( $V_L$ ) and heavy ( $V_H$ ) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention  
10 the numbering of the constant region domains increases as they become more distal from the antigen-binding site or amino-terminus of the antibody. The N-terminal portion is a variable region and at the C-terminal portion is a constant region; the CH3 and CL domains actually comprise the carboxy-terminus of the heavy and light chain, respectively. As indicated above, the variable region allows the antibody to selectively recognize and specifically bind epitopes  
15 on antigens. That is, the  $V_L$  domain and  $V_H$  domain, or subset of the complementarity determining regions (CDRs), of an antibody combine to form the variable region that defines a three dimensional antigen-binding site. This quaternary antibody structure forms the antigen-binding site present at the end of each arm of the Y. More specifically, the antigen-binding site is defined by three CDRs on each of the  $V_H$  and  $V_L$  chains. Any antibody or immunoglobulin  
20 fragment which contains sufficient structure to specifically bind to HTT is denoted herein interchangeably as a "binding fragment" or an "immunospecific fragment."

In naturally occurring antibodies, an antibody comprises six hypervariable regions, sometimes called "complementarity determining regions" or "CDRs" present in each antigen-binding  
25 domain, which are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The "CDRs" are flanked by four relatively conserved "framework" regions or "FRs" which show less inter-molecular variability. The framework regions largely adopt a  $\beta$ -sheet conformation and the CDRs form loops which connect, and in  
30 some cases form part of, the  $\beta$ -sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids

comprising the CDRs and the framework regions, respectively, can be readily identified for any given heavy or light chain variable region by one of ordinary skill in the art, since they have been precisely defined; see, "Sequences of Proteins of Immunological Interest," Kabat, E., *et al.*, U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, J. Mol. Biol., 196 (1987), 901-917, which are incorporated herein by reference in their entireties.

In the case where there are two or more definitions of a term which is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term "complementarity determining region" ("CDR") to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat *et al.*, U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" (1983) and by Chothia and Lesk, J. Mol. Biol., 196 (1987), 901-917, which are incorporated herein by reference, where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth below in Table I as a comparison. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular hypervariable region or CDR of the human IgG subtype of antibody given the variable region amino acid sequence of the antibody.

**Table I: CDR Definitions<sup>1</sup>**

	<b>Kabat</b>	<b>Chothia</b>
VH CDR1	31-35	26-32
VH CDR2	50-65	52-58
VH CDR3	95-102	95-102
VL CDR1	24-34	26-32
VL CDR2	50-56	50-52
VL CDR3	89-97	91-96

<sup>1</sup>Numbering of all CDR definitions in Table I is according to the numbering conventions set forth by Kabat *et al.* (see below).



Kabat *et al.* also defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat *et al.*, U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest" (1983). Unless otherwise specified, references to the numbering of specific amino acid residue positions in an antibody or antigen-binding fragment, variant, or derivative thereof of the present invention are according to the Kabat numbering system, which however is theoretical and may not equally apply to every antibody of the present invention. For example, depending on the position of the first CDR the following CDRs might be shifted in either direction.

Unless human-derived monoclonal antibodies or an antigen-binding fragment, synthetic or biotechnological derivative thereof as particularly preferred embodiments of the present are referred to, antibodies or antigen-binding fragments, immunospecific fragments, variants, or derivatives thereof of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, primatized, murinized or chimeric antibodies, single chain antibodies, epitope-binding fragments, *e.g.*, Fab, Fab' and F(ab')<sub>2</sub>, Fd, Fvs, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv), fragments comprising either a V<sub>L</sub> or V<sub>H</sub> domain, fragments produced by a Fab expression library, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies disclosed herein). ScFv molecules are known in the art and are described, *e.g.*, in US patent 5,892,019. Immunoglobulin or antibody molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

In one embodiment, the antibody of the present invention is not IgM or a derivative thereof with a pentavalent structure. Particular, in specific applications of the present invention, especially therapeutic use, IgMs are less useful than IgG and other bivalent antibodies or corresponding binding molecules since IgMs due to their pentavalent structure and lack of affinity maturation often show unspecific cross-reactivities and very low affinity.

In a particularly preferred embodiment, the antibody of the present invention is not a polyclonal antibody, *i.e.* it substantially consists of one particular antibody species rather than being a mixture obtained from a plasma immunoglobulin sample.

5     Antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are HTT binding fragments which comprise any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. Antibodies or immunospecific fragments thereof of the present invention may be from any  
10    animal origin including birds and mammals. Preferably, the antibodies are human, murine, donkey, rabbit, goat, guinea pig, camel, llama, horse, or chicken antibodies. In another embodiment, the variable region may be chondrichthoid in origin (*e.g.*, from sharks).

In one aspect, the antibody of the present invention is a human-derived monoclonal antibody  
15    isolated from a human, wherein the B cell expressing the antibody is isolated from a human and in turn the antibody or preferably the cDNA encoding the variable domain and optionally the cDNA for the cognate constant domain. Optionally, the framework region of the human antibody is aligned and adopted in accordance with the pertinent human germ line variable region sequences in the database; see, *e.g.*, Vbase (<http://vbase.mrc-cpe.cam.ac.uk/>)  
20    (<http://www.vbase2.org/>) hosted by the MRC Centre for Protein Engineering (Cambridge, UK). For example, amino acids considered to potentially deviate from the true germ line sequence could be due to the PCR primer sequences incorporated during the cloning process. Compared to artificially generated human-like antibodies such as single chain antibody fragments (scFvs) from a phage displayed antibody library or xenogeneic mice the human monoclonal antibody  
25    of the present invention is characterized by (i) being obtained using the human immune response rather than that of animal surrogates, *i.e.* the antibody has been generated in response to natural HTT in its relevant conformation in the human body, (ii) having protected the individual or is at least significant for the presence of HTT, and (iii) since the antibody is of human origin the risks of cross-reactivity against self-antigens is minimized. Thus, in  
30    accordance with the present invention the terms "human monoclonal antibody", "human monoclonal autoantibody", "human antibody" and the like are used to denote a HTT binding molecule which is of human origin, *i.e.* which has been isolated from a human cell such as a B cell or hybridoma thereof or the cDNA of which has been directly cloned from mRNA of a human cell, for example a human memory B cell. A human antibody is still "human", *i.e.*

human-derived even if amino acid substitutions are made in the antibody, *e.g.*, to improve binding characteristics. In this context, contrary to humanized antibodies and otherwise human-like antibodies, see also the discussion *infra*, the human-derived antibodies of the present invention are characterized by comprising CDRs which have been seen by human body and therefore are substantially devoid of the risk of being immunogenic. Therefore, the antibody of the present invention may still be denoted human-derived if at least one, preferably two and most preferably all three CDRs of one or both the variable light and heavy chain of the antibody are derived from the human antibodies illustrated herein.

In one embodiment the human-derived antibodies of the present invention comprises heterologous regions compared to the natural occurring antibodies, *e.g.* amino acid substitutions in the framework region, constant region exogenously fused to the variable region, different amino acids at the C- or N- terminal ends and the like.

Antibodies derived from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulins and that do not express endogenous immunoglobulins, as described *infra* and, for example in, US patent no 5,939,598 by Kucherlapati *et al.* are denoted human-like antibodies in order distinguish them from truly human antibodies of the present invention.

For example, the pairing of heavy and light chains of human-like antibodies such as synthetic and semi-synthetic antibodies typically isolated from phage display do not necessarily reflect the original pairing as it occurred in the original human B cell. Accordingly Fab and scFv fragments obtained from recombinant expression libraries as commonly used in the prior art can be considered as being artificial with all possible associated effects on immunogenicity and stability.

In contrast, the present invention provides isolated affinity-matured antibodies from selected human subjects, which are characterized by their therapeutic utility and their tolerance in man.

As used herein, the term "rodentized antibody" or "rodentized immunoglobulin" refers to an antibody comprising one or more CDRs from a human antibody of the present invention; and a human framework region that contains amino acid substitutions and/or deletions and/or insertions that are based on a rodent antibody sequence. When referred to rodents, preferably sequences originating in mice and rats are used, wherein the antibodies comprising such sequences are referred to as "murinized" or "ratinized" respectively. The human

immunoglobulin providing the CDRs is called the "parent" or "acceptor" and the rodent antibody providing the framework changes is called the "donor". Constant regions need not be present, but if they are, they are usually substantially identical to the rodent antibody constant regions, *i.e.* at least about 85 % to 90 %, preferably about 95 % or more identical. Hence, in some embodiments, a full-length murinized human heavy or light chain immunoglobulin contains a mouse constant region, human CDRs, and a substantially human framework that has a number of "murinizing" amino acid substitutions. Typically, a "murinized antibody" is an antibody comprising a murinized variable light chain and/or a murinized variable heavy chain. For example, a murinized antibody would not encompass a typical chimeric antibody, *e.g.*, because the entire variable region of a chimeric antibody is non-mouse. A modified antibody that has been "murinized" by the process of "murinization" binds to the same antigen as the parent antibody that provides the CDRs and is usually less immunogenic in mice, as compared to the parent antibody. The above explanations in respect of "murinized" antibodies apply analogously for "rodentized" antibodies, such as "ratinized antibodies", wherein rat sequences are used instead of the murine.

As used herein, the term "heavy chain portion" includes amino acid sequences derived from an immunoglobulin heavy chain. A polypeptide comprising a heavy chain portion comprises at least one of: a CH1 domain, a hinge (*e.g.*, upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant or fragment thereof. For example, a binding polypeptide for use in the invention may comprise a polypeptide chain comprising a CH1 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH2 domain; a polypeptide chain comprising a CH1 domain and a CH3 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH3 domain, or a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, a CH2 domain, and a CH3 domain. In another embodiment, a polypeptide of the invention comprises a polypeptide chain comprising a CH3 domain. Further, a binding polypeptide for use in the invention may lack at least a portion of a CH2 domain (*e.g.*, all or part of a CH2 domain). As set forth above, it will be understood by one of ordinary skill in the art that these domains (*e.g.*, the heavy chain portions) may be modified such that they vary in amino acid sequence from the naturally occurring immunoglobulin molecule.

In certain antibodies, or antigen-binding fragments, variants, or derivatives thereof disclosed herein, the heavy chain portions of one polypeptide chain of a multimer are identical to those

on a second polypeptide chain of the multimer. Alternatively, heavy chain portion-containing monomers of the invention are not identical. For example, each monomer may comprise a different target binding site, forming, for example, a bispecific antibody or diabody.

5 As used herein, the term "bispecific" or "bifunctional" antibody molecule is an antibody molecule that has two different epitope/antigen binding sites, and accordingly has binding specificities for two different target epitopes. These two epitopes may be epitopes of the same antigen or of different antigens. In contrast thereto a "bivalent antibody" may have binding sites of identical antigenic specificity. Methods of making a bispecific antibody are known in the art,  
10 *e.g.* chemical conjugation of two different monoclonal antibodies as illustrated in Example 36 or for example, also chemical conjugation of two antibody fragments, for example, of two Fab fragments (Brennan *et al.*, Science 229 (1985), 81-83; Nitta *et al.*, Eur. J. Immunol. 19 (1989), 1437-1441; Glennie *et al.*, J. Immunol. 139 (1987), 2367-2375; Jung *et al.*, Eur. J. Immunol., 21 (1991), 2431-2435). Alternatively, bispecific antibodies are made recombinantly (Gruber *et al.*,  
15 J. Immunol. 152 (1994), 5368-5374; Kurucz *et al.*, J. Immunol. 154 (1995), 4576-4582; Mallender and Voss, J. Biol. Chem. 269 (1994), 199-206). Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different binding specificities. Because of the random assortment of heavy and light chains, a potential mixture of ten different antibody  
20 structures are produced of which only one has the desired binding specificity (Milstein and Cuello, Nature 305 (1983), 537-540; Lanzavecchia and Scheidegger, Eur. J. Immunol. 17 (1987), 105-111. An alternative approach involves fusing the variable domains with the desired binding specificities to heavy chain constant region including at least part of the hinge region, CH2 and CH3 regions. In one embodiment the CH1 region containing the site necessary for  
25 light chain binding is present in at least one of the fusions. DNA encoding these fusions, and if desired the light chains are inserted into separate expression vectors and are then co-transfected into a suitable host organism. It is possible though to insert the coding sequences for two or all three chains into one expression vector.

30 In another embodiment, the antibodies, or antigen-binding fragments, variants, or derivatives thereof disclosed herein are composed of a single polypeptide chain such as scFvs and are to be expressed intracellularly (intrabodies) for potential *in vivo* therapeutic and diagnostic applications.

The heavy chain portions of a binding polypeptide for use in the diagnostic and treatment methods disclosed herein may be derived from different immunoglobulin molecules. For example, a heavy chain portion of a polypeptide may comprise a CH1 domain derived from an IgG1 molecule and a hinge region derived from an IgG3 molecule. In another example, a heavy chain portion can comprise a hinge region derived, in part, from an IgG1 molecule and, in part, from an IgG3 molecule. In another example, a heavy chain portion can comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule.

As used herein, the term "light chain portion" includes amino acid sequences derived from an immunoglobulin light chain. Preferably, the light chain portion comprises at least one of a V<sub>L</sub> or CL domain.

The minimum size of a peptide or polypeptide epitope for an antibody is thought to be about four to five amino acids. Peptide or polypeptide epitopes preferably contain at least seven, more preferably at least nine and most preferably between at least about 15 to about 30 amino acids. Since a CDR can recognize an antigenic peptide or polypeptide in its tertiary form, the amino acids comprising an epitope need not be contiguous, and in some cases, may not even be on the same peptide chain. In the present invention, a peptide or polypeptide epitope recognized by antibodies of the present invention contains a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, or between about 15 to about 30 contiguous or non-contiguous amino acids of HTT, in particular of a N-terminal, polyP region, P-rich region or the C-terminal region of exon 1.

By "specifically binding", or "specifically recognizing", used interchangeably herein, it is generally meant that a binding molecule, *e.g.*, an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D".

Where present, the term "immunological binding characteristics," or other binding characteristics of an antibody with an antigen, in all of its grammatical forms, refers to the specificity, affinity, cross-reactivity, and other binding characteristics of an antibody.

5 By "preferentially binding", it is meant that the binding molecule, *e.g.*, antibody specifically binds to an epitope more readily than it would bind to a related, similar, homologous, or analogous epitope. Thus, an antibody which "preferentially binds" to a given epitope would more likely bind to that epitope than to a related epitope, even though such an antibody may cross-react with the related epitope.

10

By way of non-limiting example, a binding molecule, *e.g.*, an antibody may be considered to bind a first epitope preferentially if it binds said first epitope with a dissociation constant ( $K_D$ ) that is less than the antibody's  $K_D$  for the second epitope. In another non-limiting example, an antibody may be considered to bind a first antigen preferentially if it binds the first epitope with  
15 an affinity that is at least one order of magnitude less than the antibody's  $K_D$  for the second epitope. In another non-limiting example, an antibody may be considered to bind a first epitope preferentially if it binds the first epitope with an affinity that is at least two orders of magnitude less than the antibody's  $K_D$  for the second epitope.

20 In another non-limiting example, a binding molecule, *e.g.*, an antibody may be considered to bind a first epitope preferentially if it binds the first epitope with an off rate ( $k(\text{off})$ ) that is less than the antibody's  $k(\text{off})$  for the second epitope. In another non-limiting example, an antibody may be considered to bind a first epitope preferentially if it binds the first epitope with an affinity that is at least one order of magnitude less than the antibody's  $k(\text{off})$  for the second  
25 epitope. In another non-limiting example, an antibody may be considered to bind a first epitope preferentially if it binds the first epitope with an affinity that is at least two orders of magnitude less than the antibody's  $k(\text{off})$  for the second epitope.

A binding molecule, *e.g.*, an antibody or antigen-binding fragment, variant, or derivative  
30 disclosed herein may be said to bind HTT or a fragment, variant or specific conformation thereof with an off rate ( $k(\text{off})$ ) of less than or equal to  $5 \times 10^{-2} \text{ sec}^{-1}$ ,  $10^{-2} \text{ sec}^{-1}$ ,  $5 \times 10^{-3} \text{ sec}^{-1}$  or  $10^{-3} \text{ sec}^{-1}$ . More preferably, an antibody of the invention may be said to bind HTT or a fragment, variant or specific conformation thereof with an off rate ( $k(\text{off})$ ) less than or equal to  $5 \times 10^{-4} \text{ sec}^{-1}$ ,  $10^{-4} \text{ sec}^{-1}$ ,  $5 \times 10^{-5} \text{ sec}^{-1}$ , or  $10^{-5} \text{ sec}^{-1}$ ,  $5 \times 10^{-6} \text{ sec}^{-1}$ ,  $10^{-6} \text{ sec}^{-1}$ ,  $5 \times 10^{-7} \text{ sec}^{-1}$  or  $10^{-7} \text{ sec}^{-1}$ .

A binding molecule, *e.g.*, an antibody or antigen-binding fragment, variant, or derivative disclosed herein may be said to bind HTT or a fragment, variant or specific conformation thereof with an on rate ( $k(\text{on})$ ) of greater than or equal to  $10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $10^4$   
5  $\text{M}^{-1} \text{ sec}^{-1}$  or  $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ . More preferably, an antibody of the invention may be said to bind HTT or a fragment, variant or specific conformation thereof with an on rate ( $k(\text{on})$ ) greater than or equal to  $10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$ ,  $10^6 \text{ M}^{-1} \text{ sec}^{-1}$ , or  $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$  or  $10^7 \text{ M}^{-1} \text{ sec}^{-1}$ .

A binding molecule, *e.g.*, an antibody is said to competitively inhibit binding of a reference  
10 antibody to a given epitope if it preferentially binds to that epitope to the extent that it blocks, to some degree, binding of the reference antibody to the epitope. Competitive inhibition may be determined by any method known in the art, for example, competition ELISA assays. An antibody may be said to competitively inhibit binding of the reference antibody to a given epitope by at least 90%, at least 80%, at least 70%, at least 60%, or at least 50%.

As used herein, the term "affinity" refers to a measure of the strength of the binding of an individual epitope with the CDR of a binding molecule, *e.g.*, an immunoglobulin molecule; *see, e.g.*, Harlow *et al.*, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd ed. (1988) at pages 27-28. As used herein, the term "avidity" refers to the overall stability  
20 of the complex between a population of immunoglobulins and an antigen, that is, the functional combining strength of an immunoglobulin mixture with the antigen; *see, e.g.*, Harlow at pages 29-34. Avidity is related to both the affinity of individual immunoglobulin molecules in the population with specific epitopes, and also the valences of the immunoglobulins and the antigen. For example, the interaction between a bivalent monoclonal antibody and an antigen  
25 with a highly repeating epitope structure, such as a polymer, would be one of high avidity. The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method; *see, for example*, Berzofsky *et al.*, "Antibody-Antigen Interactions" In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press New York, N Y (1984), Kuby, Janis *Immunology*, W. H. Freeman and Company New York, N Y (1992), and methods described  
30 herein. General techniques for measuring the affinity of an antibody for an antigen include ELISA, RIA, and surface plasmon resonance. The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions, *e.g.*, salt concentration, pH. Thus, measurements of affinity and other antigen-binding parameters, *e.g.*,  $K_D$ ,  $IC_{50}$ , are preferably made with standardized solutions of antibody and antigen, and a standardized buffer.



Binding molecules, *e.g.*, antibodies or antigen-binding fragments, variants or derivatives thereof of the invention may also be described or specified in terms of their cross-reactivity. As used herein, the term "cross-reactivity" refers to the ability of an antibody, specific for one antigen, to react with a second antigen; a measure of relatedness between two different antigenic substances. Thus, an antibody is cross reactive if it binds to an epitope other than the one that induced its formation. The cross reactive epitope generally contains many of the same complementary structural features as the inducing epitope, and in some cases, may actually fit better than the original.

For example, certain antibodies have some degree of cross-reactivity, in that they bind related, but non-identical epitopes, *e.g.*, epitopes with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a reference epitope. An antibody may be said to have little or no cross-reactivity if it does not bind epitopes with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a reference epitope. An antibody may be deemed "highly specific" for a certain epitope, if it does not bind any other analog, ortholog, or homolog of that epitope.

Binding molecules, *e.g.*, antibodies or antigen-binding fragments, variants or derivatives thereof of the invention may also be described or specified in terms of their binding affinity to HTT and/or mutated, misfolded, and/or aggregated HTT species and/or fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

As previously indicated, the subunit structures and three dimensional configuration of the constant regions of the various immunoglobulin classes are well known. As used herein, the term " $V_H$  domain" includes the amino terminal variable domain of an immunoglobulin heavy chain and the term "CH1 domain" includes the first (most amino terminal) constant region

domain of an immunoglobulin heavy chain. The CH1 domain is adjacent to the V<sub>H</sub> domain and is amino terminal to the hinge region of an immunoglobulin heavy chain molecule.

As used herein the term "CH2 domain" includes the portion of a heavy chain molecule that extends, *e.g.*, from about residue 244 to residue 360 of an antibody using conventional numbering schemes (residues 244 to 360, Kabat numbering system; and residues 231-340, EU numbering system; see Kabat EA *et al. op. cit*). The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It is also well documented that the CH3 domain extends from the CH2 domain to the C-terminal of the IgG molecule and comprises approximately 108 residues.

As used herein, the term "hinge region" includes the portion of a heavy chain molecule that joins the CH1 domain to the CH2 domain. This hinge region comprises approximately 25 residues and is flexible, thus allowing the two N-terminal antigen-binding regions to move independently. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains; see Roux *et al.*, J. Immunol. 161 (1998), 4083-4090.

As used herein the term "disulfide bond" includes the covalent bond formed between two sulfur atoms. The amino acid cysteine comprises a thiol group that can form a disulfide bond or bridge with a second thiol group. In most naturally occurring IgG molecules, the CH1 and CL regions are linked by a disulfide bond and the two heavy chains are linked by two disulfide bonds at positions corresponding to 239 and 242 using the Kabat numbering system (position 226 or 229, EU numbering system).

As used herein, the terms "linked", "fused" or "fusion" are used interchangeably. These terms refer to the joining together of two more elements or components, by whatever means including chemical conjugation or recombinant means. An "in-frame fusion" refers to the joining of two or more polynucleotide open reading frames (ORFs) to form a continuous longer ORF, in a manner that maintains the correct translational reading frame of the original ORFs. Thus, a recombinant fusion protein is a single protein containing two or more segments that correspond to polypeptides encoded by the original ORFs (which segments are not normally so joined in nature). Although the reading frame is thus made continuous throughout the fused segments, the segments may be physically or spatially separated by, for example, in-frame linker sequence. For example, polynucleotides encoding the CDRs of an immunoglobulin variable

region may be fused, in-frame, but be separated by a polynucleotide encoding at least one immunoglobulin framework region or additional CDR regions, as long as the "fused" CDRs are co-translated as part of a continuous polypeptide.

5 The term "expression" as used herein refers to a process by which a gene produces a biochemical, for example, an RNA or polypeptide. The process includes any manifestation of the functional presence of the gene within the cell including, without limitation, gene knockdown as well as both transient expression and stable expression. It includes without limitation transcription of the gene into messenger RNA (mRNA), transfer RNA (tRNA), small  
10 hairpin RNA (shRNA), small interfering RNA (siRNA) or any other RNA product, and the translation of mRNA into polypeptide(s). If the final desired product is a biochemical, expression includes the creation of that biochemical and any precursors. Expression of a gene produces a "gene product." As used herein, a gene product can be either a nucleic acid, *e.g.*, a messenger RNA produced by transcription of a gene, or a polypeptide which is translated from  
15 a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, *e.g.*, polyadenylation, or polypeptides with post translational modifications, *e.g.*, methylation, glycosylation, the addition of lipids, association with other protein subunits, proteolytic cleavage, and the like.

20 As used herein, the term "sample" refers to any biological material obtained from a subject or patient. In one aspect, a sample can comprise blood, peritoneal fluid, CSF, saliva or urine. In other aspects, a sample can comprise whole blood, blood plasma, blood serum, B cells enriched from blood samples, and cultured cells (*e.g.*, B cells from a subject). A sample can also include a biopsy or tissue sample including neural tissue. In still other aspects, a sample can comprise  
25 whole cells and/or a lysate of the cells. Blood samples can be collected by methods known in the art. In one aspect, the pellet can be resuspended by vortexing at 4°C in 200 µl buffer (20 mM Tris, pH. 7.5, 0.5 % Nonidet, 1 mM EDTA, 1 mM PMSF, 0.1 M NaCl, IX Sigma Protease Inhibitor, and IX Sigma Phosphatase Inhibitors 1 and 2). The suspension can be kept on ice for 20 min. with intermittent vortexing. After spinning at 15,000 x g for 5 min at about 4°C, aliquots  
30 of supernatant can be stored at about -70°C.

Diseases:

Unless stated otherwise, the terms "disorder" and "disease" are used interchangeably herein and comprise any undesired physiological change in a subject, an animal, an isolated organ, tissue or cell/cell culture.

5

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by the expansion of a CAG trinucleotide repeat within the huntingtin (HTT) gene (Huntington's Disease Collaborative Research Group, Cell 72(6) (1993), 971–983), wherein the pathogenic threshold of this expansion is approximately 37 repeats, whereas fewer repeats  
10 below this number do not result in pathogenesis, see *e.g.* Trottier *et al.*, Nature 378(6555) (1995), 403–406. The expansion of the CAG trinucleotide repeat results in an expanded polyglutamine (Poly-Gln, Poly-Q) tract in the amino terminus of the huntingtin protein (HTT), which is associated with the aggregation of HTT. However, the precise mechanism leading to the accumulation of HTT and its associated symptoms has not been elucidated so far.

15

Studies have shown that both flanking regions of the polyglutamine (Poly-Q) tract, *i.e.* amino-terminal region consisting of an amphipathic alpha-helical targeting domain and the carboxy-terminal region characterized by two proline tracts (Poly-P region) and a leucine-proline-rich tract (P-rich region) seem to be critical in mediating the toxicity of the mutated HTT, see *e.g.*  
20 Caron *et al.*, PNAS 110 (2013), 14610–14615.

The mechanism contributing to the pathological symptoms of HD, such as hyperkinesia, hypokinesia, mental and movement disorders including disturbances of affect and the drive, lack of motor persistence, thoughtless and impulsive behavior, resignation and depression,  
25 disorders of visual information processing, subcortical dementia, loss of cognitive abilities, disorientation and paucity of speech, delusions, restlessness of the arms, legs, face, head and the trunk, choreic hyperkinesia, dysarthria, dysphagia, anarthria, dystonias, has not been elucidated so far. Possible mechanisms include but are not limited to a reduced flexibility of the hinge region due to the expanded Poly-Q tract of HTT as well as to proteases which lead to  
30 the formation of different HTT fragments due to the expanded Poly-Q tract.

Since the antibodies of the present invention have been shown to be therapeutically effective in a HD mouse model, see *e.g.* Example 24 and Fig. 17 as well as Example 34 and Fig. 34 and in addition are capable of binding to HTT amyloids in tissue sections from HD patients, see *e.g.*

Example 31 and Fig. 27-30, the human-derived antibodies and biotechnological derivatives thereof are useful in both the treatment and diagnosis of HD and the above-mentioned symptoms. Therefore, in one embodiment of the present invention the antibodies of the present invention, binding molecules having substantially the same binding specificities of any one thereof, the polynucleotides, the vectors or the cells of the present invention are used for preparation of a pharmaceutical or diagnostic composition for prophylactic and/or therapeutic treatment of HD, in particular HTT amyloidosis diseases and/or disorders, for monitoring disease progression and/or treatment response, and for the diagnosis of diseases associated with HTT amyloidosis.

Treatment:

As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development of cardiac deficiency.

Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the manifestation of the condition or disorder is to be prevented.

If not stated otherwise the term "drug," "medicine," or "medicament" are used interchangeably herein and shall include but are not limited to all (A) articles, medicines and preparations for internal or external use, and any substance or mixture of substances intended to be used for diagnosis, cure, mitigation, treatment, or prevention of disease of either man or other animals; and (B) articles, medicines and preparations (other than food) intended to affect the structure or any function of the body of man or other animals; and (C) articles intended for use as a component of any article specified in clause (A) and (B). The term "drug," "medicine," or "medicament" shall include the complete formula of the preparation intended for use in either man or other animals containing one or more "agents," "compounds", "substances" or "(chemical) compositions" as and in some other context also other pharmaceutically inactive excipients as fillers, disintegrants, lubricants, glidants, binders or ensuring easy transport,

disintegration, disaggregation, dissolution and biological availability of the "drug," "medicine," or "medicament" at an intended target location within the body of man or other animals, *e.g.*, at the skin, in the stomach or the intestine. The terms "agent," "compound", or "substance" are used interchangeably herein and shall include, in a more particular context, but are not limited to all pharmacologically active agents, *i.e.* agents that induce a desired biological or pharmacological effect or are investigated or tested for the capability of inducing such a possible pharmacological effect by the methods of the present invention.

By "subject" or "individual" or "animal" or "patient" or "mammal", is meant any subject, particularly a mammalian subject, *e.g.*, a human patient, for whom diagnosis, prognosis, prevention, or therapy is desired.

Pharmaceutical carriers:

Pharmaceutically acceptable carriers and administration routes can be taken from corresponding literature known to the person skilled in the art. The pharmaceutical compositions of the present invention can be formulated according to methods well known in the art; see for example Remington: The Science and Practice of Pharmacy (2000) by the University of Sciences in Philadelphia, ISBN 0-683-306472, Vaccine Protocols 2nd Edition by Robinson *et al.*, Humana Press, Totowa, New Jersey, USA, 2003; Banga, Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems. 2nd Edition by Taylor and Francis. (2006), ISBN: 0-8493-1630-8. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well-known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways. Examples include administering a composition containing a pharmaceutically acceptable carrier via oral, intranasal, rectal, topical, intraperitoneal, intravenous, intramuscular, subcutaneous, subdermal, transdermal, intrathecal, and intracranial methods. Aerosol formulations such as nasal spray formulations include purified aqueous or other solutions of the active agent with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Pharmaceutical compositions for oral administration, such as single domain antibody molecules (*e.g.*, "nanobodies™") etc. are also envisaged in the present invention. Such oral formulations may be in tablet, capsule, powder,

liquid or semi-solid form. A tablet may comprise a solid carrier, such as gelatin or an adjuvant. Formulations for rectal or vaginal administration may be presented as a suppository with a suitable carrier; see also O'Hagan *et al.*, Nature Reviews, Drug Discovery 2(9) (2003), 727-735. Further guidance regarding formulations that are suitable for various types of administration can be found in Remington's Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985) and corresponding updates. For a brief review of methods for drug delivery see Langer, Science 249 (1990), 1527-1533.

## II. Antibodies of the present invention

The present invention generally relates to human-derived anti-HTT antibodies and HTT-binding fragments thereof, which preferably demonstrate the immunological binding characteristics and/or biological properties as outlined for the antibodies illustrated in the Examples. In accordance with the present invention human monoclonal antibodies specific for HTT were cloned from B cells of a pool of healthy human subjects. However, in another embodiment of the present invention, the human monoclonal anti-HTT antibodies might also be cloned from B cells of patients showing symptoms of a disease and/or disorder associated with HTT amyloidosis.

In the course of the experiments performed in accordance with the present invention, antibodies present in the conditioned media of cultured human memory B cell were evaluated for their capacity to bind to HTT and to more than 10 other proteins including bovine serum albumin (BSA); see Examples 8, 13, 18, 31 and 33. Only the B-cell supernatants able to bind to the HTT protein but not to any of the other proteins in the screen were selected for further analysis, including determination of the antibody class and light chain subclass. The selected B-cells were then processed for antibody cloning.

In brief, this consisted in the extraction of messenger RNAs from the selected B-cells, retro-transcription by RT-PCR, amplification of the antibody-coding regions by PCR, cloning into plasmid vectors and sequencing. Selected human antibodies were then produced by recombinant expression in HEK293 or CHO cells and purification, and subsequently characterized for their capacity to bind human HTT protein. The combination of various tests, *e.g.* recombinant expression of the antibodies in HEK293 or CHO cells and the subsequent characterization of their binding specificities towards human HTT protein, and their distinctive binding to pathologically mutated and/or aggregated forms thereof confirmed that for the first

time human antibodies have been cloned that are highly specific for HTT and distinctively recognize and selectively bind the pathologically aggregated forms of HTT protein. In some cases, mouse chimeric antibodies were also generated on the basis of the variable domains of the human antibodies of the present invention.

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Thus, the present invention generally relates to recombinant human-derived monoclonal anti-HTT antibodies and HTT-binding fragments, synthetic and biotechnological derivatives and variants thereof. In one embodiment of the invention, the antibody is capable of binding human HTT.

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In one embodiment of the present invention the antibody specifically binds an epitope in a polyP-region of HTT, which comprises the amino acid sequence PPPPPPPP (NI-302.33C11; NI-302.44D7; NI-302.7A8; NI-302.3D8; NI-302.46C9) (SEQ ID Nos. 139, 151, 154, 158, 161), amino acid sequence PPPPPP (NI-302.11H6, NI-302.18A1, NI-302.52C9) (SEQ ID Nos.: 157, 159, 160), amino acid sequence PPPPPPPPPP (NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-302.71F6) (SEQ ID Nos.: 146, 147, 148, 149, 150, 152, 153, 155, 156), an epitope in the P-rich-region which comprises the amino acid sequence PQPPPQAQPL (NI-302.63F3 SEQ ID No. 140, NI-302.64E5 SEQ ID No. 200), the amino acid sequence PPPQLPQPPP (NI-302.31F11, SEQ ID No. 141), the amino acid sequence QAQPLLQPQPPPPP (NI-302.2A2; SEQ ID No. 142), or the amino acid sequence PPPQLPQPPPQAQPL (NI302.15D3; SEQ ID No. 143), an epitope in the C-terminal region which comprise the amino acid sequence PPGPAVAEEPLHRP (NI-302.35C1, SEQ ID No. 145) or PPPGPAVAEEPLH (NI-302.72F10, SEQ ID No. 202), an epitope in the N-terminal region which comprises the amino acid sequence KAFESLKSFQ (NI-NI-302.15E8, SEQ ID No. 144) or an epitope in the P/Q-rich-region which comprises the amino acid sequence QQQQQQQQPPPP (NI-302.7D8 SEQ ID No. 201), or a conformational epitope.

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In another embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope in a polyP-region of HTT as a reference antibody selected from the group consisting of NI-302.33C11, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.37C12, NI-302.55D8, NI-302.7A8, 302.78H12, NI-302.71F6, NI-302.11H6, NI-302.3D8, NI-302.18A1, NI-302.8F1, NI-



302.52C9, NI-302.46C9. Epitope mapping identified a sequence within the polyP-region of human HTT including amino acids PPPPPPPPPP (SEQ ID Nos.: 146, 147, 148, 149, 150, 152, 153, 155, 156) as the unique linear epitope recognized by antibodies NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-302.71F6 of this invention. Additionally, epitope mapping identified a sequence within the polyP-region of human HTT including amino acids PPPPPPPP (SEQ ID Nos. 139, 151, 154, 158, 161) as the unique linear epitope recognized by antibodies NI-302.33C11, NI-302.44D7, NI-302.7A8, NI-302.3D8, NI-302.46C9 of this invention, and amino acids PPPPPP (SEQ ID Nos.: 157, 159, 160) as the unique linear epitope recognized by antibodies NI-302.11H6, NI-302.18A1, NI-302.52C9 of this invention. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in a polyP-region of HTT, which comprises the amino acid sequence PPPPPPPPPP (SEQ ID Nos.: 146, 147, 148, 149, 150, 152, 153, 155, 156), PPPPPPPP (SEQ ID Nos. 139, 151, 154, 158, 161), or PPPPPP (SEQ ID Nos.: 157, 159, 160).

In one embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope in the P-rich region of HTT as a reference antibody selected from the group consisting of NI-302.63F3, NI-302.31F11, NI-302.2A2, and NI-302.15D3. Epitope mapping identified a sequence within the P-rich-region of human HTT including amino acids PQPPPQAQPL (SEQ ID No. 140) as the unique linear epitope recognized by antibody NI-302.63F3 of this invention, PPPQLPQPPP (SEQ ID No. 141), as the unique linear epitope recognized by antibody NI-302.31F11 of this invention, PPPQLPQPPP (SEQ ID No. 141), as the unique linear epitope recognized by antibody NI-302.31F11 of this invention, QAQPLLQPQPPPPP (SEQ ID No. 142) as the unique linear epitope recognized by antibody NI-302.2A2, PPPQLPQPPPQAQPL (SEQ ID No. 143) as the unique linear epitope recognized by antibody NI302.15D3, PQPPPQAQPL as the unique linear epitope recognized by antibody NI302.64E5. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in the P-rich-region of HTT which comprises the amino acid sequence PQPPPQAQPL (SEQ ID No. 140), PPPQLPQPPP (SEQ ID No. 141), QAQPLLQPQPPPPP (SEQ ID No. 142), PPPQLPQPPPQAQPL (SEQ ID No. 143).

In another embodiment the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, wherein the antibody specifically binds to the same epitope in the polyQ/polyP-region of HTT as reference antibody NI-302.7D8. Epitope mapping identified a sequence within the Q/P-rich-region of human HTT including amino acids QQQQQQQPPP (SEQ ID No. 201) as the unique linear epitope recognized by antibody NI-302.7D8 of this invention. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in the polyQ/polyP-region of HTT which comprises the amino acid sequence QQQQQQQPPP (SEQ ID No. 201)

In one embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope in the C-terminal region of HTT as a reference antibody selected from the group consisting of NI-302.35C1. Epitope mapping identified a sequence within the C-terminal region of human HTT including amino acids PPGPAVAEEPLHRP (SEQ ID No. 145) as the unique linear epitope recognized by antibody NI-302.35C1 of this invention. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in the C-terminal region of HTT which comprises the amino acid sequence PPGPAVAEEPLHRP (SEQ ID No. 145).

In a further embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope in the C-terminal region of HTT as reference antibody NI-302.72F10. Epitope mapping identified a sequence within the C-terminal region of human HTT including amino acids PPPGPAVAEEPLH (SEQ ID No. 202) as the unique linear epitope recognized by antibody NI-302.72F10 of this invention. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in the C-terminal region of HTT which comprises the amino acid sequence PPPGPAVAEEPLH (SEQ ID No. 202).

In another embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope in the N-terminal region of HTT as reference antibody NI-302.15E8. Epitope mapping identified a sequence within the N-terminal region of human

HTT including amino acids KAFESLKSFQ (SEQ ID No. 144) as the unique linear epitope recognized by antibody NI-302.15E8 of this invention. Therefore, in one embodiment the antibody of the present invention is provided, wherein the antibody specifically binds to an epitope in the N-terminal region of HTT which comprises the amino acid sequence KAFESLKSFQ (SEQ ID No. 144).

In one embodiment, the present invention is directed to an anti-HTT antibody, or antigen-binding fragment, variant or biotechnological derivatives thereof, where the antibody specifically binds to the same epitope of HTT exon 1 as a reference antibody selected from the group consisting of NI-302.6N9, NI-302.4A6, NI-302.12H2 or NI-302.8M1 which have been shown not to bind to linear peptides of HTT exon 1 but aggregated HTT exon 1 proteins with 21 or 49 polyQ (HD21 and HD49) with high affinity and an  $EC_{50}$  value in the subnanomolar range; see, *e.g.*, Example 25 and Figure 20 for overview. Therefore, in one preferred embodiment the antibody of the present invention specifically binds aggregated forms of HTT, in particular protein aggregates derived from HTT exon 1 with an  $EC_{50}$  value of below 1 nM, preferably below 0,1 nM and most preferably below 0,01 nM.

Furthermore, without intending to be bound by initial experimental observations as demonstrated in the Examples and shown in Figures, the human monoclonal NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302.31F11, NI-302.6N9, NI-302.46C9, NI-302.8F1, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.55D8, NI-302.7A8, NI-302.78H12, NI-302.71F6, NI-302.11H6, NI-302.3D8, and NI-302-64E5 and NI-302-72F10 anti-HTT antibodies of the present invention are preferably characterized in specifically binding to pathological mutated and/or aggregated HTT and to substantially smaller affinity recognizing HTT in the physiological form, see *e.g.* Examples 7, 13, 18 and Figs. 3, 7, 11, 21, 32. Hence, the present invention provides a set of human anti-HTT antibodies with binding properties particularly useful for diagnostic and therapeutic purposes. Thus, in one embodiment the present invention provides antibodies which are capable of specifically binding pathologically aggregated forms of HTT. However, in addition or alternatively, the antibodies of the present invention which are capable to bind to a polyP-region or a P-rich region of HTT exon 1 may be also utilized in other applications. In particular, these antibodies are not limited to HTT but can also bind to other targets showing also a polyP-tract or a P-rich region.

In one embodiment, the antibody of the present invention exhibits the binding properties of the exemplary NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302-7D8 and NI-302-72F10 antibodies as described in the Examples. The anti-HTT antibody of the present invention preferentially recognizes pathologically altered HTT, such as mutated and/or aggregated HTT species and fragments thereof rather than physiological HTT. Thus, in one embodiment, the antibody of the present invention does not substantially recognize physiological HTT species.

The term "does not substantially recognize" when used in the present application to describe the binding affinity of a molecule of a group comprising an antibody, a fragment thereof or a binding molecule for a specific target molecule, antigen and/or conformation of the target molecule and/or antigen means that the molecule of the aforementioned group binds said molecule, antigen and/or conformation with a binding affinity which is at least 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold or 9-fold less than the binding affinity of the molecule of the aforementioned group for binding another molecule, antigen and/or conformation. Very often the dissociation constant (KD) is used as a measure of the binding affinity. Sometimes, it is the EC<sub>50</sub> on a specific assay as for example an ELISA assay that is used as a measure of the binding affinity. Preferably the term "does not substantially recognize" when used in the present application means that the molecule of the aforementioned group binds said molecule, antigen and/or conformation with a binding affinity which is at least or 10-fold, 20-fold, 50-fold, 100-fold, 1000-fold or 10000-fold less than the binding affinity of said molecule of the aforementioned group for binding to another molecule, antigen and/or conformation.

As described above, the aggregation of HTT in HD is suggested to occur due to an extension of the poly-glutamine tract within the HTT exon 1. In particular, it has been shown that HD mainly occurs in patients having a threshold over the 35-40 glutamine residues in length in the HTT. Accordingly, as shown in Example 3, aggregated and soluble construct of HTT exon 1 with 21, 35 or 49 polyQ repeats were generated in order to identify the utility of the anti-HTT-antibodies of the present invention to specifically bind to pathological altered HTT.

The term HDX as used in the following describes the HTT constructs which were generated in accordance with Example 3. Particularly the X denotes the number of glutamine repeats (Qs), e.g. HTT exon 1 protein with 21 polyQ repeats will be denoted HD21.

Utilizing the constructs as described in the Examples, it could be shown that the anti-HTT antibody of the present invention in addition, or alternatively, binds to pathologically, disease causing and/or mutated and/or aggregated forms of human HTT. In this context, the binding affinities may be in the range as shown for the exemplary NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302.31F11, NI-302.6N9, NI-302.46C9, NI-302.8F1, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.55D8, NI-302.7A8, NI-302.78H12, NI-302.71F6, NI-302.11H6, and NI-302.3D8 antibodies in Fig. 3(A), 7(A), 11(A), 14(A), respective Fig. 19, 20 and 31, *i.e.* having half maximal effective concentrations ( $EC_{50}$ ) of about 1 pM to 250 nM, preferably an  $EC_{50}$  of about 25 pM to 50 nM, most preferably an  $EC_{50}$  of about 0.05 nM to 30 nM for human aggregated HD49-HTT and aggregated recombinant HD49-HTT, or an  $EC_{50}$  of about 0.05 nM to 5 nM for human aggregated HD21-HTT and aggregated recombinant HD21-HTT.

In particular, the anti-HTT antibody, binding fragment or biotechnological derivative thereof has a binding affinity corresponding to an  $EC_{50}$  value of  $\leq 20$  nM, preferably  $\leq 10$  nM and most preferably  $\leq 1$  nM for binding aggregated HD49 HTT and/or of  $\leq 40$  nM, preferably  $\leq 10$  nM and most preferably  $\leq 1$  nM for binding HD21 HTT; see Fig. 3, 7, 11, 19 and 31.

HTT aggregation associated with the development of HD is most frequently associated with poly-glutamine (polyQ) tracts of  $> 35$  repeats. As shown in the present invention, the anti-HTT antibodies described herein showed high binding efficiency to HD tracts with higher repetitions, see *e.g.* Examples 7, 13, 18, 31 and 33. Therefore, in one embodiment of the present invention the anti-HTT antibody, HTT-binding molecule, fragment, synthetic or biotechnological variant thereof binds to HTT with expanded poly-glutamine (Q) tract. In a preferred embodiment it binds to HTT with more than 35 repeats. In a particular preferred embodiment of the present invention, the antibody binds to HTT with expanded poly-glutamine (Q) tract consisting of 49 (HD49) repeats over 35 repeats (HD35) and more over 21 repeats (HD21).

However, in accordance with the present invention also anti-HTT antibodies, HTT-binding molecules, fragments, synthetic or biotechnological variants thereof binding to poly-glutamine (polyQ) tracts under 35 (HD35) are described. Therefore, in one embodiment of the present invention, the antibody, binding molecule or variants thereof binds to HTT showing "normal" polyQ tracts. In particular, the antibody is capable of binding to HTT with polyQ tracts  $< 35$  repeats (HD35).

- Some antibodies are able to bind to a wide array of biomolecules, *e.g.*, proteins. As the skilled artisan will appreciate, the term specific is used herein to indicate that other biomolecules than HTT proteins or fragments thereof do not significantly bind to the antigen-binding molecule, *e.g.*, one of the antibodies of the present invention. Preferably, the level of binding to a biomolecule other than HTT results in a binding affinity which is at most only 20% or less, 10% or less, only 5% or less, only 2% or less or only 1% or less (*i.e.* at least 5, 10, 20, 50 or 100 fold lower, or anything beyond that) of the affinity to HTT, respectively; see *e.g.*, Fig. 20.
- 10 In one embodiment, the anti-HTT antibody of the present invention binds preferentially to aggregated forms of HTT and/or fragments, derivatives, fibrils and/or oligomers thereof. In another embodiment the anti-HTT antibody of the present invention preferentially binds to both native HTT and pathologically mutated and/or aggregated forms of HTT.
- 15 In a further embodiment of the present invention, the anti-HTT antibody or HTT-binding fragment, synthetic or biotechnological derivative thereof is a bispecific antibody. Thus, the antibody of the present invention may be capable of recognizing at least two distinct epitopes either on the same or on different antigens; see also, *supra*.
- 20 In one embodiment, at least one binding site/domain of the bispecific antibody specifically recognizes an epitope in a polyP-region of HTT, which comprises the amino acid sequence PPPPPPP (NI-302.33C11; NI-302.44D7; NI-302.7A8; NI-302.3D8; NI-302.46C9) (SEQ ID Nos. 139, 151, 154, 158, 161), amino acid sequence PPPPPP (NI-302.11H6, NI-302.18A1, NI-302.52C9) (SEQ ID Nos.: 157, 159, 160), amino acid sequence PPPPPPPPPPP (NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-302.71F6) (SEQ ID Nos.: 146, 147, 148, 149, 150, 152, 153, 155, 156), an epitope in the P-rich-region which comprises the amino acid sequence QPPPPQAQPL (NI-302.63F3 SEQ ID No. 140, NI-302.64E5 SEQ ID No. 200), the amino acid sequence PPPQLPQPPP (NI-302.31F11, SEQ ID No. 141), the amino acid sequence QAQPLLPQPQPPPP (NI-302.2A2; SEQ ID No. 142), or the amino acid sequence PPPQLPQPPPQAQPL (NI302.15D3; SEQ ID No. 143), an epitope in the C-terminal region which comprise the amino acid sequence PPGPAVAEEPLHRP (NI-302.35C1, SEQ ID No. 145) or PPPGPAVAEEPLH (NI-302.72F10, SEQ ID No. 202), an epitope in the N-terminal region which comprises the amino acid sequence KAFESLKSFQ (NI-302.15E8, SEQ ID No.
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144), an epitope in the P/Q-rich-region which comprises the amino acid sequence QQQQQQQQPPPP (NI-302.7D8 SEQ ID No. 201), or a conformational epitope recognized by any one of antibodies NI-302.6N9, NI-302.4A6, NI-302.12H2 or NI-302.8M1.

5 As mentioned before, accumulation of polyglutamine (poly-Gln, polyQ)-containing HTT protein aggregates in neuronal intranuclear inclusions is a hallmark of the progressive neurodegenerative disorder Huntington's disease (HD). Electron micrographs of these aggregates revealed fibrillar structures showing a closely related morphology as in B-amyloid  
10 fibrils in Alzheimer's disease, see *e.g.* Caughey *et al.*, Trends Cell Biol. 7 (1997), 56–62 and Caputo *et al.*, Arch. Biochem. Biophys. 292 (1992), 199–205, suggesting that HD, wherein degenerative process primarily involves medium spiny striatal neurons and cortical neurons leading to dysfunction and subsequently neuronal loss, tissue damage due to excitotoxicity, mitochondrial damage, free radicals, and possibly also inflammatory mechanisms including  
15 microglia activation and further progressive nature of symptoms, are a result of toxic amyloid fibrillogenesis. Therefore, in one embodiment the antibody of the present invention is useful for the treatment of Huntington's disease (HD) and symptoms thereof.

So far, intracellularly expressed antibodies (intrabodies) have been described and considered as therapeutic tools in HD which perturb the HTT function, see *e.g.* Ali *et al.* in Neurobiology of  
20 Huntington's Disease: Applications to Drug Discovery, Lo *et al.*, Chapter 10, CRC Press (2011). Although these intrabodies showed a positive effect on the aggregation and cell death induced by HTT in cell based assays, see *e.g.* Khoshnan *et al.*, Proc Natl Acad Sci U S A. 99 (2002), 1002–1007, one disadvantage in their therapeutic utility is the route of administration. In particular, the preferred method for the delivery of the therapeutic intrabodies to the brain is  
25 a viral vector-based gene therapy. However, a major disadvantage of using this kind of administration is among other the high host immunogenicity. Therefore, non-viral methods utilizing other routes of administration as are preferably used in the therapeutic or diagnostic approaches. The antibodies of the present invention have been shown to attenuate the dendritic spine density loss upon addition to the culture medium, *i.e.* extracellularly. Therefore, in  
30 contrast to the intrabodies described before, the antibodies of the present invention can be expected to be efficacious following therapeutically preferred administration routes. Accordingly, in one embodiment of the present invention the antibody is administrated by a subcutaneous injection (*s.c.*), intravenous injection (*i.v.*), intramuscular injection (*i.m.*),

intraperitoneal (*i.p.*), intrathecal, jet injection, wherein the radius of action is not limited to the intracellular expression of the antibody.

As already mentioned before, and as shown in Example 24 and Fig. 17 the therapeutic utility of the antibodies of the present invention has been shown. In particular, it has been shown that the anti-HTT antibodies of the present invention are capable of attenuating the dendritic spine density loss. Therefore, in one embodiment of the present invention the anti-HTT antibody, the HTT-binding fragment, synthetic or biotechnological derivative thereof leads to an attenuation of spine density loss.

Furthermore, the therapeutic utility of the antibodies of the present invention has been demonstrated in Example 34 and Fig. 34. In particular, it has been shown that the anti-HTT antibodies of the present invention improve behavioral recovery during task-specific training and enhance loco-motor ability. Therefore, in one embodiment of the present invention the anti-HTT antibody, the HTT-binding fragment, synthetic or biotechnological derivative thereof leads to an improvement of behavioral performance during task-specific training and enhancement of sensorimotor ability.

The present invention is also drawn to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody comprises an antigen-binding domain identical to that of an antibody selected from the group consisting of NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302.31F11, NI-302.2A2, NI-302.6N9, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.37C12, NI-302.55D8, NI-302.7A8, NI-302.78H12, NI-302.71F6, NI-302.11H6, NI-302.3D8, NI-302.18A1, NI-302.8F1, NI-302.52C9, NI-302.46C9, NI-302.15E8, NI-302.15D3, NI-302.64E5, NI-302.7D8, NI-302.72F10, NI-302.12H2, NI-302.8M1 and NI-302.4A6.

The present invention further exemplifies several binding molecules, *e.g.*, antibodies and binding fragments thereof, recognizing a polyP-region of HTT, which may be characterized by comprising in their variable region, *e.g.*, binding domain at least one complementarity determining region (CDR) of the V<sub>H</sub> and/or V<sub>L</sub> variable region comprising any one of the amino acid sequences depicted in Fig. 1. The corresponding nucleotide sequences encoding the above-identified variable regions are set forth in Table II below. Exemplary sets of CDRs of the above amino acid sequences of the V<sub>H</sub> and/or V<sub>L</sub> region are depicted in Fig. 1. However, as discussed



in the following the person skilled in the art is well aware of the fact that in addition or alternatively CDRs may be used, which differ in their amino acid sequence from those set forth in Fig. 1 by one, two, three or even more amino acids in case of CDR2 and CDR3. Therefore, in one embodiment the antibody of the present invention or a HTT-binding fragment thereof is provided comprising in its variable region at least one complementarity determining region (CDR) as depicted in Fig. 1 and/or one or more CDRs thereof comprising one or more amino acid substitutions.

Further the present invention exemplifies several binding molecules, *e.g.*, antibodies and binding fragments thereof, recognizing the P-rich region of HTT which may be characterized by comprising in their variable region, *e.g.*, binding domain at least one complementarity determining region (CDR) of the  $V_H$  and/or  $V_L$  variable region comprising any one of the amino acid sequences depicted in Fig. 1. The corresponding nucleotide sequences encoding the above-identified variable regions are set forth in Table III below. Exemplary sets of CDRs of the above amino acid sequences of the  $V_H$  and/or  $V_L$  region are depicted in Fig. 1. However, as discussed in the following the person skilled in the art is well aware of the fact that in addition or alternatively CDRs may be used, which differ in their amino acid sequence from those set forth in Fig. 1 by one, two, three or even more amino acids in case of CDR2 and CDR3. Therefore, in one embodiment the antibody of the present invention or a HTT-binding fragment thereof is provided comprising in its variable region at least one complementarity determining region (CDR) as depicted in Fig. 1 and/or one or more CDRs thereof comprising one or more amino acid substitutions.

The present invention in addition exemplifies several binding molecules, *e.g.*, antibodies and binding fragments thereof, recognizing the C-terminal region of HTT which may be characterized by comprising in their variable region, *e.g.*, binding domain at least one complementarity determining region (CDR) of the  $V_H$  and/or  $V_L$  variable region comprising any one of the amino acid sequences depicted in Fig. 1. The corresponding nucleotide sequences encoding the above-identified variable regions are set forth in Table IV below. Exemplary sets of CDRs of the above amino acid sequences of the  $V_H$  and/or  $V_L$  region are depicted in Fig. 1. However, as discussed in the following the person skilled in the art is well aware of the fact that in addition or alternatively CDRs may be used, which differ in their amino acid sequence from those set forth in Fig. 1 by one, two, three or even more amino acids in case of CDR2 and CDR3. Therefore, in one embodiment the antibody of the present invention or a HTT-binding

fragment thereof is provided comprising in its variable region at least one complementarity determining region (CDR) as depicted in Fig. 1 and/or one or more CDRs thereof comprising one or more amino acid substitutions.

5 Additionally, the present invention exemplifies several binding molecules, *e.g.*, antibodies and binding fragments thereof, recognizing the N-terminal-region of HTT which may be characterized by comprising in their variable region, *e.g.*, binding domain at least one complementarity determining region (CDR) of the  $V_H$  and/or  $V_L$  variable region comprising any one of the amino acid sequences depicted in Fig. 1. The corresponding nucleotide sequences  
10 encoding the above-identified variable regions are set forth in Table VI below. Exemplary sets of CDRs of the above amino acid sequences of the  $V_H$  and/or  $V_L$  region are depicted in Fig. 1. However, as discussed in the following the person skilled in the art is well aware of the fact that in addition or alternatively CDRs may be used, which differ in their amino acid sequence from those set forth in Fig. 1 by one, two, three or even more amino acids in case of CDR2 and  
15 CDR3. Therefore, in one embodiment the antibody of the present invention or a HTT-binding fragment thereof is provided comprising in its variable region at least one complementarity determining region (CDR) as depicted in Fig. 1 and/or one or more CDRs thereof comprising one or more amino acid substitutions.

20 In one embodiment, the antibody of the present invention is any one of the antibodies comprising an amino acid sequence of the  $V_H$  and/or  $V_L$  region as depicted in Fig. 1 or a  $V_H$  and/or  $V_L$  region thereof comprising one or more amino acid substitutions. Preferably, the antibody of the present invention is characterized by the preservation of the cognate pairing of the heavy and light chain as was present in the human B-cell.

25 In a further embodiment of the present invention the anti-HTT antibody, HTT-binding fragment, synthetic or biotechnological variant thereof can be optimized to have appropriate binding affinity to the target and pharmacokinetic properties. Therefore, at least one amino acid in the CDR or variable region, which is prone to modifications selected from the group  
30 consisting of glycosylation, oxidation, deamination, peptide bond cleavage, iso-aspartate formation and/or unpaired cysteine is substituted by a mutated amino acid that lack such alteration or wherein at least one carbohydrate moiety is deleted or added chemically or enzymatically to the antibody. Examples for amino acid optimization can be found in Table VII, wherein antibodies showing primer-induced alterations are shown. Additional

modification optimizing the antibody properties are described in Gavel *et al.*, Protein Engineering 3 (1990), 433-442 and Helenius *et al.*, Annu. Rev. Biochem. 73 (2004), 1019-1049.

5 Alternatively, the antibody of the present invention is an antibody or antigen-binding fragment, derivative or variant thereof, which competes for binding to HTT with at least one of the antibodies having the V<sub>H</sub> and/or V<sub>L</sub> region as depicted in Fig. 1.

10 The antibody with at least one antibody having the V<sub>H</sub> and/or V<sub>L</sub> region as depicted in Fig. 1 competing for binding to HTT may be further characterized in a dot blot assay and/or filter retardation, as described in Example 6, 13, 18, 31 and/or 32. Therefore, in one embodiment of the present invention the antibody binds to HTT, preferably to HTT with an expanded poly-Q tract consisting of 49 (HD49) repeats in a dot blot assay and/or filter retardation.

15 Experimental results provided in Figs. 3, 7, 11, 21, 22 as well as Figs. 32 and 33, and Examples 6, 7, 13, 18, 26 and 32 suggest that some of the anti-HTT antibodies of the present invention preferentially bind to disease causing mutated and/or aggregated forms of human anti-HTT over the other amyloid forming proteins. In one embodiment thus, the antibody of the present invention preferentially recognizes mutated and/or aggregated HTT and/or fragment and/or  
20 derivatives thereof over other amyloid forming proteins.

In one embodiment of the present invention the anti-HTT antibody, HTT-binding fragment, synthetic or biotechnological derivative thereof does preferentially recognize mutated, aggregated and/or soluble forms of HTT over physiological HTT.

25

The antibody of the present invention may be human, in particular for therapeutic applications. Alternatively, the antibody of the present invention is a rodent, rodentized or chimeric rodent-human antibody, preferably a murine, murinized or chimeric murine-human antibody or a rat, ratinized or chimeric rat-human antibody which are particularly useful for diagnostic methods  
30 and studies in animals. In one embodiment the antibody of the present invention is a chimeric rodent-human or a rodentized antibody. Furthermore, in one embodiment, the chimeric antibody of the present invention, *i.e.* comprising the variable domains of a human antibody and generic murine light and heavy constant domains bind with a high affinity to human HTT. Preferably, the binding affinity of chimeric antibodies is similar to their human counterparts.

In one embodiment the antibody of the present invention is provided by cultures of single or oligoclonal B-cells that are cultured and the supernatant of the culture which contains antibodies produced by said B-cells, is screened for presence and affinity of anti-HTT antibodies therein.

5 The screening process comprises screening for binding to native monomeric, fibrillar or non-fibrillar aggregates like oligomers of hHTT derived from a synthetic full-length hHTT peptide or *e.g.* purified from human plasma or recombinant expression.

As mentioned above, due to its generation upon a human immune response the human  
10 monoclonal antibody of the present invention will recognize epitopes which are of particular pathological relevance and which might not be accessible or less immunogenic in case of immunization processes for the generation of, for example, mouse monoclonal antibodies and *in vitro* screening of phage display libraries, respectively. Accordingly, it is prudent to stipulate that the epitope of the human anti-HTT antibody of the present invention is unique and no other  
15 antibody which is capable of binding to the epitope recognized by the human monoclonal antibody of the present invention exists. A further indication for the uniqueness of the antibodies of the present invention is the fact that, as indicated in Figs. 19, 20, 24, and 27 to 29, antibodies of the present invention bind epitopes that are specific for the mutated and/or aggregated forms of HTT, which as indicated above, are of particular pathological relevance  
20 and may not be obtainable by the usual processes for antibody generation, such as immunization or *in vitro* library screenings.

Therefore, in one embodiment the present invention also extends generally to anti-HTT antibodies and HTT-binding molecules which compete with the human monoclonal antibody  
25 of the present invention for specific binding to HTT. The present invention is more specifically directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody specifically binds to the same epitope in a polyP-region of HTT as a reference antibody selected from the group consisting of NI-302.33C11, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.44D7, NI-302.37C12, NI-302.55D8, NI-  
30 302.7A8, NI-302.71F6, NI-302.11H6, NI-302.3D8, NI-302.18A1, NI-302.8F1, NI-302.52C9, NI-302.78H12 and NI-302.46C9. Further, in one embodiment the present invention is more specifically directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody specifically binds to the same epitope in the P-rich-region of HTT as a reference antibody selected from the group consisting of NI-302.63F3, NI-302.31F11, NI-

302.2A2, NI-302.15D3 and/or NI-302.64E5. In another embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope in the C-terminal-region of HTT as a reference antibody selected from the group consisting of NI-302.35C1 and/or NI.302-72F10. In a further embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope in the N-terminal-region of HTT as a reference antibody selected from the group consisting of NI-302.15E8. In another embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope of HTT as a reference antibody selected from the group consisting of NI-302.6N9, NI-320.12H2, NI-302.8M1 and/or NI-302.4A6. In one embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope of HTT as reference antibody NI-302.7D8. In a preferred embodiment the present invention also extends generally to anti-HTT antibodies and HTT-binding molecules which compete with the human monoclonal antibody of the present invention for specific binding to mutated and/or aggregated HTT species or fragments thereof, as shown in Examples 7, 13, 18, 31 and 33 as well as Figs. 7, 13, 19 and 31. The present invention is therefore, more specifically also directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody specifically binds to the same epitope in a polyP-region of mutated and/or aggregated HTT species or fragments thereof as a reference antibody selected from the group consisting of NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-302.71F6, NI-302.33C11, NI-302.44D7, NI-302.7A8, NI-302.3D8, NI-302.46C9, NI-302.11H6, NI-302.18A1, NI-302.52C9, and/or NI-302.8F1. Further, in one embodiment the present invention is more specifically directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody specifically binds to the same epitope in the P-rich-region of mutated and/or aggregated HTT species or fragments thereof as a reference antibody selected from the group consisting of NI-302.63F3, NI-302.31F11, NI-302.2A2, NI-302.15D3 and/or NI-302.64E5. In another embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope in the C-terminal-region of mutated and/or aggregated HTT species or fragments thereof as a reference antibody selected from the group consisting of NI-302.35C1 and/or NI.302-72F10. In a further embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope in the N-terminal-region of mutated and/or aggregated HTT species or fragments thereof as a

reference antibody selected from the group consisting of NI-302.15E8. In another embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or derivatives thereof, which binds to the same epitope of HTT as a reference antibody selected from the group consisting of NI-302.6N9, NI-320.12H2, NI-302.8M1 and/or NI-302.4A6. In one embodiment the present invention is directed to an antibody, or antigen-binding fragment, variant or biotechnological derivative thereof, which binds to the same epitope of HTT as reference antibody NI-302.7D8.

Competition between antibodies is determined by an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as HTT. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay; see Stahli *et al.*, Methods in Enzymology 9 (1983), 242-253; solid phase direct biotin-avidin EIA; see Kirkland *et al.*, J. Immunol. 137 (1986), 3614-3619 and Cheung *et al.*, Virology 176 (1990), 546-552; solid phase direct labeled assay, solid phase direct labeled sandwich assay; see Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Press (1988); solid phase direct label RIA using I<sup>125</sup> label; see Morel *et al.*, Molec. Immunol. 25 (1988), 7-15 and Moldenhauer *et al.*, Scand. J. Immunol. 32 (1990), 77-82. Typically, such an assay involves the use of purified HTT or mutated and/or aggregated HTT, such as oligomers and/or fibrils thereof bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin, *i.e.* the human monoclonal antibody of the present invention. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Preferably, the competitive binding assay is performed under conditions as described for the ELISA assay in the appended Examples. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50% or 75%. Hence, the present invention is further drawn to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody competitively inhibits a reference antibody selected from the group consisting of NI-302.33C11, NI-302.63F3, NI-302.35C1, NI-302.31F11, NI-302.2A2, NI-302.6N9, NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-

302.22H9, NI-302.44D7, NI-302.37C12, NI-302.55D8, NI-302.7A8, NI-302.78H12, NI-302.71F6, NI-302.11H6, NI-302.3D8, NI-302.18A1, NI-302.8F1, NI-302.52C9, NI-302.46C9, NI-302.15E8, NI-302.64E5, NI-302.7D8, NI-302.72F10, NI-302.12H2, NI-302.8M1 and/or NI-302.4A6 from binding to HTT.

5

The present invention is further drawn to an antibody, or antigen-binding fragment, variant or derivatives thereof, where the antibody competitively inhibits a reference antibody selected from the group consisting of NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-302.71F6, NI-302.33C11, NI-302.44D7, NI-302.7A8, NI-302.3D8, NI-302.46C9, NI-302.11H6, NI-302.18A1, NI-302.52C9, NI-302.8F1, NI-302.63F3, NI-302.31F11, NI-302.2A2, NI302.15D3, NI-302.35C1, NI-302.6N9, NI-302.7D8 and/or NI-302.72F10 from binding to mutated and/or aggregated HTT species or fragments thereof.

10

15 In a preferred embodiment the antibody, the binding of an antibody, binding fragment, synthetic or biotechnological variant thereof, to HTT, preferably to HTT with an expanded poly-Q tract consisting of 49 (HD49) repeats can be measured in a dot blot assay and/or filter retardation as described in the Examples, in particular in 7, 13, 18, 31 and/or 33.

20 In another embodiment, the present invention provides an isolated polypeptide comprising, consisting essentially of, or consisting of an immunoglobulin heavy chain variable region ( $V_H$ ), where at least one of  $V_H$ -CDRs of the heavy chain variable region or at least two of the  $V_H$ -CDRs of the heavy chain variable region are at least 80%, 85%, 90% or 95% identical to reference heavy chain  $V_H$ -CDR1,  $V_H$ -CDR2 or  $V_H$ -CDR3 amino acid sequences from the antibodies disclosed herein. Alternatively, the  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 regions of the  $V_H$  are at least 80%, 85%, 90% or 95% identical to reference heavy chain  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 amino acid sequences from the antibodies disclosed herein. Thus, according to this embodiment a heavy chain variable region of the invention has  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 polypeptide sequences related to the groups shown in Fig. 1  
25 respectively. While Fig. 1 shows  $V_H$ -CDRs defined by the Kabat system, other CDR definitions, *e.g.*,  $V_H$ -CDRs defined by the Chothia system, are also included in the present invention, and can be easily identified by a person of ordinary skill in the art using the data presented in Fig. 1.  
30

In another embodiment, the present invention provides an isolated polypeptide comprising, consisting essentially of, or consisting of an immunoglobulin heavy chain variable region ( $V_H$ ) in which the  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 regions have polypeptide sequences which are identical to the  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 groups shown in Fig. 1 respectively.

5 In another embodiment, the present invention provides an isolated polypeptide comprising, consisting essentially of, or consisting of an immunoglobulin heavy chain variable region ( $V_H$ ) in which the  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 regions have polypeptide sequences which are identical to the  $V_H$ -CDR1,  $V_H$ -CDR2 and  $V_H$ -CDR3 groups shown in Fig. 1 respectively, except for one, two, three, four, five, or six amino acid substitutions in any one  $V_H$ -CDR. In  
10 certain embodiments the amino acid substitutions are conservative.

In another embodiment, the present invention provides an isolated polypeptide comprising, consisting essentially of, or consisting of an immunoglobulin light chain variable region ( $V_L$ ), where at least one of the  $V_L$ -CDRs of the light chain variable region or at least two of the  $V_L$ -  
15 CDRs of the light chain variable region are at least 80%, 85%, 90% or 95% identical to reference light chain  $V_L$ -CDR1,  $V_L$ -CDR2 or  $V_L$ -CDR3 amino acid sequences from antibodies disclosed herein. Alternatively, the  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 regions of the  $V_L$  are at least 80%, 85%, 90% or 95% identical to reference light chain  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 amino acid sequences from antibodies disclosed herein. Thus, according to this  
20 embodiment a light chain variable region of the invention has  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 polypeptide sequences related to the polypeptides shown in Fig. 1 respectively. While Fig. 1 shows  $V_L$ -CDRs defined by the Kabat system, other CDR definitions, *e.g.*,  $V_L$ -CDRs defined by the Chothia system, are also included in the present invention.

25 In another embodiment, the present invention provides an isolated polypeptide comprising, consisting essentially of, or consisting of an immunoglobulin light chain variable region ( $V_L$ ) in which the  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 regions have polypeptide sequences which are identical to the  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 groups shown in Fig. 1 respectively. In another embodiment, the present invention provides an isolated polypeptide comprising,  
30 consisting essentially of, or consisting of an immunoglobulin light chain variable region ( $V_L$ ) in which the  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 regions have polypeptide sequences which are identical to the  $V_L$ -CDR1,  $V_L$ -CDR2 and  $V_L$ -CDR3 groups shown in Fig. 1 respectively, except for one, two, three, four, five, or six amino acid substitutions in any one  $V_L$ -CDR. In certain embodiments the amino acid substitutions are conservative.



An immunoglobulin or its encoding cDNA may be further modified. Thus, in a further embodiment the method of the present invention comprises any one of the step(s) of producing a chimeric antibody, murinized antibody, single-chain antibody, Fab-fragment, bi-specific antibody, fusion antibody, labeled antibody or an analog of any one of those. Corresponding methods are known to the person skilled in the art and are described, *e.g.*, in Harlow and Lane "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor (1988). When derivatives of said antibodies are obtained by the phage display technique, surface plasmon resonance as employed in the BIAcore system can be used to increase the efficiency of phage antibodies which bind to the same epitope as that of any one of the antibodies described herein (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmborg, J. Immunol. Methods 183 (1995), 7-13). The production of chimeric antibodies is described, for example, in international application WO 89/09622. Methods for the production of humanized antibodies are described in, *e.g.*, European application EP-A1 0 239 400 and international application WO 90/07861. Further sources of antibodies to be utilized in accordance with the present invention are so-called xenogeneic antibodies. The general principle for the production of xenogeneic antibodies such as human-like antibodies in mice is described in, *e.g.*, international applications WO 91/10741, WO 94/02602, WO 96/34096 and WO 96/33735. As discussed above, the antibody of the invention may exist in a variety of forms besides complete antibodies; including, for example, Fv, Fab and F(ab)<sub>2</sub>, as well as in single chains; see *e.g.* international application WO 88/09344. In one embodiment therefore, the antibody of the present invention is provided, which is selected from the group consisting of a single chain Fv fragment (scFv), a F(ab') fragment, a F(ab) fragment, and a F(ab')<sub>2</sub> fragment.

The antibodies of the present invention or their corresponding immunoglobulin chain(s) can be further modified using conventional techniques known in the art, for example, by using amino acid deletion(s), insertion(s), substitution(s), addition(s), and/or recombination(s) and/or any other modification(s) known in the art either alone or in combination. Methods for introducing such modifications in the DNA sequence underlying the amino acid sequence of an immunoglobulin chain are well known to the person skilled in the art; see, *e.g.*, Sambrook, Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y. and Ausubel, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y. (1994). Modifications of the antibody of the invention include chemical and/or enzymatic derivatizations at one or more constituent amino acids, including side chain

modifications, backbone modifications, and N- and C-terminal modifications including acetylation, hydroxylation, methylation, amidation, and the attachment of carbohydrate or lipid moieties, cofactors, and the like. Likewise, the present invention encompasses the production of chimeric proteins which comprise the described antibody or some fragment thereof at the amino terminus fused to heterologous molecule such as an immunostimulatory ligand at the carboxyl terminus; see, *e.g.*, international application WO 00/30680 for corresponding technical details.

The antibodies of the present invention may also include additional modifications which optimize their therapeutic potential. These modifications comprise but are not limited to modifications to the amino acid sequence of the antibody (*e.g.*, the variable regions) and post-translational modifications. Post-translational modifications (PTMs) are chemical modifications that play a key role in functional proteomics, because they regulate activity, localization and interaction with other cellular molecules such as proteins, nucleic acids, lipids, and cofactors. Therefore, the optimization of the antibodies may provide several advantages such as an improved stability during storage as well as pharmacokinetics and/or pharmacodynamics profile such as the *in vivo* or *in vitro* circulating time of the antibody, increased solubility, stability, increased affinity to the target, decreased off-rate, an improved effector function of the constant region (Fc region) and safety profile of the antibody, such as a decreased immunogenicity, or reduced susceptibility to posttranslational modifications, as shown *e.g.* in Igawa *et al.*, MAbs 3 (2011), 243-52. Accordingly, in one embodiment of the present invention the anti-HTT antibody, HTT-binding fragment, synthetic or biotechnological variant thereof can be optimized, wherein at least one amino acid in the CDR or variable region, which is prone to modifications including but are not limited to acetylation, acylation, ADP-ribosylation, amidation, deamidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, isomerization, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,  $\gamma$ -carboxylation, glycosylation, GPI anchor formation, hydroxylation, hydrolysis, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, *e.g.*, Creighton, "Proteins: Structures and Molecular Properties," 2nd eds., Freeman and Co., N.Y., 1992; "Postranslational Covalent

Modification of Proteins," Johnson, eds., Academic Press, New York, 1983; Seifter *et al.*, Meth. Enzymol. 182 (1990), 626-646; Rattan *et al.*, Ann. NY. Acad. Sci. 663 (1992) 48-62) is substituted by a mutated amino acid that lack such alteration or wherein at least one carbohydrate moiety is deleted or added chemically or enzymatically to the antibody. In a preferred embodiment the modifications are selected from the group consisting of glycosylation, oxidation, deamination, peptide bond cleavage, iso-aspartate formation and/or unpaired cysteine. Additional modification that optimize the utility of the HTT-antibodies or binding molecules as a therapeutic agent are well known in the art and described *e.g.* in Igawa *et al.*, MAbs 3 (2011), 243-52 which disclosure content is incorporated herein. Means of adding or deleting carbohydrate moieties can be achieved chemically or enzymatically and is described in detail in *e.g.* Berg *et al.* "Biochemistry" 5th eds W H Freeman, New York 2002; WO 87/05330; Aplin *et al.*, CRC Crit. Rev. Biochem., 22 (1981), 259-306; Hakimuddin *et al.*, Arch. Biochem. Biophys., 259 (1987), 10-52; Edge *et al.*, Anal. Biochem., 118 (1981), 131; Thotakura *et al.*, Meth. Enzymol. 138. (1987), 350.

Additionally, the present invention encompasses peptides including those containing a binding molecule as described above, for example containing the CDR3 region of the variable region of any one of the mentioned antibodies, in particular CDR3 of the heavy chain since it has frequently been observed that heavy chain CDR3 (HCDR3) is the region having a greater degree of variability and a predominant participation in antigen-antibody interaction. Such peptides may easily be synthesized or produced by recombinant means to produce a binding agent useful according to the invention. Such methods are well known to those of ordinary skill in the art. Peptides can be synthesized for example, using automated peptide synthesizers which are commercially available. The peptides can also be produced by recombinant techniques by incorporating the DNA expressing the peptide into an expression vector and transforming cells with the expression vector to produce the peptide.

Hence, the present invention relates to any binding molecule, *e.g.*, an antibody or binding fragment thereof which is oriented towards the anti-HTT antibodies and/or antibodies capable of binding mutated and/or aggregated HTT species and/or fragments thereof of the present invention and displays the mentioned properties, *i.e.* which specifically recognizes HTT and/or mutated and/or aggregated HTT species and/or fragments thereof. Such antibodies and binding molecules can be tested for their binding specificity and affinity by ELISA and

immunohistochemistry as described herein, see, *e.g.*, the Examples. These characteristics of the antibodies and binding molecules can be tested by Western Blot as well.

As an alternative to obtaining immunoglobulins directly from the culture of B cells or memory  
5 B cells, the cells can be used as a source of rearranged heavy chain and light chain loci for subsequent expression and/or genetic manipulation. Rearranged antibody genes can be reverse transcribed from appropriate mRNAs to produce cDNA. If desired, the heavy chain constant region can be exchanged for that of a different isotype or eliminated altogether. The variable regions can be linked to encode single chain Fv regions. Multiple Fv regions can be linked to  
10 confer binding ability to more than one target or chimeric heavy and light chain combinations can be employed. Once the genetic material is available, design of analogs as described above which retain both their ability to bind the desired target is straightforward. Methods for the cloning of antibody variable regions and generation of recombinant antibodies are known to the person skilled in the art and are described, for example, Gilliland *et al.*, Tissue Antigens 47  
15 (1996), 1-20; Doenecke *et al.*, Leukemia 11 (1997), 1787-1792.

Once the appropriate genetic material is obtained and, if desired, modified to encode an analog, the coding sequences, including those that encode, at a minimum, the variable regions of the heavy and light chain, can be inserted into expression systems contained on vectors which can  
20 be transfected into standard recombinant host cells. A variety of such host cells may be used; for efficient processing, however, mammalian cells are preferred. Typical mammalian cell lines useful for this purpose include, but are not limited to, CHO cells, HEK 293 cells, or NSO cells.

The production of the antibody or analog is then undertaken by culturing the modified  
25 recombinant host under culture conditions appropriate for the growth of the host cells and the expression of the coding sequences. The antibodies are then recovered by isolating them from the culture. The expression systems are preferably designed to include signal peptides so that the resulting antibodies are secreted into the medium; however, intracellular production is also possible.

30 In accordance with the above, the present invention also relates to a polynucleotide encoding the antibody or equivalent binding molecule of the present invention, in case of the antibody preferably at least a variable region of an immunoglobulin chain of the antibody described above. Typically, said variable region encoded by the polynucleotide comprises at least one

complementarity determining region (CDR) of the V<sub>H</sub> and/or V<sub>L</sub> of the variable region of the said antibody.

The person skilled in the art will readily appreciate that the variable domain of the antibody having the above-described variable domain can be used for the construction of other polypeptides or antibodies of desired specificity and biological function. Thus, the present invention also encompasses polypeptides and antibodies comprising at least one CDR of the above-described variable domain and which advantageously have substantially the same or similar binding properties as the antibody described in the appended examples. The person skilled in the art knows that binding affinity may be enhanced by making amino acid substitutions within the CDRs or within the hypervariable loops (Chothia and Lesk, *J. Mol. Biol.* 196 (1987), 901-917) which partially overlap with the CDRs as defined by Kabat; see, *e.g.*, Riechmann, *et al*, *Nature* 332 (1988), 323-327. Thus, the present invention also relates to antibodies wherein one or more of the mentioned CDRs comprise one or more, preferably not more than two amino acid substitutions. Preferably, the antibody of the invention comprises in one or both of its immunoglobulin chains two or all three CDRs of the variable regions as set forth in Fig. 1.

Binding molecules, *e.g.*, antibodies, or antigen-binding fragments, synthetic or biotechnological variants, or derivatives thereof of the invention, as known by those of ordinary skill in the art, can comprise a constant region which mediates one or more effector functions. For example, binding of the C1 component of complement to an antibody constant region may activate the complement system. Activation of complement is important in the opsonization and lysis of cell pathogens. The activation of complement also stimulates the inflammatory response and may also be involved in autoimmune hypersensitivity. Further, antibodies bind to receptors on various cells via the Fc region, with a Fc receptor binding site on the antibody Fc region binding to a Fc receptor (FcR) on a cell. There are a number of Fc receptors which are specific for different classes of antibody, including IgG (gamma receptors), IgE (epsilon receptors), IgA (alpha receptors) and IgM (mu receptors). Binding of antibody to Fc receptors on cell surfaces triggers a number of important and diverse biological responses including engulfment and destruction of antibody-coated particles, clearance of immune complexes, lysis of antibody-coated target cells by killer cells (called antibody-dependent cell-mediated cytotoxicity, or ADCC), release of inflammatory mediators, placental transfer and control of immunoglobulin production.

Accordingly, certain embodiments of the present invention include an antibody, or antigen-binding fragment, variant, or derivative thereof, in which at least a fraction of one or more of the constant region domains has been deleted or otherwise altered so as to provide desired biochemical characteristics such as reduced effector functions, the ability to non-covalently dimerize, increased ability to localize at the site of HTT aggregation and deposition, reduced serum half-life, or increased serum half-life when compared with a whole, unaltered antibody of approximately the same immunogenicity. For example, certain antibodies for use in the diagnostic and treatment methods described herein are domain deleted antibodies which comprise a polypeptide chain similar to an immunoglobulin heavy chain, but which lack at least a portion of one or more heavy chain domains. For instance, in certain antibodies, one entire domain of the constant region of the modified antibody will be deleted, for example, all or part of the CH2 domain will be deleted. In other embodiments, certain antibodies for use in the diagnostic and treatment methods described herein have a constant region, *e.g.*, an IgG heavy chain constant region, which is altered to eliminate glycosylation, referred to elsewhere herein as aglycosylated or "agly" antibodies. Such "agly" antibodies may be prepared enzymatically as well as by engineering the consensus glycosylation site(s) in the constant region. While not being bound by theory, it is believed that "agly" antibodies may have an improved safety and stability profile *in vivo*. Methods of producing aglycosylated antibodies, having desired effector function are found for example in international application WO 2005/018572, which is incorporated by reference in its entirety.

In certain antibodies, or antigen-binding fragments, variants, or derivatives thereof described herein, the Fc portion may be mutated to decrease effector function using techniques known in the art. For example, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating modified antibody thereby increasing HTT localization. In other cases it may be that constant region modifications consistent with the instant invention moderate complement binding and thus reduce the serum half-life and nonspecific association of a conjugated cytotoxin. Yet other modifications of the constant region may be used to modify disulfide linkages or oligosaccharide moieties that allow for enhanced localization due to increased antigen specificity or antibody flexibility. The resulting physiological profile, bioavailability and other biochemical effects of the modifications, such as HTT localization, biodistribution and serum half-life, may easily be

measured and quantified using well know immunological techniques without undue experimentation.

In certain antibodies, or antigen-binding fragments, variants, or derivatives thereof described  
5 herein, the Fc portion may be mutated or exchanged for alternative protein sequences to increase the cellular uptake of antibodies by way of example by enhancing receptor-mediated endocytosis of antibodies via Fcγ receptors, LRP, or Thy1 receptors or by 'SuperAntibody Technology', which is said to enable antibodies to be shuttled into living cells without harming them (Expert Opin. Biol. Ther. (2005), 237-241). For example, the generation of fusion proteins  
10 of the antibody binding region and the cognate protein ligands of cell surface receptors or bi- or multi-specific antibodies with a specific sequences binding to HTT as well as a cell surface receptor may be engineered using techniques known in the art.

In certain antibodies, or antigen-binding fragments, variants, or derivatives thereof described  
15 herein, the Fc portion may be mutated or exchanged for alternative protein sequences or the antibody may be chemically modified to increase its blood brain barrier penetration.

Modified forms of antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention can be made from whole precursor or parent antibodies using techniques known in the art. Exemplary techniques are discussed in more detail herein. Antibodies, or antigen-  
20 binding fragments, variants, or derivatives thereof of the invention can be made or manufactured using techniques that are known in the art. In certain embodiments, antibody molecules or fragments thereof are "recombinantly produced", *i.e.*, are produced using recombinant DNA technology. Exemplary techniques for making antibody molecules or fragments thereof are discussed in more detail elsewhere herein.

25 Antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention also include derivatives that are modified, *e.g.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from specifically binding to its cognate epitope. For example, but not by way of limitation, the antibody  
30 derivatives include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to

specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

In particular preferred embodiments, antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention will not elicit a deleterious immune response in the animal to be treated, *e.g.*, in a human. In certain embodiments, binding molecules, *e.g.*, antibodies, or antigen-binding fragments thereof of the invention are derived from a patient, *e.g.*, a human patient, and are subsequently used in the same species from which they are derived, *e.g.*, human, alleviating or minimizing the occurrence of deleterious immune responses.

De-immunization can also be used to decrease the immunogenicity of an antibody. As used herein, the term "de-immunization" includes alteration of an antibody to modify T cell epitopes; *see, e.g.*, international applications WO 98/52976 and WO 00/34317. For example, V<sub>H</sub> and V<sub>L</sub> sequences from the starting antibody are analyzed and a human T cell epitope "map" from each V region showing the location of epitopes in relation to complementarity determining regions (CDRs) and other key residues within the sequence. Individual T cell epitopes from the T cell epitope map are analyzed in order to identify alternative amino acid substitutions with a low risk of altering activity of the final antibody. A range of alternative V<sub>H</sub> and V<sub>L</sub> sequences are designed comprising combinations of amino acid substitutions and these sequences are subsequently incorporated into a range of binding polypeptides, *e.g.*, HTT-specific antibodies or immunospecific fragments thereof for use in the diagnostic and treatment methods disclosed herein, which are then tested for function. Typically, between 12 and 24 variant antibodies are generated and tested. Complete heavy and light chain genes comprising modified V and human C regions are then cloned into expression vectors and the subsequent plasmids introduced into cell lines for the production of whole antibody. The antibodies are then compared in appropriate biochemical and biological assays, and the optimal variant is identified.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow *et al.*, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd ed. (1988); Hammerling *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* Elsevier, N.Y., 563-681 (1981), said references incorporated by reference in their entireties. The term "monoclonal antibody" as used



herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Thus, the term "monoclonal antibody" is not limited to antibodies produced through hybridoma  
5 technology. In certain embodiments, antibodies of the present invention are derived from human B cells which have been immortalized via transformation with Epstein-Barr virus, as described herein.

In the well-known hybridoma process (Kohler *et al.*, Nature 256 (1975), 495) the relatively  
10 short-lived, or mortal, lymphocytes from a mammal, *e.g.*, B cells derived from a human subject as described herein, are fused with an immortal tumor cell line (*e.g.*, a myeloma cell line), thus, producing hybrid cells or "hybridomas" which are both immortal and capable of producing the genetically coded antibody of the B cell. The resulting hybrids are segregated into single genetic strains by selection, dilution, and re-growth with each individual strain comprising specific  
15 genes for the formation of a single antibody. They produce antibodies, which are homogeneous against a desired antigen and, in reference to their pure genetic parentage, are termed "monoclonal".

Hybridoma cells thus prepared are seeded and grown in a suitable culture medium that  
20 preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. Those skilled in the art will appreciate that reagents, cell lines and media for the formation, selection and growth of hybridomas are commercially available from a number of sources and standardized protocols are well established. Generally, culture medium in which the hybridoma cells are growing is assayed for production of monoclonal antibodies  
25 against the desired antigen. The binding specificity of the monoclonal antibodies produced by hybridoma cells is determined by *in vitro* assays such as immunoprecipitation, radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA) as described herein. After hybridoma cells are identified that produce antibodies of the desired specificity, affinity and/or activity, the clones may be subcloned by limiting dilution procedures and grown  
30 by standard methods; *see, e.g.*, Goding, Monoclonal Antibodies: Principles and Practice, Academic Press (1986), 59-103. It will further be appreciated that the monoclonal antibodies secreted by the subclones may be separated from culture medium, ascites fluid or serum by conventional purification procedures such as, for example, protein-A, hydroxylapatite chromatography, gel electrophoresis, dialysis or affinity chromatography.

In another embodiment, lymphocytes can be selected by micromanipulation and the variable genes isolated. For example, peripheral blood mononuclear cells can be isolated from an immunized or naturally immune mammal, *e.g.*, a human, and cultured for about 7 days *in vitro*.

5 The cultures can be screened for specific IgGs that meet the screening criteria. Cells from positive wells can be isolated. Individual Ig-producing B cells can be isolated by FACS or by identifying them in a complement-mediated hemolytic plaque assay. Ig-producing B cells can be micromanipulated into a tube and the V<sub>H</sub> and V<sub>L</sub> genes can be amplified using, *e.g.*, RT-PCR. The V<sub>H</sub> and V<sub>L</sub> genes can be cloned into an antibody expression vector and transfected  
10 into cells (*e.g.*, eukaryotic or prokaryotic cells) for expression.

Alternatively, antibody-producing cell lines may be selected and cultured using techniques well known to the skilled artisan. Such techniques are described in a variety of laboratory manuals and primary publications. In this respect, techniques suitable for use in the invention as described below are described in Current Protocols in Immunology, Coligan *et al.*, Eds., Green  
15 Publishing Associates and Wiley-Interscience, John Wiley and Sons, New York (1991) which is herein incorporated by reference in its entirety, including supplements.

Antibody fragments that recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments may be produced recombinantly or by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab  
20 fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Such fragments are sufficient for use, for example, in immunodiagnostic procedures involving coupling the immunospecific portions of immunoglobulins to detecting reagents such as radioisotopes.

25 In one embodiment, an antibody of the invention comprises at least one CDR of an antibody molecule. In another embodiment, an antibody of the invention comprises at least two CDRs from one or more antibody molecules. In another embodiment, an antibody of the invention comprises at least three CDRs from one or more antibody molecules. In another embodiment, an antibody of the invention comprises at least four CDRs from one or more antibody  
30 molecules. In another embodiment, an antibody of the invention comprises at least five CDRs from one or more antibody molecules. In another embodiment, an antibody of the invention comprises at least six CDRs from one or more antibody molecules. Exemplary antibody molecules comprising at least one CDR that can be included in the subject antibodies are described herein.

Antibodies of the present invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably by recombinant expression techniques as described herein.

5

In one embodiment, an antibody, or antigen-binding fragment, variant, or derivative thereof of the invention comprises a synthetic constant region wherein one or more domains are partially or entirely deleted ("domain-deleted antibodies"). In certain embodiments compatible modified antibodies will comprise domain deleted constructs or variants wherein the entire CH2 domain  
10 has been removed ( $\Delta$ CH2 constructs). For other embodiments a short connecting peptide may be substituted for the deleted domain to provide flexibility and freedom of movement for the variable region. Those skilled in the art will appreciate that such constructs are particularly preferred due to the regulatory properties of the CH2 domain on the catabolic rate of the antibody. Domain deleted constructs can be derived using a vector encoding an IgG<sub>1</sub> human  
15 constant domain, *see, e.g.*, international applications WO 02/060955 and WO 02/096948A2. This vector is engineered to delete the CH2 domain and provide a synthetic vector expressing a domain deleted IgG<sub>1</sub> constant region.

In certain embodiments, antibodies, or antigen-binding fragments, variants, or derivatives  
20 thereof of the present invention are minibodies. Minibodies can be made using methods described in the art, *see, e.g.*, US patent 5,837,821 or international application WO 94/09817.

In one embodiment, an antibody, or antigen-binding fragment, variant, or derivative thereof of the invention comprises an immunoglobulin heavy chain having deletion or substitution of a  
25 few or even a single amino acid as long as it permits association between the monomeric subunits. For example, the mutation of a single amino acid in selected areas of the CH2 domain may be enough to substantially reduce Fc binding and thereby increase HTT localization. Similarly, it may be desirable to simply delete that part of one or more constant region domains that control the effector function (*e.g.* complement binding) to be modulated. Such partial  
30 deletions of the constant regions may improve selected characteristics of the antibody (serum half-life) while leaving other desirable functions associated with the subject constant region domain intact. Moreover, as alluded to above, the constant regions of the disclosed antibodies may be synthetic through the mutation or substitution of one or more amino acids that enhances the profile of the resulting construct. In this respect it may be possible to disrupt the activity

provided by a conserved binding site (*e.g.* Fc binding) while substantially maintaining the configuration and immunogenic profile of the modified antibody. Yet other embodiments comprise the addition of one or more amino acids to the constant region to enhance desirable characteristics such as an effector function or provide for more cytotoxin or carbohydrate attachment. In such embodiments it may be desirable to insert or replicate specific sequences derived from selected constant region domains.

The present invention also provides antibodies that comprise, consist essentially of, or consist of, variants (including derivatives) of antibody molecules (*e.g.*, the V<sub>H</sub> regions and/or V<sub>L</sub> regions) described herein, which antibodies or fragments thereof immunospecifically bind to HTT. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding an antibody, including, but not limited to, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference V<sub>H</sub> region, V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, V<sub>H</sub>-CDR3, V<sub>L</sub> region, V<sub>L</sub>-CDR1, V<sub>L</sub>-CDR2, or V<sub>L</sub>-CDR3. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (*e.g.*, the ability to bind HTT and/or mutated and/or aggregated HTT species and/or fragments thereof).

For example, it is possible to introduce mutations only in framework regions or only in CDR regions of an antibody molecule. Introduced mutations may be silent or neutral missense mutations, *e.g.*, have no, or little, effect on an antibody's ability to bind antigen, indeed some such mutations do not alter the amino acid sequence whatsoever. These types of mutations may be useful to optimize codon usage, or improve a hybridoma's antibody production. Codon-optimized coding regions encoding antibodies of the present invention are disclosed elsewhere herein. Alternatively, non-neutral missense mutations may alter an antibody's ability to bind antigen. The location of most silent and neutral missense mutations is likely to be in the framework regions, while the location of most non-neutral missense mutations is likely to be in CDR, though this is not an absolute requirement. One of skill in the art would be able to design and test mutant molecules with desired properties such as no alteration in antigen-binding activity or alteration in binding activity (*e.g.*, improvements in antigen-binding activity or change in antibody specificity). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (*e.g.*, ability to immunospecifically bind at least one epitope of HTT and/or mutated and/or aggregated HTT species and/or fragments thereof) can be determined using techniques described herein or by routinely modifying techniques known in the art.

### III. Polynucleotides Encoding Antibodies

A polynucleotide encoding an antibody, or antigen-binding fragment, variant, or derivative thereof can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, a polynucleotide encoding an antibody, or antigen-binding fragment, variant, or derivative thereof can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single-stranded and double-stranded regions. In addition, a polynucleotide encoding an antibody, or antigen-binding fragment, variant, or derivative thereof can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide encoding an antibody, or antigen-binding fragment, variant, or derivative thereof may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and

RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

An isolated polynucleotide encoding a non-natural variant of a polypeptide derived from an immunoglobulin (*e.g.*, an immunoglobulin heavy chain portion or light chain portion) can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of the immunoglobulin such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations may be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more non-essential amino acid residues.

As is well known, RNA may be isolated from the original B cells, hybridoma cells or from other transformed cells by standard techniques, such as a guanidinium isothiocyanate extraction and precipitation followed by centrifugation or chromatography. Where desirable, mRNA may be isolated from total RNA by standard techniques such as chromatography on oligo dT cellulose. Suitable techniques are familiar in the art. In one embodiment, cDNAs that encode the light and the heavy chains of the antibody may be made, either simultaneously or separately, using reverse transcriptase and DNA polymerase in accordance with well-known methods. PCR may be initiated by consensus constant region primers or by more specific primers based on the published heavy and light chain DNA and amino acid sequences. As discussed above, PCR also may be used to isolate DNA clones encoding the antibody light and heavy chains. In this case the libraries may be screened by consensus primers or larger homologous probes, such as human constant region probes. DNA, typically plasmid DNA, may be isolated from the cells using techniques known in the art, restriction mapped and sequenced in accordance with standard, well known techniques set forth in detail, *e.g.*, in the foregoing references relating to recombinant DNA techniques. Of course, the DNA may be synthetic according to the present invention at any point during the isolation process or subsequent analysis.

In this context, the present invention also relates to a polynucleotide encoding at least the binding domain or variable region of an immunoglobulin chain of the antibody of the present invention. In one embodiment, the present invention provides an isolated polynucleotide comprising, consisting essentially of, or consisting of a nucleic acid encoding an immunoglobulin heavy chain variable region ( $V_H$ ), where at least one of the CDRs of the heavy

chain variable region or at least two of the V<sub>H</sub>-CDRs of the heavy chain variable region are at least 80%, 85%, 90%, or 95% identical to reference heavy chain V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, or V<sub>H</sub>-CDR3 amino acid sequences from the antibodies disclosed herein. Alternatively, the V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, or V<sub>H</sub>-CDR3 regions of the V<sub>H</sub> are at least 80%, 85%, 90%, or 95% identical to reference heavy chain V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, and V<sub>H</sub>-CDR3 amino acid sequences from the antibodies disclosed herein. Thus, according to this embodiment a heavy chain variable region of the invention has V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, or V<sub>H</sub>-CDR3 polypeptide sequences related to the polypeptide sequences shown in Fig. 1.

In another embodiment, the present invention provides an isolated polynucleotide comprising, consisting essentially of, or consisting of a nucleic acid encoding an immunoglobulin light chain variable region (V<sub>L</sub>), where at least one of the V<sub>L</sub>-CDRs of the light chain variable region or at least two of the V<sub>L</sub>-CDRs of the light chain variable region are at least 80%, 85%, 90%, or 95% identical to reference light chain V<sub>L</sub>-CDR1, V<sub>L</sub>-CDR2, or V<sub>L</sub>-CDR3 amino acid sequences from the antibodies disclosed herein. Alternatively, the V<sub>L</sub>-CDR1, V<sub>L</sub>-CDR2, or V<sub>L</sub>-CDR3 regions of the V<sub>L</sub> are at least 80%, 85%, 90%, or 95% identical to reference light chain V<sub>L</sub>-CDR1, V<sub>L</sub>-CDR2, and V<sub>L</sub>-CDR3 amino acid sequences from the antibodies disclosed herein. Thus, according to this embodiment a light chain variable region of the invention has V<sub>L</sub>-CDR1, V<sub>L</sub>-CDR2, or V<sub>L</sub>-CDR3 polypeptide sequences related to the polypeptide sequences shown in Fig. 1.

In another embodiment, the present invention provides an isolated polynucleotide comprising, consisting essentially of, or consisting of a nucleic acid encoding an immunoglobulin heavy chain variable region (V<sub>H</sub>) in which the V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, and V<sub>H</sub>-CDR3 regions have polypeptide sequences which are identical to the V<sub>H</sub>-CDR1, V<sub>H</sub>-CDR2, and V<sub>H</sub>-CDR3 groups shown in Fig. 1.

As known in the art, "sequence identity" between two polypeptides or two polynucleotides is determined by comparing the amino acid or nucleic acid sequence of one polypeptide or polynucleotide to the sequence of a second polypeptide or polynucleotide. When discussed herein, whether any particular polypeptide is at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to another polypeptide can be determined using methods and computer programs/software known in the art such as, but not limited to, the BESTFIT program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics

Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). BESTFIT uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2 (1981), 482-489, to find the best segment of homology between two sequences. When using BESTFIT or any other sequence alignment program to determine whether a particular sequence is, for example, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference polypeptide sequence and that gaps in homology of up to 5% of the total number of amino acids in the reference sequence are allowed.

In a preferred embodiment of the present invention, the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody recognizing a polyP-region in the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table II. Additionally, in one embodiment the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody recognizing the P-rich-region in the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table III and/or further recognizing the C-terminal region in the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table IV and/or further recognizing the Q/P-rich region of HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in Table VII. In addition, in one embodiment the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody recognizing the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table V. Furthermore, in one embodiment the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody recognizing the N-terminal region in the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table VI. In addition, in one embodiment the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody recognizing the HTT and/or mutated and/or aggregated HTT species and/or fragments thereof as depicted in and Table V. Additionally or alternatively, in one embodiment the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide



sequence of the V<sub>H</sub> or V<sub>L</sub> region of an anti-HTT antibody and/or antibody as depicted in and Table VIII.

In this respect, the person skilled in the art will readily appreciate that the polynucleotides encoding at least the variable domain of the light and/or heavy chain may encode the variable domain of both immunoglobulin chains or only one. In one embodiment therefore, the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> and the V<sub>L</sub> region of an anti-HTT antibody and/or fragments thereof as depicted in Table II, III, IV, V, VI, VII or VIII.

**Table II:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing an epitope of a polyP-region of HTT, *i.e* exon 1 in aggregated form.

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.33C11- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTTGTCCAGCCTGGGAACCTCC CTGAGACTCTCCTGTGCAGCGTCTGGATTCAAGTTCACTGACTTTGGCATGC ACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGCTGGCACTTATAT GGTATGATGGAGGGTATAAGTACTATGCAGACTCCGTGAAGGGCCGATTCA CCATCTCCAGAGACAATTCCAAGAATACGATGTTTCTACAAATGAACAGCCT GAGAGCCGAGGACACGGCTGTTTATTACTGTGCGACCCACCTAGAATATTGC AGTAGAACCACCTGCTATCTCGGCCACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCG SEQ ID NO: 1
NI-302.33C11- V <sub>K</sub>	GACATCCAGTTGACCCAGTCTCCGTCCTTCTATCTGCGTCTGTGGGAGACA CAGTCACCTTCACTTGCCGGGGCCAGTCAGGGCATTAGCGATTATTTAGCCTG GTTTCAGCAGAAACCAGGGATTGCCCTAAGCTCCTGATCTATGCTGCGTCC ACTTTGCAAACCGGGTCCCATCAAGGTTCAAGCGCAGTGGATCTGGGACA GAATTCCTCTCACAATCCGCAGCCTGCAGTCTGAAGATTTTGGAACCTTATT ACTGTCAGCAGCTTAAAACCTTACCCGTACACTTTTGGCCAGGGGACCAAGGT GGAAATCAAA SEQ ID NO: 3
NI-302.74C11- V <sub>H</sub>	GAGGTGCAGCTGGTGCAGTCTGGGACTGAGGTGCAGAAGCCTGGGGCCTCA GTAAAAGTCTCCTGCAAGGCTTCTGGATACAGTTTCACCGGCTACTTTTTGC ACTGGGTACGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGGTGGATCA ACCCTAACAGTGGTGACACAACTATGCAGAGAAGTTTCGGGGCAGAATCA TCATGACCAGGGACACGTCTGTGACGACAGCCACATGGAGTTGAGCAGCC TGAGATTTGACGACACGGCCCTATATTACTGTACGAGAGAGGCCCTGACCC GGGCGCTGAGACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTC G SEQ ID NO: 25
NI-302.74C11- V <sub>L</sub>	CAGTCTGTGCTGACTCAGCCACCCTCGGTGTCAGTGTCCCCAGGACAGACGG CCAGGATCACCTGCTCTGGAGATGCAGTGCCAAAGCAGTATATTTATTGGTA CCAGCAGAAGCCAGGCCAGGCCCTATTCTGGTGATATATAAAGACACTCA GAGGCCTTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACCTCAGGGACAACA GTCACGTTGACCATAACTGGCGTCCAGGCAGACGACGAGGGTGACTATTAC TGTCAATCAGCAGACAGTAGTGCTACTTGGGTGTTTCGGCGGAGGGACCAAA TTGACCGTCCTA SEQ ID NO: 27
NI-302.15F9- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCACGCCGGGGGGGTCC CTGAGACTCTCGTGTGAGGCCTCTGGATTTCTCTTCAAGAATTCTAGCATGA ACTGGGTCCGTGAGACTCCGGGGAAGGGGCTGGAGTGGGTCTCGTCCATTG ACACTTCTGCTACAAATTATAAGTATTATGCAGACTCTGTGAAGGGCCGATT TACCATCTCCAGGGATGACGCCACCAACTCTCTATCTGCAAATGAATAGC

	CTGCGAGCCGACGACACGGCTACTTATTACTGTGCGCGAGGTTATTATACCC CCCGGGACTTTGACTACTGGGGCCAGGGCACCTGGTCACCGTCTCCTCG SEQ ID NO: 29
NI-302.15F9- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACAGACCCTGTCCGTCAGCCTTGGACAGG CGGCCTCCATCTCCTGCAGGTTCAGTCAAAGCCTCTTGATCGTGATAACAA CACATACTTGAATTGGTTTCACCAGAGGGCCAGGCCAATCTCCAAGGCGCCTC ATTTATAGGGCTTCTGACCGGGACTCTGGGGTCCCAGACAGATTTCAGCGGCG GTGGGTCAAGGCACTGATTTACATTGAAAATCAGTGGAGTGGAGGCTGAAG ATGTTGGCACTTATTACTGCATGCAAGGAACACACTGGCCTCGGACGTTTCGG CCAAGGGACCAAGGTGGAGATCAAA SEQ ID NO: 31
NI-302.39G12- V <sub>H</sub>	GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCACCCTTGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTTCAGCGTCTCTAATTACGCCATAA CTTGGGTCCGCCGGGCTCCAGGGAAGGGGCTGCAATATATTTTCAGTAATTTA TCGTGATGGCAGGACATACTACGGAGACTCCGTGAGGGGCCGCTTCACCAT CTTAGGGACGATTCCAAGAACAACACTCTCTATCTTCAAATGAACAGCCTGAGA TTTGAGGACACGGCTGTGTATTACTGTGCGAGAGCGCACGGCCAATATTACT ATGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCG SEQ ID NO: 33
NI-302.39G12- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGTCCGTCAGCCCTGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGATA CAACTATTTGGATTGGTACCGGCAGAAACCAGGGCAGTCTCCACAGCTCCTG ATCTATTTGAGTTCTAATCGGGCCTCCGGGGTCCCTGATAGGTTTCAGTGCCA GTGGATCAGGCACAGAGTTTCACTGCAAATCAGCAGAGTGGAGGCTGAGG ATGTTGGGGTTTATTACTGCATGCAATCTCTGCAAACGTTCACTTTTCGGCGG AGGGACCAAAGTGGATATCAAA SEQ ID NO: 35
NI-302.11A4- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGATCCAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGGTTCCTCGTCAGTAGCAGTTACATGA GCTGGGTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTCTCAGTTCTTTA TAGAGACGGTGACACATACTACGCAGACTCCGTGCAGGGCCGATTACCAT CTCCAGAGACAATTCCCAGAACACGTTCTATCTTCAAATGAACAGCCTGAAA GCCGAGGACACGGCCGTGTATTACTGTGCGGGTGATAGAAGGTTCGTCACAC TACTATTACGGTATGGACGTCTGGGGCCAGGGGACCACGGTCACCGTCTCCT CG SEQ ID NO: 37
NI-302.11A4- V <sub>K</sub>	GAAATTGTGATGACACAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGAGAAA GAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTCGC CTGGTACCAACAAAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTACG TCCCGCAGGGCCACTGCCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGG ACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGT ATTACTGTCAACAGTATGGTAGCTCGTGGACGTTTCGGCCCAGGGACCAAGGT GGAGATCAAA SEQ ID NO: 39
NI-302.22H9- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCACCCTTGGGGGTCC CTGAGAGTCTCCTGTGCAGCCTCTGGATTTCAGCGTCTCTAATTACGCCATAA CTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATATATTTTCAGTGATTTA TCGTGATGGCAGGACATACTACGGAGACTCCGTGAGGGGCCGCTTCACCAT CTTAGGGACGATTCCAAGAACAACACTATCTATCTTCAAATGAACAGCCTGAGA TTTGAGGACACGGCTGTGTATTACTGTGCGAGAGCGCACGGCCAATATTATT ATGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCG SEQ ID NO: 41:
NI-302.22H9- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGTCCGTCAGCCCTGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGATA CAACTATTTGGATTGGTACCGGCAGAAACCAGGGCAGTCTCCACAACCTCCTG ATCTATTTGAATTCTAATCGGGCCTCCGGGGTCCCTGATAGGTTTCAGTGCCA GTGGATCAGGCACAGAGTTTCACTGACAATCAGCAGAGTGGAGGCTGAGG ATGTTGGGGTTTATTACTGCATGCAATCTCTGCAAACGTTCACTTTTCGGCGG AGGGACCAAGGTGGAGATCAAA SEQ ID NO: 43

NI-302.44D7- V <sub>H</sub>	GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGA GTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTG GTTATAGTGATACTAGCACATATTACGCAGACTCCGTGAAGGGCCGCTTCAC CGTCTCCAGAGACATTTCCAAGAACACGCTGTATCTGCAAATGAATAGCCTG AGGGCCGAGGACACGGCCGTATATTACTGCGCGAAAGGTACCAGGGACTAT TACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCG SEQ ID NO: 45
NI-302.44D7- V <sub>K</sub>	CAGACTGTGGTGACTCAGGAGCCATCGTTCTCAGTGTCCCCTGGAGGGACAG TCACACTCACTTGTGGCTTGAGTTCTGGCTCAGTTTCTACTAGTTACTACCCC AGCTGGTACCAGCAGACCCCAGGCCGGGCTCCACGCACGCTCATCTACAGC ACAAACACTCGCTCTTCTGGGGTCCCTGATCGTTCTCTGGCTCCATCCTTGG GAACAAGGCTGCCCTCACCATCACGGGGGGCCAGGCAGATGATGAATCTGA TTATTACTGTGTGCTGTTTATGGGTAGTGGCATTGGGGTGTTCGGCGGAGGG ACCAGGCTGACCGTCCTA SEQ ID NO: 47
NI-302.37C12- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGTGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCTTGTGTTGCCTCTGCACTCACCGTCACTAACAGCCAAATGA CCTGGGTCCGCCGGGCTCCAGGGAGGGGGTGGAGTGGGTCTCAGTTATTTA CACCAGTGGTAGTGCATACTACGCAGACTCCGTGAAGGGCAGATTCACCAT CTCCAGAGACAATTCCAAGAACACAGTGTTCCTTCAAATGAACAGCCTGAG AGTCGAAGACACGGCTGTGTATTACTGTGCGAAAGGCCCATCAGCCTATTAT TACGGTTTGACCTTTGGGGCCAAGGGACCACGGTCACCGTCTCCTCG SEQ ID NO: 49
NI-302.37C12- V <sub>K</sub>	GATATTGTGATGACTCAATCACCCTCTCCCTGCCCGTCACCCCTGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATA CAACTATTTGGATTGGTACCTGCAGAAGCCGGGGCAGTCTCCACAGCTCCTG ATCTATTTGGGTCTACTCGGGCCTCCGGGGTCCCTGACAGGTTCAAGTGGCA GTGGATCAGGCACAGATTTTACACTGAAGATCAGCAGAGTGGAGGCTGAGG ATGTTGGGGTTTATTACTGCATGCAAGGTCTACAGACGTACACTTTTGCCA GGGGACCAAGCTGGAGATCAAA SEQ ID NO: 51
NI-302.55D8- V <sub>H</sub>	CAGGTGCAGCTGGTGCAGTCTGGGTCTGAGGTGAAGAAGCCTGGGGCCTCA GTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGACTACTATATAC ACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGACGGATCA ACCCTAACAAATGGTGGCACAACCTATGCACAGAACTTTCAGGGCTGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAGCTCAGCAGAC TGAGATCTGACGACACGGCCGTCTATTACTGTGCGAGAGTGGGGGGCGAGC TGCTACGAGAAGGCGGCTATCACTACTACATGGACGTCTGGGGCAAGGGGA CCACGGTCACCGTCTCCTCG SEQ ID NO: 53
NI-302.55D8- V <sub>L</sub>	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGG GTCACCATCTCCTGCACTGGGAACAGCTCCAACATCGGGGCAGGTTATGATG TACACTGGTACCAGCAGCTTCCAGGAACAGCCCCAACTCCTCATCTTTGA TAATACCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCT GGCACCTCAGCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTA ATTATCACTGCCAGTCCTATGACAACAGCCTGAGTGGTTCTTGGGTGTTTCG CGGAGGGACCAAGCTGACCGTCCTA SEQ ID NO: 55
NI-302.7A8- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGTAGCCTCTGGATTCAATTTAGAAACAGTTGGATGA CCTGGGTCCGCCAGGATCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGGAAGATGGAAGTCGGACATACTATGTGGACTCTGTGAAGGGCCGATTCA CCATCTCCAGAGACAACGCCAAGAAGTCACTGTATCTGCAGATGAACAGCC TGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGATTATAATT CGGGCATCTATTACTTTCCCGGGGACTACTGGGGCCAGGGCACCTGGTCAC CGTCTCCTCG SEQ ID NO: 57
NI-302.7A8- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGACAGC CGGCCTCCATCTCCTGTAGGTCTAGTCAAAGCCTCGTATACAGTGATGGAAA CACCTACTTGAATTGGTTTCAGCAGAGGGCCAGGCCAGTCTCCAAGGCGCCTC

	<p>ATTTATAAGGTTTCTAACCAGGACTCTGGGGTCCCAGACAGATTTCAGCGGCA GTGGGTCAGGCACTGATTTACACTGAGAATCAGCAGGGTGGAGGCTGAGG ATGTTGGCATTTATTACTGCATGCAAGGTACACACTGGCCTGGGACGTTTCGG CCAAGGGACCAAGGTGGAGATCAAA</p> <p style="text-align: right;">SEQ ID NO: 59</p>
NI-302.78H12- V <sub>H</sub>	<p>CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACC CTGTCCCTCACCTGTCTTGTCTCTAGTTACTCCATCAGCAATGGTTACTACTG GGGCTGGATTTCGGCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGAGTAT CTATCATAATGGGAACACCTATTACAACCCGTCCTCAAGAGTCGAGTCATC ATTTTCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAAGTTGAGGTCTGTGA CCGCCGCAGACACGGCCGTGTACTACTGTGCGATGCCAAGTGCCACCTATTA TTATGGTTCGGGGACTCAATTCCATGCGTTTGATGTCTGGGGCCAAGGGACC ACGGTCACCGTCTCCTCG</p> <p style="text-align: right;">SEQ ID NO: 61</p>
NI-302.78H12- V <sub>L</sub>	<p>CAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTCTCCTGGACAGTCAG TCACCATCTCCTGCACTGGAACCAGCAGAGATGTTGGTAATTATAACTATGT CTCCTGGTACCAACAACACCCAGGCGAAGTCCCCAACTCATAATTTATGAT GTCAGTGAGCGGCCCTCAGGGGTCCCTGATCGTTCTCTGGCTCCAAGTCTG GCAACACGGCCTCGCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTG ACTATTACTGCTGCTCATATGCTGGCAGTTACACCTTCGAGGTATTTGGCGG AGGGACCAAGCTGACCGTCCTA</p> <p style="text-align: right;">SEQ ID NO: 63</p>
NI-302.71F6- V <sub>H</sub>	<p>CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTATTGAAGCCTTCGGAGACC CTGTCCCTCACGTGCGCTGTCTATGGTGGGTCCCTCAGTGGTTACTACTGGA GCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATAGGGGAAGTCA ATCATAGTGGAGGCACCAACCTCAATTCGTCCTCAAGAGTCGAGTCATCAT TTCAGTAGACAAGTCCAAGAAGCAGTTCTCCCTGAAACTGAGCTCTGTGACC GCCGCGGACACGGCTATGTACTTCTGTGCGAGAGGATACAGCTATGACCCA AAATACTACTTTGACTCCTGGAGCCAGGGCACCTGGTCACCGTCTCCTCG</p> <p style="text-align: right;">SEQ ID NO: 65</p>
NI-302.71F6- V <sub>L</sub>	<p>CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGGCGA TCACCATCTCCTGCACTGGAACCAGTAGTGATATTGGGAGTTATGATTTTGT CTCCTGGTACCAGCAGGACCCAGGCAAAGCCCCCAAAGTCATTATTTATGGG GTCAATAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTG GCAACACGGCCTCCCTGACAATCTCTGGAAGTCCAGGCTGACGACGAGGCTG ATTATTACTGCTGCTCATATGCTGGTAGTACCCTGGGTGTTTCGGCGGAGG GACCAAAGTACCGTCCTA</p> <p style="text-align: right;">SEQ ID NO: 67</p>
NI-302.11H6- V <sub>H</sub>	<p>GAGGTGCAGCTGGTGCAGTCTGGAGCTGTGATGAAGAAGCCTGGAGACTCA GTGAGGGTCTCCTGCAGGGCTTCTACTTACAGCTTTTCCACCTATAGTTTAC CTGGGTGCGACAGGTCCCTGGACAAGGCCTTGAGTGGATGGGATGGATCAG CGCTTATAATGGTACACAACTATGTAGACAGCTTCCAGGGCAGACTCAG TTGACCACAGACACATCCGCGAGTACAGCGTACATGGAAGTACAGGAGCCTC AGATCTGACGACACGGCCATCTATTATTGTGCGGCTGTAGACACCACTTACT ACTATTACGGCATGGACGTCTGGGGCCAAGGCACCCTGGTCACCGTCTCCTC G</p> <p style="text-align: right;">SEQ ID NO: 69</p>
NI-302.11H6- V <sub>L</sub>	<p>CAGACTGTGGTGAAGTGCAGGAGCCAACGTTCTCAGTGTCCCTGGAGGGACA GTCACACTCACTTGTGCCTTGAGGTTTGGCTCAGTCTCTAGTAGCTACTATCC CAGCTGGTTCCAGCAGACCCAGGCCAGGCTCCACGCACGCTCATCTACAGC ACAAACACCCGCTCTTCGGGGGTCCCTGCTCGATTCTCTGGCTCCATTCTTGG GAACAAAGCTGCCCTACCATCGCGGGGGGCCAGGCAAATGATGAGGCTGA CTATTACTGTGTGCTGTATATGGGTAGTGGAATCGGGGTGTTTCGGCGGAGGG ACCAAGTTGACCGTCCTA</p> <p style="text-align: right;">SEQ ID NO: 71</p>
NI-302.3D8- V <sub>H</sub>	<p>GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC CTGAGACTCTCTTGTGAAGCCTCCGATTCTCTTTAAACCTATGCCATGA GCTGGGTCCGCCAGCTTCCCGGGAGGGGGCTGGAATGGGTCTCAGCTATAA GTGCCACTGGTGGAAGCACCTTCTACGCAGAGTCCGTGAAGGGCCGGCTCA CCATTTCCAGAGACACTGCCAAGAATACAGTGTATCTGCAAATGAACAACCT</p>

	GAGAGCCGAAGACACGGCCATGTATTACTGTGCGAAAGGGTCTGACTGCGGT ATATCTCTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG SEQ ID NO: 73
NI-302.3D8- V <sub>K</sub>	GACATCCAGATGACCCAGTCTCCGTCTACTGTCTGCATCTGTAGGGGACA GAGTCACCCTCACTTGTCTGGGCGAGTCAGGACATCAGAAATTTCTTGGCCTG GATTCAGCAGAAGCCAGGGAAACCCCTAAGTCCCTGATCTATGCTGCGTCC ACTTTGCAAAGTGGGGTCCCATCACGATTCAGCGGCAGTGGATCCGGGACA GATTTCACTCTCACCATCAGCAGCCTGCACCCTGAAGATTTTGCTACTTATTA CTGCCAGCAGTTTTATAATTACCCTCCGACGTTCTGGCCAAGGGACCAAGGTG GAGATCAAA SEQ ID NO: 75
NI-302.18A1- V <sub>H</sub>	CAGCTGCAGCTGCAGGAGTCGGGGCCAGGACTAGTGAAGCCTTCGGAGGCC CTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCACTACTGATTATTACTA TTGGGGCTGGATCCGCCAGTCCCCAGGCAAGGGACTAGAGTGGGTGGGAC AATATACTTTGGTGGGGCCACCTACTACAATCCGTCCCTCAGGAACCGGGT TCGATATCTGTGGACACGTCCAACACTCGCCTCTCCCTGAGACTTATCTCTCT GAGCGCCGCTGACACGGCCGTCTATTATTGTGCGAGAGTGGGCTACTTGGAT AGGAGTGGTCTTCTTGTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCG SEQ ID NO: 77
NI-302.18A1- V <sub>K</sub>	GAAATTGTGCTGACGCAGTCTCCACTCTCCGTGCCCGTCACCCCGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAATAATGGATA CAACTATTTGGATTGGTACCTGAAGAAGCCTGGGCAGTCTCCACAACCTCTG ATCTATTTGGGCTCTACTCGGGCCTCCGGGGTCCCTGACAGGTTCAAGTGCCA GTGGATCAGGCACAGACTTTACACTGGAAATCAGCAGAGTGGAGGCTGAAG ATGTTGGCGTTTACTACTGCATGCAAGCTCTGCAGACTCCTCCGACTTTCGG CAGAGGGACCAAGGTGGAGATCAAA SEQ ID NO: 79
NI-302.52C9- V <sub>H</sub>	GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAACCTGGGGGGTCC CTGAGACTCTCCTGTGCAGGCTCTGGATTACCGTCAGTGACACCTACATGA GTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTC ATGCCGGTGGTGAAACATATTACGCAGACTCCGTGAAGGGCCGATTACCA TCTCCAGAGACAACCTCCAAGAACACGCTGTATCTTCAAATGAATAGGCTGAC ACCTGAGGACACGGCTGTCTTTTATTGTGCGAGACACTACTACGGTAATGAC GACGACACTGATTATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG SEQ ID NO: 85
NI-302.52C9- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATA CAACTATTTGGATTGGTACGTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTC ATCTATTTGGGTTCTACTCGGGCCTCCGGGGTCCCTGACAGATTCAAGTGCCA GTGGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGG ATGTTGGGGTTTATTACTGCTTACAAGCTCAACAAATTCCGTGGACGTTCCG CCAAGGGACCAAGGTGGAGATCAAA SEQ ID NO: 87
NI-302.46C9- V <sub>H</sub>	CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTAAAGCCTTCACAGACC CTGTCCCTCACCTGCACTGTTTCTGGTGCCTCCGTACAGAGTGGTGCCTACTA CTGGAGTTGGATCCGGCAGCCCCGCCGGAAGCGACTGGAGTGGATTGGGCG TGTCTATCCCACTTGGAGCACCAACTACAACCCCTCCCTCGAGAGTCGAGTC ACCATATCGTTAGACACGTCCAACAACCAAGTTCTCCCTGAAGCTGACCTCTT TGACTGCCGCAGACACGGCCGTTTATTACTGTGCGAGAGAGGCTCCTGGTGA CTACGATGCTGCGCCCCTAGCCTACTGGGGCCAGGGCACCCCTGGTCACCGTC TCCTCG SEQ ID NO: 89
NI-302.46C9- V <sub>K</sub>	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGTACATTAGCCACTATTTAAATTG GTATCGGCAGAAACCAGGGAAAGCCCCTCAGCTCGTAATCTATGCTGCATCC AGTTTGCAAAGTGAGGTCCCATCAAGGTTCAAGTGGGAGTGGATCTGGGCCA GAGTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTATT ACTGTCAACAGAGTTACACTACCCCTCGAACTTTTGCCAGGGGACCAAGCT GGAGATCAAA SEQ ID NO: 91

**Table III:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing an epitope of the P-rich region of HTT, *i.e* exon 1 in aggregated form.

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.63F3- V <sub>H</sub>	CAGGTGCAGCTGGTGCAATCTGGGTCTGCGTTC AAGAAGCCTGGGACCTCA GTGAAAGTTTCCTGCAAGGCCTCTGGATACACCTTCGAGACCCGTTCTATGA ACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAATACATGGGATGGATCA ACACCAACACTGGCAACCGCACGTATGTCCAGGCCTTCAGAGGACGATTTGT CTTCTCCTTGACACCTCTGTCAGCACGGCATATCTGCAGATCAGCAACTTA AAGACTGAGGACACTGCCGTGTATTACTGTGCGAGAGGGGCAGGTGGGGGA TATTGGTTCGACTCCTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCG SEQ ID NO: 5
NI-302.63F3- V <sub>K</sub>	GACATCCAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGA GGGCCACCATCAACTGCAAGTCCAATCAGAGTCTTTTCTACAGTTCCAACAA TAACAACACTTAGCTTGGTACCAGCACAAATCCGGACAGCCTCCTAAGCTG CTCGTTTACTGGGGATCTACCCGGGAATCCGGGGTCCCTGACCGCTTCAGTG GCAGCGGTCTGGGACTGACTTCACTCTCACCATCAGTAGCCTGCAGGCTGA GGATGTTGCAATTTATTACTGTCAACCAATATTATCATAATCCGTACACTTTTG GCCAGGGGACCAAGCTGGAGATCAAA SEQ ID NO: 7
NI-302.31F11- V <sub>H</sub>	GAGGTGCAGCTGGTGAGTCCGGAGGAGGCTTGATCCAGCCGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGGTTCACCGTCAGCAGCACCTACATGA GTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTTGAGTGCGTCTCAGTTATTTT TAGTGGCGCTGACACATATTACGCAGACTCCGTGAAGGGCCGATTACCGTCT TCCAGAGACAATTCCAAGAACACACTGTTTCTTCAGATGAACAGCCTGAGA GTCGAGGACACGGCCACATATTACTGTGTGAGACATTATTATGGTTCAGACC TTCCATCTGACTTCTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCG SEQ ID NO: 13
NI-302.31F11- V <sub>K</sub>	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCGCCCCCTGGAGAGC CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTATACAGTAATGGATA CAACTATTTGGATTGGTACCTGCAGAAGCCAGGGAAGCCTCCACAGCTCCTG GTCTATTTGGGTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTCACTGGCA GTGGATCAGGCAAAGATTTTACACTGAACATCAGCAGAGTGGAGGCTGAGG ATGTTGGGGTTTATTACTGCATGCAAGGTCTACAAAGTCCGTGGACGTTCCG CCAAGGGACCAAGCTGGAGATCAAA SEQ ID NO: 15
NI-302.2A2- V <sub>H</sub>	GAGGTGCAGCTGGTGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTACCTATTGGATGA ACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAACATAA AACCAGATGGAAGTGACAAATACTATGTGGACTCTGTGAAGGGCCGATTCA CCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCC TGAGAGACGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGACGGCAGTG GCTGGAACGTCTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG SEQ ID NO: 17
NI-302.2A2- V <sub>K</sub>	GACATCCAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGA GGGCCACCATCAACTGCAAGTCCAGCCAGAGTCTTTTATACACCTCCAAAAA TAAGGACAGTAAGAACTACTTAGGTTGGTACCAGCAGAAACCAGGACAGCC TCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGAC CGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCC TGCAGGCTGAGGATGTGGCAGTTTATTACTGTACGAGTATTATACTACTCC TCAGTTCGGCGGAGGGACCAAGGTGGAGATCAAA SEQ ID NO: 19
NI-302.15D3- V <sub>H</sub>	GAGGTGCAGCTGGTGAGTCTGGGGGAGACTTAGTTACAGCCTGGGGGGTCC CTAAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTACTGGATGC ACTGGGTCCGCCAAGCTCCAGGGAAGGGTCTGGTGTGGGTCTCACGTATTAG TAATGATGGCAGTAGCAAAACCTACGCGGACTCCGTGAAGGGCCGATTAC CATCTCCAGAGACAACGCCAAAAACACGCTGTATCTGCAAATGAACAGTCT GAGAGCCGAGGACACGGCTGTGTATTACTGTGCAATACTTGGCGGATATTGT AGTAGTACCAGTTGTCGTCCTTTGACAACTGGGGCCAGGGAACCCTGGTCA CCGTCTCCTCG SEQ ID NO: 135
NI-302.15D3- V <sub>L</sub>	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGA TCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGTTTATAACTATGT CTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACATGATTTTTGAT GTCAGTAATCGGCCCTCAGGGATTCTAATCGCTTCTCTGGCTCCAAGTCTG

	GCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTG ATTATTACTGCAGCTCATATACAAGCAGCGACACTTGGGTGTTCCGGCGGAGG GACCAAGCTGACCATCCTA SEQ ID NO: 137
NI-302.64E5- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGACTGGGGGAGGCTTGGTAAAGCCTGGGGGGTCC CTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTTCGACCAGGCCTGGATGA GCTGGGTCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTGTCGGCGGATTA AAACGAAAAGTGAAGGGAAGCAACAGACTACGCAGCGCCCGTGAGAGGC AGATTACCATCTCAAGAGATGATTTCAGAAGACACGGTGTCTTCTGCAAATGA ACAGCCTGAAAACCGAGGACACAGCCCTGTATTACTGTACGTCAACGGGAG TCTTAGCAGCAGCTGTGATGTCTACTGGGGCCAGGGAACCCCTGGTCACCGT CTCCTCG SEQ ID NO: 164
NI-302.64E5- V <sub>K</sub>	GACATCCAGTTGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGA GGGCCACCATGACCTGCAAGTCCAGCCAGAGTCTTTTCTACAGTTACAACAA TGAGAACTACTTAGCCTGGTATCAGCAGAGACCAGGACAGCCTCCTAAGTT GCTCATTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCACT GGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTG AAGATGTGGCAGTTTATTACTGTGCAATATTATAGTACTCCTCAGACGTT CGGCCAAGGGACCAAAGTGGATATCAAA SEQ ID NO: 166

**Table IV:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing an epitope of the C-terminal region of HTT, *i.e* exon 1 in aggregated form.

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.35C1-V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAACTTGGTACAGCCGGGGGGTCC CTGAGACTCTCCTGTACTGCCTCTGGATTCACTTTAGTATAACGGCCCTGA GTTGGGTCCGCCAGGCTCCAGAAAAGGGGCGCAGTGGGTCTCAGCAATCA CTGGAAATGCTTATGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCA CCATTTCCAGAGACAACGCCAAGAACACACTGTACTTGCAAATGAACGGCC TGAGAGCCGAGGACACGGCCATCTATTACTGTGTGAAAGGAATTGCCTCCG ATAGTAGTGGTTATTCTGCCTTCTGGGGCCCCGGGCACCCTGGTCACCGTCTC CTCG SEQ ID NO: 9
NI-302.35C1-V <sub>K</sub>	GAAATTGTGCTGACTCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGGCCAGTCAAAGTGTTGACAACCAAGTTTGCTG GTACCAACAGAAACCTGGCCAGGCTCCAGGCTCCTCATTTATGATGCATCC AGGAGGGCCCCCTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCTGGGACA GACTTCACTCTCACCATTAGCAGCCTAGAGCCTGAAGATTTTCGAATTTATT ACTGTCAGCATCGTTACACCTGGCTCTACACTTTTGCCAGGGGACACGACT GGAGATTAAA SEQ ID NO: 11
NI-302.72F10- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGACTGGGGGAGGCTTCGTACAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCAACTTCGGCAGTTATGCCATGA GCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGTCAGATATCA GTGGTATTGGTAGTAACACATACTACGCAGACTCCGTGAAGGGCCGTTTCAC CATTTCCAGAGACAATTCCGACAATACGTTGTACCTGGACATGAGCAGCCTG AGAGCCGAGGACACGGCCAGATATTACTGTGCGAAGGATCGAAAGCGCAGT GGCTGGTACGAACAGTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCG SEQ ID NO: 176
NI-302.72F10- V <sub>K</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTCGTACAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCAACTTCGGCAGTTATGCCATGA GCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGTCAGATATCA GTGGTATTGGTAGTAACACATACTACGCAGACTCCGTGAAGGGCCGTTTCAC CATTTCCAGAGACAATTCCGACAATACGTTGTACCTGGACATGAGCAGCCTG AGAGCCGAGGACACGGCCAGATATTACTGTGCGAAGGATCGAAAGCGCAGT GGCTGGTACGAACAGTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCG SEQ ID NO: 178

**Table V:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing HTT species and/or fragments thereof.

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.6N9- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGTAGTCTCTGGATTACCTTTAGTAGTTATGCCATGAC CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGCCTGGGTCTCAACAATTAG TGCTACTGGTGGTAGTACATTCTACACAGACTCCGTGAGGGGCCGTTTACC ATCTCCCGAGACAATTCCAAGAACACACTGTATCTGCAAATGAATAGCCTGA GAACCGACGACACGGCCATATATTATTGTGTGAAAGATCTATTTGGAGTGGA CACCTCCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC TCCTCG SEQ ID NO: 21
NI-302.6N9- V <sub>K</sub>	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGCCAGTCAGAGTGTACCGGCAGGTATGTGG CCTGGTATCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCTTCTATGCTGC ATCCAACAGGGCCATTGGCATCCCAGACAGGTTTCAAGTGGCAGTGGGTCTGG GACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTG TATTACTGTCAGCACTATGGTGCCTCATCGTACACTTTTGGCCCCGGGGACCA AAGTGGATATCAAA SEQ ID NO: 23
NI-302.8F1- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGAAGCCGGGGGGTCC CTTACAATCTCCTGTGCAGCCTCTGGTTTACCTTCAGTAATGCCTGGATGAA CTGGGTCCGCCAGGCTCCAGGTAAGGGGCTGGAGTGGGTGCGCCATATTAG AACGCAAGCTGAAGGAGGGACATCAGACTATGCTGCACCCGTGAAAGGCAG ATCACCATCTCAAGAGATGACTCAAAAAACACGCTGTATCTGCAAATGAA CAGCCTGAAAACCGAGGACACAGCCGTATATTATTGTATCCCCCCCCCTAC TACTACTATTACGGTCTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT CCTCG SEQ ID NO: 81
NI-302.8F1- V <sub>L</sub>	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGA TCACCATCTCCTGCACTGGAGCCAGCAGTGATGTTGGGACTTATGACCTTGT CTCCTGGTACCAACAACATCCAGGCAAAGCCCCCAAACCTCATTATTTATGAG GTCAATAAGCGGCCCTCAGGGGTTTCTTATCGTTCTCTGCCTCCAAGTCTGC CAACACGGCCTCCCTGACAATATCTGGGCTCCAGGCTGAGGACGAGGCTGA ATATTACTGCTGCTCATATGCAGGTTATAGCACGGTATTTCGGCGGAGGGACC AAGCTGACCGTCCTA SEQ ID NO: 83
NI-302.4A6- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCGCTTATGCCATGA GCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTA GTGGTAGTGGTGGTAGTACATACTACGCAGACTCCGTGAAGGGCCGTTCTC CATCTCCAGAGACAACCTCCAAAAACACCCTGTATCTGCAAATGAACAGCCT GAGAGCCGAGGACACGGCCGTATATTCTGTGCGAAAGTTACCACGGAAC CTACGGTGCTAACTCCTACTACTACTACATGGACGTCTGGGGCAAAGGGACC ACGGTCACCGTCTCCTCG SEQ ID NO: 184
NI-302.4A6- V <sub>K</sub>	GAAATTGTGTTGACACAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGTCAGCAGGTATTTAGC CTGGTACCAGCAAAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCA TCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAAGTGGCAGTGGGTCTGGG ACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCATGT ATTACTGTCAGCTGTATGGTAACTCACAGACGTTTCGGCCAGGGGACCAAGGT GGAGATCAAA SEQ ID NO: 186
NI-302.12H2- V <sub>H</sub>	GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC CTGAGACTTTCTGTGAAGCCTCTGGATTACCTTTAGCAACTATGCCATGG GCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGTAATTA GTGGTACTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGTTCA CCATCTCCAGAGACAATTCCATGAACACGCTGTATCTGCAAATGAACAGCCC GAGAGCCGACGACACGGCCGTATATTACTGTGCGAAAGATCTGAGGAAGAT



	TAGCGGTCCTTTATACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG GTCACCGTCTCCTCG SEQ ID NO: 188
NI-302.12H2- V <sub>K</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC CTGAGACTTTCCTGTGAAGCCTCTGGATTACCTTTAGCAACTATGCCATGG GCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGTAATTA GTGGTACTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCA CCATCTCCAGAGACAATTCCATGAACACGCTGTATCTGCAAATGAACAGCCC GAGAGCCGACGACACGGCCGTATATTACTGTGCGAAAGATCTGAGGAAGAT TAGCGGTCCTTTATACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG GTCACCGTCTCCTCG SEQ ID NO: 192
NI-302.8M1- V <sub>H</sub>	GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCA GTGAAAGTTTCCTGCAAGGCATCCGGATACACCTTACCATCTACTATATGC ACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGAGGAATCA GCCCCAGTGGTGCCACACAATGTACGCACAGAATTTCCAGGGCAGAGTCA CCGTGACCAGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGCAGCC TGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGAGCACGGTGA CTAACTATCGACCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTC CTCG SEQ ID NO: 194
NI-302.8M1- V <sub>K</sub>	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACTATCACTTGCCGGGCGAGTCAGGACATTAGCAATTATTTAGCCTG GTATCAGCAGAAACCAGGGAAAGTTCCTAACTCCTGATCTTTGCTGCATCC ACTTTGCAATCAGGGGTCCCGTCTCGGTTCCGGTGGCAGTGGATCTGGGACAG ATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTA CTGTCAAACTATAACAGTGGCCCTCCGCCTTTCGGCCCTGGGACCAAAGTG GATATCAAA SEQ ID NO: 198

**Table VI:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies an epitope of the N-terminal-region of HTT, *i.e* exon 1 in aggregated form

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.15E8- V <sub>H</sub>	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGATACAGCCGGGGGGTCC CTGAGACTCTCCTGTGCAGTCTCTGGATTACCGTCAGTAGTTATAGCATGA ACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATACTA GTAGTAGCAGAAGTAATACCAAAAAGTACGCAGACTCTGTGAAGGGCCGAT TCACCATCTCTAGAGACAATGCCAGGAACCTCACTCTATCTGCAAATGAACAG CCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGAGAGCAGGGGACTT CGGGGAGTTACTCACTGGTGAGGGGTATTACGGTATGGACGTCTGGGGCCA AGGGACCACGGTCACCGTCTCCTCG SEQ ID NO: 131
NI-302.15E8- V <sub>L</sub>	TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGACAG CCACCATCACCTGCTCGGGAGATGAATTGGGGGATAAATATGTTGGTTGGTA TCAACAGAAGCCAGGCCAGTCCCCTCTGCTGGTCATCTATCAAGATGCGAAG CGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACCTCTGGGAACACAG CCACTCTGACCATCAGCGGGACCCAGGCTATGGATGAGGCTGACTACTACTG TCAGGCGTGGGACAGCGGCACGATGGTTTTTCGGCGGAGGGACCAGGCTGAC CGTCCTA SEQ ID NO: 133

**Table VII:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing an epitope of the Q/P-rich region of HTT, *i.e* exon 1 in aggregated form.

Antibody	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.7D8- V <sub>H</sub>	CAGGTGCAGCTGGTGCAATCTGGATCTGAGTTGAAGAAGCCTGGGGCCTCA GTGAAGGTTTCCTGCAAGGCTTCTGGATACAACCTCAATAACTATGCCATCA ATTGGTTGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCA ACACCATCACTGGGCACCCAACGTATGCCCAGGGCTTCAAAGGACGATTTGT CTTCTCCTTGGACACCTCTGTCAGCACGGCATATCTGCAGATCAGCAGCCTA AAGCCTGAGGACACTGCCGTCTATTACTGTGCGAGAACTTACAGTAACTACG GCGAATTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG SEQ ID NO: 172
NI-302.7D8- V <sub>L</sub>	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCGTGGACAGTCTGA TCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGAAGTTATAACCTTGT CTCCTGGTACCAACAGTACCCAGGCAAGGCCCCCAAGCTCATAATTCATGAG GGCAGTGAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTG GCAACACGGCCTCCCTGACAATTTCTGGGCTCCAGGCTGAGGACGAGGCTG ATTATTACTGCTGCTCATATGCAGGTACTACTACTTTCGTGCTATTCGGCGGA GGGACCAAGCTGACCGTCCTC SEQ ID NO: 174

Due to the cloning strategy the amino acid sequence at the N- and C-terminus of the heavy chain and light chains may potentially contain primer-induced alterations in FR1 and FR4, which however do not substantially affect the biological activity of the antibody. In order to provide a consensus human antibody, the nucleotide and amino acid sequences of the original clone can be aligned with and tuned in accordance with the pertinent human germ line variable region sequences in the database; see, *e.g.*, Vbase2, as described above. The amino acid sequence of human antibodies are indicated in bold when N- and C-terminus amino acids are considered to potentially deviate from the consensus germ line sequence due to the PCR primer and thus have been replaced by primer-induced mutation correction (PIMC), see Table VI. Accordingly, in one embodiment of the present invention, the polynucleotide comprises, consists essentially of, or consists of a nucleic acid having a polynucleotide sequence of the V<sub>H</sub> and the V<sub>L</sub> region of an anti-HTT antibody and/or fragments thereof as depicted in Table VI.

**Table VIII:** Nucleotide sequences of the V<sub>H</sub> and V<sub>L</sub> region of antibodies recognizing HTT species and/or fragments thereof showing replacement by PIMC (bold).

Alternative Antibody-regions with PIMC	Nucleotide sequences of variable heavy (V <sub>H</sub> ) and variable light (V <sub>L</sub> ) chains
NI-302.33C11-PIMC V <sub>H</sub>	<b>CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTTGTCCAGCCTGGGA</b> ACTC CCTGAGACTCTCCTGTGCAGCGTCTGGATTCAAGTTCACTGACTTTGGCATG CACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGCTGGCACTTATA TGGTATGATGGAGGGTATAAGTACTATGCAGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCAAGAATACGATGTTTCTACAAATGAACAGCC TGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGACCCACCTAGAATATTG CAGTAGAACCACCTGCTATCTCGGCCACTGGGGCCAGGGAACCCTGGTCAC <b>CGTCTCCTCG</b> SEQ ID NO: 97

NI-302.33C11-PIMC V <sub>k</sub>	<b>GACATCCAGTTGACCCAGTCTCCGTCCTTCCTATCTGCGTCTGTGGGAGAC ACAGTCACCTTCACCTTGCCGGGCCAGTCAGGGCATTAGCGATTATTTAGCCT GGTTTCAGCAGAAACCAGGGATTGCCCTAAGCTCCTGATCTATGCTGCGTC CACTTTGCAAACCGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGAC AGAATTCACCTCTCACAATCCGCAGCCTGCAGTCTGAAGATTTTGGAACTTAT TACTGTCAGCAGCTTAAAACTTACCCGTACACTTTTGGCCAGGGGACCAAG CTGGAGATCAAA</b> SEQ ID NO: 99
NI-302.63F3-PIMC V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATCAACTGCAAGTCCAATCAGAGTCTTTTCTACAGTTCCAACA ATAACAACCTAGCTTGGTACCAGCACAAATCCGGACAGCCTCCTAAGCT GCTCGTTTACTGGGGATCTACCCGGGAATCCGGGGTCCCTGACCGCTTCAGT GGCAGCGGGTCTGGGACTGACTTCACTCTCACCATCAGTAGCCTGCAGGCTG AGGATGTTGCAATTTATTACTGTCACCAATATTATCATAATCCGTACACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA</b> SEQ ID NO: 101
NI-302.63F3-PIMC- NS V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATCAACTGCAAGTCCCTACAGAGTCTTTTCTACAGTTCCAACA ATAACAACCTAGCTTGGTACCAGCACAAATCCGGACAGCCTCCTAAGCT GCTCGTTTACTGGGGATCTACCCGGGAATCCGGGGTCCCTGACCGCTTCAGT GGCAGCGGGTCTGGGACTGACTTCACTCTCACCATCAGTAGCCTGCAGGCTG AGGATGTTGCAATTTATTACTGTCACCAATATTATCATAATCCGTACACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA</b> SEQ ID NO: 103
NI-302.63F3-PIMC- SG V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATCAACTGCAAGTCCAATCAGGGCCTTTTCTACAGTTCCAACA ATAACAACCTAGCTTGGTACCAGCACAAATCCGGACAGCCTCCTAAGCT GCTCGTTTACTGGGGATCTACCCGGGAATCCGGGGTCCCTGACCGCTTCAGT GGCAGCGGGTCTGGGACTGACTTCACTCTCACCATCAGTAGCCTGCAGGCTG AGGATGTTGCAATTTATTACTGTCACCAATATTATCATAATCCGTACACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA</b> SEQ ID NO: 105
NI-302.63F3-PIMC- NQ V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATCAACTGCAAGTCCCAACAGAGTCTTTTCTACAGTTCCAACA ATAACAACCTAGCTTGGTACCAGCACAAATCCGGACAGCCTCCTAAGCT GCTCGTTTACTGGGGATCTACCCGGGAATCCGGGGTCCCTGACCGCTTCAGT GGCAGCGGGTCTGGGACTGACTTCACTCTCACCATCAGTAGCCTGCAGGCTG AGGATGTTGCAATTTATTACTGTCACCAATATTATCATAATCCGTACACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA</b> SEQ ID NO: 107
NI-302.35C1-PIMC V <sub>k</sub>	<b>GAAATTGTGCTGACTCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAAAGTGTGACAACCAAGTTTGCCCT GGTACCAACAGAAACCTGGCCAGGCTCCAGGCTCCTCATTTATGATGCATC CAGGAGGGCCCCTGGCATCCAGACAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATTAGCAGCCTAGAGCCTGAAGATTTTCGAATTTAT TACTGTCAGCATCGTTACACCTGGCTCTACACTTTTGGCCAGGGGACCAAG CTGGAGATCAAA</b> SEQ ID NO: 109
NI-302.31F11-PIMC V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGCCGTCGCCCCTGGAGAG CCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTATACAGTAATGGAT ACAACCTATTTGGATTGGTACCTGCAGAAGCCAGGGAAGCCTCCACAGCTCCT GGTCTATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTCACTGGC AGTGGATCAGGCAAAGATTTTACACTGAACATCAGCAGAGTGGAGGCTGAG GATGTTGGGGTTTATTACTGCATGCAAGGTCTACAAAGTCCGTGGACGTTTCG GCCAAGGGACCAAGGTGGAAATCAAA</b> SEQ ID NO: 111
NI-302.2A2-PIMC V <sub>k</sub>	<b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTCTTTTATACACCTCCAAAA ATAAGGACAGTAAGAACTACTTAGGTTGGTACCAGCAGAAACCAGGACAGC CTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGA CCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGC</b>

	CTGCAGGCTGAGGATGTGGCAGTTTATTACTGTCAGCAGTATTATACTACTC CTCAGTTCGGCGGAGGGACCAAGGTGGAAATCAAA SEQ ID NO: 113
NI-302.74C11-PIMC V <sub>H</sub>	<b>CAGGTGCAGCTGGTGC</b> AATCTGGGACTGAGGTGCAGAAAGCCTGGGGCCTC AGTAAAAGTCTCCTGCAAGGCTTCTGGATACAGTTTCACCGGCTACTTTTTG CACTGGGTACGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGGTGGATC AACCCTAACAGTGGTGACACAACTATGCAGAGAAGTTTCGGGGGCAGAATC ATCATGACCAGGGACACGTCTGTCAGCACAGCCCACATGGAGTTGAGCAGC CTGAGATTTGACGACACGGCCCTATATTACTGTACGAGAGAGGCCCTGACC CGGGCGCTGAGACGGACGTCTGGGGCCAAGGA <b>ACCACGGTCACCGTCTCC</b> <b>TCG</b> SEQ ID NO: 115
NI-302.74C11-PIMC V <sub>L</sub>	<b>TCCTATGAGCTGACTCAGCCACCCTCGGTGTCAGTGTCCCCAGGACAGAC</b> GGCCAGGATCACCTGCTCTGGAGATGCAGTGCCAAAGCAGTATATTTATTGG TACCAGCAGAAGCCAGGCCAGGCCCTATTCTGGTGATATATAAAGACACT CAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACCTCAGGGACAA CAGTCACGTTGACCATAACTGGCGTCCAGGCAGACGACGAGGGTGACTATT ACTGTCAATCAGCAGACAGTAGTGCTACTTGGGTGTTTCGGCGGAGGGACCA AATTGACCGTCCTA SEQ ID NO: 117
NI-302.39G12-PIMC V <sub>H</sub>	<b>GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCACCCTTGGGGGTC</b> CCTGAGACTCTCCTGTGCAGCCTCTGGATTACGCGTCTCTAATTACGCCATA ACTTGGGTCCGCCGGGCTCCAGGGAAGGGGCTGCAATATATTTTCAGTAATTT ATCGTGATGGCAGGACATACTACGGAGACTCCGTGAGGGGCCGCTTCACCA TCTCTAGGGACGATTCCAAGAACACTCTCTATCTTCAAATGAACAGCCTGAG ATTTGAGGACACGGCTGTGTATTACTGTGCGAGAGCGCACGGCCAATATTAC TATGGTGTGGACGTCTGGGGCCAAGGA <b>ACCACGGTCACCGTCTCCTCG</b> SEQ ID NO: 119
NI-302.39G12-PIMC V <sub>K</sub>	<b>GACATCGTGATGACCCAGTCTCCACTCTCCCTGTCCGTGAGCCCTGGAGAG</b> CCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGAT ACAACCTATTTGGATTGGTACCGGCAGAAACCAGGGCAGTCTCCACAGCTCCT GATCTATTTGAGTTCTAATCGGCCCTCCGGGGTCCCTGATAGGTTCAAGTGGC AGTGGATCAGGCACAGAGTTCACACTGCAAATCAGCAGAGTGGAGGCTGAG GATGTTGGGGTTTATTACTGCATGCAATCTCTGCAAACGTTCACTTTTCGGCG GAGGGACCAAGGTGGAAATCAAA SEQ ID NO: 121
NI-302.11A4-PIMC V <sub>K</sub>	<b>GAAATTGTGCTGACTCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGAGAA</b> AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTCG CCTGGTACCAACAAAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTAC GTCCCGCAGGGCCACTGCCATCCCAGACAGGTTCAAGTGGCAGTGGGTCTGG GACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTG TATTACTGTCAACAGTATGGTAGCTCGTGACGTTTCGGCC <b>AGGGACCAAG</b> <b>GTGGAAATCAAA</b> SEQ ID NO: 123
NI-302.22H9-PIMC V <sub>K</sub>	<b>GATATTGTGATGACTCAATCACC</b> ACTCTCCCTGTCCGTGAGCCCTGGAGAG CCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGAT ACAACCTATTTGGATTGGTACCGGCAGAAACCAGGGCAGTCTCCACAACCTCCT GATCTATTTGAATTCTAATCGGGCCTCCGGGGTCCCTGATAGGTTCAAGTGGC AGTGGATCAGGCACAGAGTTCACACTGACAATCAGCAGAGTGGAGGCTGAG GATGTTGGGGTTTATTACTGCATGCAATCTCTGCAAACGTTCACTTTTCGGCG GAGGGACCAAGGTGGAAATCAAA SEQ ID NO: 125
NI-302.44D7-PIMC V <sub>H</sub>	<b>GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGT</b> CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCAT GAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTAT TGTTTATAGTGATACTAGCACATATTACGCAGACTCCGTGAAGGGCCGCTTC ACCGTCTCCAGAGACATTTCCAAGAACACGCTGTATCTGCAAATGAATAGCC TGAGGGCCGAGGACACGGCCGTATATTACTGCGCGAAAGGTACCAGGGACT ATTACGGTATGGACGTCTGGGGCCAAGGA <b>ACCACGGTCACCGTCTCCTCG</b> SEQ ID NO: 127

NI-302.78H12-PIMC V <sub>H</sub>	<p><b>CAGCTGCAGCTGCAGGAGTCTGGGCCCCAGGACTGGTGAAGCCTTCGGAGA CCCTGTCCCTCACCTGTCTTGTCTCTAGTTACTCCATCAGCAATGGTTACTAC TGGGGCTGGATTTCGGCAGCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAGT ATCTATCATAATGGGAACACCTATTACAACCCGTCCCTCAAGAGTCGAGTCA TCATTTAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGTTGAGGTCTGT GACCGCCGCAGACACGGCCGTGTACTACTGTGCGATGCCAAGTGCCACCTAT TATTATGGTTTCGGGGACTCAATTCCATGCGTTTGTATGTCTGGGGCCAAGGGA CAATGGTCAACCGTCTCTTCG</b></p> <p>SEQ ID NO: 129</p>
NI-302.64E5-PIMC V <sub>H</sub>	<p><b>GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGGGT CCCTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCGACCAGGCCTGGAT GAGCTGGGTCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTGGCCGGAT TAAAACGAAAACCTGAGGGTGAAGCAACAGACTACGCAGCGCCCGTGAGAG GCAGATTCACCATCTCAAGAGATGATTGAGAAGACACGGTGTCTTCTGCAAAT GAACAGCCTGAAAACCGAGGACACAGCCCTGTATTACTGTACGTCAACGGG AGTCTTAGCAGCAGCTGTCGATGTCTACTGGGGCCAGGGCACCCCTGGTTCAC CGTCTCCTCG</b></p> <p>SEQ ID NO: 166</p>
NI-302.64E5-PIMC V <sub>K</sub>	<p><b>GATATTGTGATGACTCAATCACCAGACTCCCTGGCTGTGTCTCTGGGCGAG AGGGCCACCATGACCTGCAAGTCCAGCCAGAGTCTTTTCTACAGTTACAACA ATGAGAACTACTTAGCCTGGTATCAGCAGAGACCAGGACAGCCTCCTAAGT TGCTCATTTACTGGGCATCTACCCGGAATCCGGGGTCCCTGACCGATTGAG TGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCT GAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACTCCTCAGACGT TCGGCCAAGGGACCAAGGTGGAAATCAAA</b></p> <p>SEQ ID NO: 170</p>
NI-302.72F10-PIMC V <sub>H</sub>	<p><b>GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTCGTACAGCCTGGGGGGT CCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAACTTCGGCAGTTATGCCAT GAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGTCAGATAT CAGTGGTATTGGTAGTAACACATACTACGCAGACTCCGTGAAGGGCCGTTC ACCATTTCCAGAGACAATTCCGACAATACGTTGTACCTGGACATGAGCAGCC TGAGAGCCGAGGACACGGCCAGATATTACTGTGCGAAGGATCGAAAGCGCA GTGGCTGGTACGAACAGTGGGGCCAGGGCACCCCTGGTTCACCGTCTCCTCG</b></p> <p>SEQ ID NO: 178</p>
NI-302.72F10-PIMC V <sub>K</sub>	<p><b>GAAATTGTGCTGACTCAGTCTCCAGCCACCCTGACTTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTATTAGCGCCTACTTAGGCT GGTATCAACAAAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATC CATTAGGGCCACTGGCATTCCAGACAGGTTTAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTCTGCAGTTTAT TACTGTCACCAGCGTAGCAAGTGGCCTCTTACTTTCGGCGGAGGGACCAAG GTGGAAATCAAA</b></p> <p>SEQ ID NO: 182</p>
NI-302.12H2-PIMC V <sub>H</sub>	<p><b>GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGT CCCTGAGACTTTCCTGTGAAGCCTCTGGATTCACTTTAGCAACTATGCCAT GGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGTAAT TAGTGGTACTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTC ACCATCTCCAGAGACAATTCCATGAACACGCTGTATCTGCAAATGAACAGCC CGAGAGCCGACGACACGGCCGTATATTACTGTGCGAAAGATCTGAGGAAGA TTAGCGGTCTTTATACTACTACGGTATGGACGTCTGGGGCCAAGGGACCA CGGTACCGTCTCCTCG</b></p> <p>SEQ ID NO: 190</p>
NI-302.8M1-PIMC V <sub>H</sub>	<p><b>CAGGTGCAGCTGGTGCATCTGGGGGCTGAGGTGAAGAAGCCTGGGGCCTC AGTGAAAGTTTCCTGCAAGGCATCCGGATACACCTTCACCATCTACTATATG CACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGAGGAATC AGCCCGAGTGGTGCCACACAATGTACGCACAGAATTTCCAGGGCAGAGTC ACCGTGACCAGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGCAGC CTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGAGCACGGTG ACTAACTATCGACCCTTTGACTACTGGGGCCAGGGCACCCCTGGTTCACCGTC TCCTCG</b></p> <p>SEQ ID NO: 196</p>

The present invention also includes fragments of the polynucleotides of the invention, as described elsewhere. Additionally polynucleotides which encode fusion polynucleotides, Fab fragments, and other derivatives, as described herein, are also contemplated by the invention. The polynucleotides may be produced or manufactured by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides, *e.g.*, as described in Kutmeier *et al.*, BioTechniques 17 (1994), 242, which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody, or antigen-binding fragment, variant, or derivative thereof may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the antibody may be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably polyA<sup>+</sup> RNA, isolated from, any tissue or cells expressing the HTT-specific antibody, such as hybridoma cells selected to express an antibody) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody, or antigen-binding fragment, variant, or derivative thereof is determined, its nucleotide sequence may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook *et al.*, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1990) and Ausubel *et al.*, eds., Current Protocols in Molecular Biology, John Wiley & Sons, NY (1998), which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

#### IV. Expression of Antibody Polypeptides

Following manipulation of the isolated genetic material to provide antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention, the polynucleotides encoding the antibodies are typically inserted in an expression vector for introduction into host cells that may be used to produce the desired quantity of antibody. Recombinant expression of an antibody, or fragment, derivative, or analog thereof, *e.g.*, a heavy or light chain of an antibody which binds to a target molecule is described herein. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operable linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (*see, e.g.*, international applications WO 86/05807 and WO 89/01036; and US patent no. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The term "vector" or "expression vector" is used herein to mean vectors used in accordance with the present invention as a vehicle for introducing into and expressing a desired gene in a host cell. As known to those skilled in the art, such vectors may easily be selected from the group consisting of plasmids, phages, viruses, and retroviruses. In general, vectors compatible with the instant invention will comprise a selection marker, appropriate restriction sites to facilitate cloning of the desired gene and the ability to enter and/or replicate in eukaryotic or prokaryotic cells. For the purposes of this invention, numerous expression vector systems may be employed. For example, one class of vector utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV), or SV40 virus. Others involve the use of polycistronic systems with internal ribosome binding sites. Additionally, cells which have

integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells. The marker may provide for prototrophy to an auxotrophic host, biocide resistance (*e.g.*, antibiotics), or resistance to heavy metals such as copper. The selectable marker gene can either be directly linked to the DNA sequences to be expressed, or introduced into the same cell by co-transformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include signal sequences, splice signals, as well as transcriptional promoters, enhancers, and termination signals.

In particularly preferred embodiments the cloned variable region genes are inserted into an expression vector along with the heavy and light chain constant region genes (preferably human) as discussed above. In one embodiment, this is accomplished using a proprietary expression vector of Biogen IDEC, Inc., referred to as NEOSPLA, and disclosed in US patent no. 6,159,730. This vector contains the cytomegalovirus promoter/enhancer, the mouse beta globin major promoter, the SV40 origin of replication, the bovine growth hormone polyadenylation sequence, neomycin phosphotransferase exon 1 and exon 2, the dihydrofolate reductase gene, and leader sequence. This vector has been found to result in very high level expression of antibodies upon incorporation of variable and constant region genes, transfection in CHO cells, followed by selection in G418 containing medium and methotrexate amplification. Of course, any expression vector which is capable of eliciting expression in eukaryotic cells may be used in the present invention. Examples of suitable vectors include, but are not limited to plasmids pcDNA3, pHCMV/Zeo, pCR3.1, pEF1/His, pIND/GS, pRc/HCMV2, pSV40/Zeo2, pTRACER-HCMV, pUB6/V5-His, pVAX1, and pZeoSV2 (available from Invitrogen, San Diego, CA), and plasmid pCI (available from Promega, Madison, WI). In general, screening large numbers of transformed cells for those which express suitably high levels of immunoglobulin heavy and light chains is routine experimentation which can be carried out, for example, by robotic systems. Vector systems are also taught in US patent nos. 5,736,137 and 5,658,570, each of which is incorporated by reference in its entirety herein. This system provides for high expression levels, *e.g.*, > 30 pg/cell/day. Other exemplary vector systems are disclosed *e.g.*, in US patent no. 6,413,777.

In other preferred embodiments the antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention may be expressed using polycistronic constructs such as those disclosed in US patent application publication no. 2003-0157641 A1 and incorporated



herein in its entirety. In these expression systems, multiple gene products of interest such as heavy and light chains of antibodies may be produced from a single polycistronic construct. These systems advantageously use an internal ribosome entry site (IRES) to provide relatively high levels of antibodies. Compatible IRES sequences are disclosed in US patent no. 6,193,980 which is also incorporated herein. Those skilled in the art will appreciate that such expression systems may be used to effectively produce the full range of antibodies disclosed in the instant application. Therefore, in one embodiment the present invention provides a vector comprising the polynucleotide encoding at least the binding domain or variable region of an immunoglobulin chain of the antibody, optionally in combination with a polynucleotide that encodes the variable region of the other immunoglobulin chain of said binding molecule.

More generally, once the vector or DNA sequence encoding a monomeric subunit of the antibody has been prepared, the expression vector may be introduced into an appropriate host cell. Introduction of the plasmid into the host cell can be accomplished by various techniques well known to those of skill in the art. These include, but are not limited to, transfection including lipotransfection using, *e.g.*, Fugene® or lipofectamine, protoplast fusion, calcium phosphate precipitation, cell fusion with enveloped DNA, microinjection, and infection with intact virus. Typically, plasmid introduction into the host is via standard calcium phosphate co-precipitation method. The host cells harboring the expression construct are grown under conditions appropriate to the production of the light chains and heavy chains, and assayed for heavy and/or light chain protein synthesis. Exemplary assay techniques include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or fluorescence-activated cell sorter analysis (FACS), immunohistochemistry and the like.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody for use in the methods described herein. Thus, the invention includes host cells comprising a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or at least the binding domain or variable region of an immunoglobulin thereof, which preferably are operable linked to a heterologous promoter. In addition or alternatively the invention also includes host cells comprising a vector, as defined hereinabove, comprising a polynucleotide encoding at least the binding domain or variable region of an immunoglobulin chain of the antibody, optionally in combination with a polynucleotide that encodes the variable region of the other immunoglobulin chain of said binding molecule. In preferred embodiments for the expression

of double-chained antibodies, a single vector or vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

5 The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes both heavy and light chain polypeptides. In such situations, the light chain  
10 is advantageously placed before the heavy chain to avoid an excess of toxic free heavy chain; *see* Proudfoot, Nature 322 (1986), 52; Kohler, Proc. Natl. Acad. Sci. USA 77 (1980), 2197. The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

As used herein, "host cells" refers to cells which harbor vectors constructed using recombinant  
15 DNA techniques and encoding at least one heterologous gene. In descriptions of processes for isolation of antibodies from recombinant hosts, the terms "cell" and "cell culture" are used interchangeably to denote the source of antibody unless it is clearly specified otherwise. In other words, recovery of polypeptide from the "cells" may mean either from spun down whole cells, or from the cell culture containing both the medium and the suspended cells.

20 A variety of host-expression vector systems may be utilized to express antibody molecules for use in the methods described herein. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding  
25 sequences, express an antibody molecule of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *Escherichia coli*, *Bacillus subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell  
30 systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, NSO, BLK, 293, 3T3 cells) harboring

recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *E. coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese Hamster Ovary (CHO) cells, in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies; *see, e.g.*, Foecking *et al.*, Gene 45 (1986), 101; Cockett *et al.*, Bio/Technology 8 (1990), 2.

The host cell line used for protein expression is often of mammalian origin; those skilled in the art are credited with ability to preferentially determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, CHO (Chinese Hamster Ovary), DG44 and DUXB11 (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CVI (monkey kidney line), COS (a derivative of CVI with SV40 T antigen), VERY, BHK (baby hamster kidney), MDCK, WI38, R1610 (Chinese hamster fibroblast) BALBC/3T3 (mouse fibroblast), HAK (hamster kidney line), SP2/O (mouse myeloma), P3x63-Ag3.653 (mouse myeloma), BFA-1c1BPT (bovine endothelial cells), RAJI (human lymphocyte) and 293 (human kidney). CHO and 293 cells are particularly preferred. Host cell lines are typically available from commercial services, the American Tissue Culture Collection or from published literature.

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be

transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which stably express the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler *et al.*, Cell 11 (1977), 223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska and Szybalski, Proc. Natl. Acad. Sci. USA 48 (1992), 202), and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22 (1980), 817) genes can be employed in tk-, hgp<sup>rt</sup>- or ap<sup>rt</sup>-cells, respectively. Also, anti-metabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler *et al.*, Natl. Acad. Sci. USA 77 (1980), 357; O'Hare *et al.*, Proc. Natl. Acad. Sci. USA 78 (1981), 1527); gpt, which confers resistance to mycophenolic acid (Mulligan and Berg, Proc. Natl. Acad. Sci. USA 78 (1981), 2072); neo, which confers resistance to the aminoglycoside G-418 Goldspiel *et al.*, Clinical Pharmacy 12 (1993), 488-505; Wu and Wu, Biotherapy 3 (1991), 87-95; Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32 (1993), 573-596; Mulligan, Science 260 (1993), 926-932; and Morgan and Anderson, Ann. Rev. Biochem. 62 (1993), 191-217; TIB TECH 11 (1993), 155-215; and hyg<sup>ro</sup>, which confers resistance to hygromycin (Santerre *et al.*, Gene 30 (1984), 147. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification, for a review; *see* Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Academic Press, New York, Vol. 3. (1987). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the

marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase; *see* Crouse *et al.*, Mol. Cell. Biol. 3 (1983), 257.

*In vitro* production allows scale-up to give large amounts of the desired polypeptides.

5 Techniques for mammalian cell cultivation under tissue culture conditions are known in the art and include homogeneous suspension culture, *e.g.* in an airlift reactor or in a continuous stirrer reactor, or immobilized or entrapped cell culture, *e.g.* in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges. If necessary and/or desired, the solutions of polypeptides can be purified by the customary chromatography methods, for example gel  
10 filtration, ion-exchange chromatography, chromatography over DEAE-cellulose or (immuno-) affinity chromatography, *e.g.*, after preferential biosynthesis of a synthetic hinge region polypeptide or prior to or subsequent to the HIC chromatography step described herein.

Genes encoding antibodies, or antigen-binding fragments, variants or derivatives thereof of the  
15 invention can also be expressed in non-mammalian cells such as bacteria or insect or yeast or plant cells. Bacteria which readily take up nucleic acids include members of the enterobacteriaceae, such as strains of *E. coli* or *Salmonella*; Bacillaceae, such as *B. subtilis*; *Pneumococcus*; *Streptococcus*, and *Haemophilus influenzae*. It will further be appreciated that, when expressed in bacteria, the heterologous polypeptides typically become part of inclusion  
20 bodies. The heterologous polypeptides must be isolated, purified and then assembled into functional molecules. Where tetravalent forms of antibodies are desired, the subunits will then self-assemble into tetravalent antibodies; *see, e.g.*, international application WO 02/096948.

In bacterial systems, a number of expression vectors may be advantageously selected depending  
25 upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, EMBO J. 2 (1983), 1791), in which the  
30 antibody coding sequence may be ligated individually into the vector in frame with the lacZ coding region so that a fusion protein is produced; pIN vectors (Inouye and Inouye, Nucleic Acids Res. 13 (1985), 3101-3109; Van Heeke and Schuster, J. Biol. Chem. 24 (1989), 5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and

can easily be purified from lysed cells by adsorption and binding to a matrix of glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

5

In addition to prokaryotes, eukaryotic microbes may also be used. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among eukaryotic microorganisms although a number of other strains are commonly available, *e.g.*, *Pichia pastoris*. For expression in *Saccharomyces*, the plasmid YRp7, for example, (Stinchcomb *et al.*, Nature 282 (1979), 39; Kingsman *et al.*, Gene 7 (1979), 141; Tschemper *et al.*, Gene 10 (1980), 157) is commonly used. This plasmid already contains the TRP1 gene which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC No. 44076 or PEP4-1 (Jones, Genetics 85 (1977), 12). The presence of the *trp1* lesion as a characteristic of the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

15

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is typically used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

20

Once an antibody molecule of the invention has been recombinantly expressed, the whole antibodies, their dimers, individual light and heavy chains, or other immunoglobulin forms of the present invention, can be purified according to standard procedures of the art, including for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, *e.g.* ammonium sulfate precipitation, or by any other standard technique for the purification of proteins; see, *e.g.*, Scopes, "Protein Purification", Springer Verlag, N.Y. (1982). Alternatively, a preferred method for increasing the affinity of antibodies of the invention is disclosed in US patent publication 2002-0123057 A1. In one embodiment therefore, the present invention also provides a method for preparing an anti-HTT antibody or an antibody recognizing mutated and/or aggregated HTT species and/or fragments thereof or immunoglobulin chain(s) thereof, said method comprising:

30

- (a) culturing the host cell as defined hereinabove, which cell comprised a polynucleotide or a vector as defined hereinbefore; and
- (b) isolating said antibody or immunoglobulin chain(s) thereof from the culture.

5 Furthermore, in one embodiment the present invention also relates to an antibody or immunoglobulin chain(s) thereof encoded by a polynucleotide as defined hereinabove or obtainable by said method for preparing an anti-HTT antibody or an antibody recognizing mutated and/or aggregated HTT species and/or fragments thereof or immunoglobulin chain(s) thereof.

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## V. Fusion Proteins and Conjugates

In certain embodiments, the antibody polypeptide comprises an amino acid sequence or one or more moieties not normally associated with an antibody. Exemplary modifications are described in more detail below. For example, a single-chain Fv antibody fragment of the  
15 invention may comprise a flexible linker sequence, or may be modified to add a functional moiety (*e.g.*, PEG, a drug, a toxin, or a label such as a fluorescent, radioactive, enzyme, nuclear magnetic, heavy metal and the like)

An antibody polypeptide of the invention may comprise, consist essentially of, or consist of a  
20 fusion protein. Fusion proteins are chimeric molecules which comprise, for example, an immunoglobulin HTT-binding domain with at least one target binding site, and at least one heterologous portion, *i.e.*, a portion with which it is not naturally linked in nature. The amino acid sequences may normally exist in separate proteins that are brought together in the fusion polypeptide or they may normally exist in the same protein but are placed in a new arrangement  
25 in the fusion polypeptide. Fusion proteins may be created, for example, by chemical synthesis, or by creating and translating a polynucleotide in which the peptide regions are encoded in the desired relationship.

The term "heterologous" as applied to a polynucleotide or a polypeptide, means that the  
30 polynucleotide or polypeptide is derived from a distinct entity from that of the rest of the entity to which it is being compared. For instance, as used herein, a "heterologous polypeptide" to be fused to an antibody, or an antigen-binding fragment, variant, or analog thereof is derived from a non-immunoglobulin polypeptide of the same species, or an immunoglobulin or non-immunoglobulin polypeptide of a different species.

As discussed in more detail elsewhere herein, antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins; *see, e.g.*, international applications WO 92/08495; WO 91/14438; WO 89/12624; US patent no. 5,314,995; and European patent application EP 0 396 387.

Antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, *i.e.*, peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. Antibodies may be modified by natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in the antibody, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini, or on moieties such as carbohydrates. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given antibody. Also, a given antibody may contain many types of modifications. Antibodies may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic antibodies may result from posttranslational natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination; *see, e.g.*, *Proteins - Structure And Molecular Properties*, T. E. Creighton, W. H. Freeman and Company, New York 2nd Ed., (1993); *Posttranslational Covalent Modification*



Of Proteins, B. C. Johnson, Ed., Academic Press, New York, (1983) 1-12; Seifter *et al.*, Meth. Enzymol. 182 (1990), 626-646; Rattan *et al.*, Ann. NY Acad. Sci. 663 (1992), 48-62).

The present invention also provides for fusion proteins comprising an antibody, or antigen-binding fragment, variant, or derivative thereof, and a heterologous polypeptide. In one embodiment, a fusion protein of the invention comprises, consists essentially of, or consists of, a polypeptide having the amino acid sequence of any one or more of the V<sub>H</sub> regions of an antibody of the invention or the amino acid sequence of any one or more of the V<sub>L</sub> regions of an antibody of the invention or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein for use in the diagnostic and treatment methods disclosed herein comprises, consists essentially of, or consists of a polypeptide having the amino acid sequence of any one, two, three of the V<sub>H</sub>-CDRs of an antibody, or fragments, variants, or derivatives thereof, or the amino acid sequence of any one, two, three of the V<sub>L</sub>-CDRs of an antibody, or fragments, variants, or derivatives thereof, and a heterologous polypeptide sequence. In one embodiment, the fusion protein comprises a polypeptide having the amino acid sequence of a V<sub>H</sub>-CDR3 of an antibody of the present invention, or fragment, derivative, or variant thereof, and a heterologous polypeptide sequence, which fusion protein specifically binds to HTT. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of at least one V<sub>H</sub> region of an antibody of the invention and the amino acid sequence of at least one V<sub>L</sub> region of an antibody of the invention or fragments, derivatives or variants thereof, and a heterologous polypeptide sequence. Preferably, the V<sub>H</sub> and V<sub>L</sub> regions of the fusion protein correspond to a single source antibody (or scFv or Fab fragment) which specifically binds HTT. In yet another embodiment, a fusion protein for use in the diagnostic and treatment methods disclosed herein comprises a polypeptide having the amino acid sequence of any one, two, three, or more of the V<sub>H</sub> CDRs of an antibody and the amino acid sequence of any one, two, three, or more of the V<sub>L</sub> CDRs of an antibody, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the V<sub>H</sub>-CDR(s) or V<sub>L</sub>-CDR(s) correspond to single source antibody (or scFv or Fab fragment) of the invention. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

Exemplary fusion proteins reported in the literature include fusions of the T cell receptor (Gascoigne *et al.*, Proc. Natl. Acad. Sci. USA 84 (1987), 2936-2940; CD4 (Capon *et al.*, Nature 337 (1989), 525-531; Traunecker *et al.*, Nature 339 (1989), 68-70; Zettmeissl *et al.*, DNA Cell

Biol. USA 9 (1990), 347-353; and Byrn *et al.*, Nature 344 (1990), 667-670); L-selectin (homing receptor) (Watson *et al.*, J. Cell. Biol. 110 (1990), 2221-2229; and Watson *et al.*, Nature 349 (1991), 164-167); CD44 (Aruffo *et al.*, Cell 61 (1990), 1303-1313); CD28 and B7 (Linsley *et al.*, J. Exp. Med. 173 (1991), 721-730); CTLA-4 (Lisley *et al.*, J. Exp. Med. 174 (1991), 561-569); CD22 (Stamenkovic *et al.*, Cell 66 (1991), 1133-1144); TNF receptor (Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA 88 (1991), 10535-10539; Lesslauer *et al.*, Eur. J. Immunol. 27 (1991), 2883-2886; and Peppel *et al.*, J. Exp. Med. 174 (1991), 1483-1489 (1991); and IgE receptor  $\alpha$  (Ridgway and Gorman, J. Cell. Biol. 115 (1991), Abstract No. 1448).

As discussed elsewhere herein, antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention may be fused to heterologous polypeptides to increase the *in vivo* half-life of the polypeptides or for use in immunoassays using methods known in the art. For example, in one embodiment, PEG can be conjugated to the antibodies of the invention to increase their half-life *in vivo*; see, *e.g.*, Leong *et al.*, Cytokine 16 (2001), 106-119; Adv. in Drug Deliv. Rev. 54 (2002), 531; or Weir *et al.*, Biochem. Soc. Transactions 30 (2002), 512.

Moreover, antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention can be fused to marker sequences, such as a peptide to facilitate their purification or detection. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide (HIS), such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86 (1989), 821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37 (1984), 767), GST, c-myc and the "flag" tag; see, *e.g.*, Bill Brizzard, BioTechniques 44 (2008) 693-695 for a review of epitope tagging techniques, and Table 1 on page 694 therein listing the most common epitope tags usable in the present invention, the subject matter of which is hereby expressly incorporated by reference.

Fusion proteins can be prepared using methods that are well known in the art; see for example US patent nos. 5,116,964 and 5,225,538. The precise site at which the fusion is made may be selected empirically to optimize the secretion or binding characteristics of the fusion protein. DNA encoding the fusion protein is then transfected into a host cell for expression, which is performed as described hereinbefore.

Antibodies of the present invention may be used in non-conjugated form or may be conjugated to at least one of a variety of molecules, *e.g.*, to improve the therapeutic properties of the molecule, to facilitate target detection, or for imaging or therapy of the patient. Antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention can be labeled or conjugated either before or after purification, when purification is performed. In particular, antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention may be conjugated to therapeutic agents, prodrugs, peptides, proteins, enzymes, viruses, lipids, biological response modifiers, pharmaceutical agents, or PEG.

Conjugates that are immunotoxins including conventional antibodies have been widely described in the art. The toxins may be coupled to the antibodies by conventional coupling techniques or immunotoxins containing protein toxin portions can be produced as fusion proteins. The antibodies of the present invention can be used in a corresponding way to obtain such immunotoxins. Illustrative of such immunotoxins are those described by Byers, *Seminars Cell. Biol.* 2 (1991), 59-70 and by Fanger, *Immunol. Today* 12 (1991), 51-54.

Those skilled in the art will appreciate that conjugates may also be assembled using a variety of techniques depending on the selected agent to be conjugated. For example, conjugates with biotin are prepared, *e.g.*, by reacting a HTT-binding polypeptide with an activated ester of biotin such as the biotin N-hydroxysuccinimide ester. Similarly, conjugates with a fluorescent marker may be prepared in the presence of a coupling agent, *e.g.* those listed herein, or by reaction with an isothiocyanate, preferably fluorescein-isothiocyanate. Conjugates of the antibodies, or antigen-binding fragments, variants or derivatives thereof of the invention are prepared in an analogous manner.

The present invention further encompasses antibodies, or antigen-binding fragments, variants, or derivatives thereof of the invention conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, demonstrate presence of a HTT amyloidosis to indicate the risk of getting a disease or disorder associated with mutated and/or aggregated HTT, to monitor the development or progression of such a disease, *i.e.* a disease showing the occurrence of, or related to aggregated HTT, or as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment and/or prevention regimen. In one embodiment thus, the present invention relates to an antibody, which is detectably labeled.

Furthermore, in one embodiment, the present invention relates to an antibody, which is attached to a drug. Detection can be facilitated by coupling the antibody, or antigen-binding fragment, variant, or derivative thereof to a detectable substance. The detectable substances or label may be in general an enzyme; a heavy metal, preferably gold; a dye, preferably a fluorescent or luminescent dye; or a radioactive label. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions; *see, e.g.*, US patent no. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ . Therefore, in one embodiment the present invention provides a detectably labeled antibody, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore and a heavy metal.

An antibody, or antigen-binding fragment, variant, or derivative thereof also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, thermotropic acridinium ester, imidazole, acridinium salt and oxalate ester.

One of the ways in which an antibody, or antigen-binding fragment, variant, or derivative thereof can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)" Microbiological Associates Quarterly Publication, Walkersville, Md., Diagnostic Horizons 2 (1978), 1-7); Voller *et al.*, J. Clin. Pathol. 31 (1978), 507-520; Butler, Meth. Enzymol. 73 (1981), 482-523; Maggio, (ed.), Enzyme Immunoassay, CRC Press, Boca Raton, Fla., (1980); Ishikawa, *et al.*, (eds.), Enzyme Immunoassay, Kigaku Shoin, Tokyo

(1981). The enzyme, which is bound to the antibody, will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibody, or antigen-binding fragment, variant, or derivative thereof, it is possible to detect the antibody through the use of a radioimmunoassay (RIA) (*see*, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, (March, 1986)), which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

An antibody, or antigen-binding fragment, variant, or derivative thereof can also be detectably labeled using fluorescence emitting metals such as  $^{152}\text{Eu}$ , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

Techniques for conjugating various moieties to an antibody, or antigen-binding fragment, variant, or derivative thereof are well known, *see, e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. (1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), Marcel Dekker, Inc., (1987) 623-53; Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), (1985) 475-506; "Analysis, Results, And Future

Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), Academic Press (1985) 303-16, and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62 (1982), 119-158.

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As mentioned, in certain embodiments, a moiety that enhances the stability or efficacy of a binding molecule, *e.g.*, a binding polypeptide, *e.g.*, an antibody or immunospecific fragment thereof can be conjugated. For example, in one embodiment, PEG can be conjugated to the binding molecules of the invention to increase their half-life *in vivo*. Leong *et al.*, Cytokine 16 (2001), 106; Adv. in Drug Deliv. Rev. 54 (2002), 531; or Weir *et al.*, Biochem. Soc. Transactions 30 (2002), 512.

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## VI. Compositions and Methods of Use

The present invention relates to compositions comprising the aforementioned HTT-binding molecule, *e.g.*, antibody or antigen-binding fragment thereof of the present invention or derivative or variant thereof, or the polynucleotide, vector or cell of the invention as defined hereinbefore. In one embodiment, the composition of the present invention is a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier. Furthermore, the pharmaceutical composition of the present invention may comprise further agents such as interleukins or interferons depending on the intended use of the pharmaceutical composition. For use in the treatment of a disease or disorder showing the occurrence of, or related to mutated and/or aggregated HTT, such as HTT amyloidosis, the additional agent may be selected from the group consisting of small organic molecules, anti-HTT antibodies, and combinations thereof. Hence, in a particular preferred embodiment the present invention relates to the use of the HTT-binding molecule, *e.g.*, antibody or antigen-binding fragment thereof of the present invention or of a binding molecule having substantially the same binding specificities of any one thereof, the polynucleotide, the vector or the cell of the present invention for the preparation of a pharmaceutical or diagnostic composition for prophylactic and therapeutic treatment of Huntington's disease (HD) and/or a disease or disorder associated with HTT and/or HTT amyloidosis, monitoring the progression of HD and/or a disease or disorder associated with HTT and/or HTT amyloidosis or a response to a HTT amyloidosis treatment in a subject or for determining a subject's risk for developing a disease or disorder associated with HTT.

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Hence, in one embodiment the present invention relates to a method of treating a disease or disorder characterized by abnormal accumulation and/or deposition of HTT and/or aggregated and/or mutated HTT in affected systems and organs which method comprises administering to a subject in need thereof a therapeutically effective amount of any one of the afore-described  
5 HTT-binding molecules, antibodies, polynucleotides, vectors or cells of the instant invention.

A particular advantage of the therapeutic approach of the present invention lies in the fact that the recombinant antibodies of the present invention are derived from B cells or memory B cells from healthy human subjects with no signs or symptoms of a disease, *e.g.* carrying an  
10 asymptomatic mutation and/or mutations, showing the occurrence of, or related to aggregated HTT and thus are, with a certain probability, capable of preventing a clinically manifest disease related to mutated and/or aggregated HTT, or of diminishing the risk of the occurrence of the clinically manifest disease or disorder, or of delaying the onset or progression of the clinically manifest disease or disorder. Typically, the antibodies of the present invention also have already  
15 successfully gone through somatic maturation, *i.e.* the optimization with respect to selectivity and effectiveness in the high affinity binding to the target HTT molecule by means of somatic variation of the variable regions of the antibody.

The knowledge that such cells *in vivo*, *e.g.* in a human, have not been activated by means of  
20 related or other physiological proteins or cell structures in the sense of an autoimmune or allergic reaction is also of great medical importance since this signifies a considerably increased chance of successfully living through the clinical test phases. So to speak, efficiency, acceptability and tolerability have already been demonstrated before the preclinical and clinical development of the prophylactic or therapeutic antibody in at least one human subject. It can  
25 thus be expected that the human-derived anti-HTT antibodies of the present invention, both its target structure-specific efficiency as therapeutic agent and its decreased probability of side effects significantly increase its clinical probability of success.

The present invention also provides a pharmaceutical and diagnostic, respectively, pack or kit  
30 comprising one or more containers filled with one or more of the above described ingredients, *e.g.* anti-HTT antibody, binding fragment, derivative or variant thereof, polynucleotide, vector or cell of the present invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale

for human administration. In addition or alternatively the kit comprises reagents and/or instructions for use in appropriate diagnostic assays. The composition, *e.g.* kit of the present invention is of course particularly suitable for the risk assessment, diagnosis, prevention and treatment of Huntington's disease and/or a disease or disorder which is accompanied with the presence of mutated and/or aggregated HTT, and in particular applicable for the treatment of disorders generally characterized by HTT amyloidosis.

The pharmaceutical compositions of the present invention can be formulated according to methods well known in the art; see for example Remington: The Science and Practice of Pharmacy (2000) by the University of Sciences in Philadelphia, ISBN 0-683-306472. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well-known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, *e.g.*, by intravenous, intraperitoneal, subcutaneous, intramuscular, intranasal, topical or intradermal administration or spinal or brain delivery. Aerosol formulations such as nasal spray formulations include purified aqueous or other solutions of the active agent with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Formulations for rectal or vaginal administration may be presented as a suppository with a suitable carrier.

The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. A typical dose can be, for example, in the range of 0.001 to 1000  $\mu$ g (or of nucleic acid for expression or for inhibition of expression in this range); however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. Generally, the dosage can range, *e.g.*, from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg (*e.g.*, 0.02 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2 mg/kg, etc.), of the host body weight. For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg. Doses intermediate in the above ranges are also intended to be within the scope of the invention. Subjects can be



administered such doses daily, on alternative days, weekly or according to any other schedule determined by empirical analysis. An exemplary treatment entails administration in multiple dosages over a prolonged period, for example, of at least six months. Additional exemplary treatment regimens entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1-10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly. In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated. Progress can be monitored by periodic assessment. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline, and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases, and the like. Furthermore, the pharmaceutical composition of the invention may comprise further agents such as dopamine or psychopharmacologic drugs, depending on the intended use of the pharmaceutical composition.

Furthermore, in a preferred embodiment of the present invention the pharmaceutical composition may be formulated as a vaccine, for example, if the pharmaceutical composition of the invention comprises an anti-HTT antibody or HTT-binding fragment, derivative or synthetic or biotechnological variant thereof for passive immunization. As mentioned in the background section mutated and/or aggregated HTT species and/or fragments or derivatives thereof are a major trigger for HTT amyloidosis. Accordingly, it is prudent to expect that passive immunization with human anti-HTT antibodies and equivalent HTT-binding molecules of the present invention will help to circumvent several adverse effects of active immunization therapy concepts and lead to a reduced aggregation of HTT. Therefore, the present anti-HTT antibodies and their equivalents of the present invention will be particularly useful as a vaccine for the prevention or amelioration of diseases or disorders showing the presence of, or caused by aggregated HTT such as HD.

In one embodiment, it may be beneficial to use recombinant Fab (rFab) and single chain fragments (scFvs) of the antibody of the present invention, which might more readily penetrate a cell membrane. For example, Robert *et al.*, Protein Eng. Des. Sel. (2008); S1741-0134, published online ahead, describe the use of chimeric recombinant Fab (rFab) and single chain fragments (scFvs) of monoclonal antibody WO-2 which recognizes an epitope in the N-terminal region of Abeta. The engineered fragments were able to (i) prevent amyloid fibrillization, (ii) disaggregate preformed Abeta1-42 fibrils and (iii) inhibit Abeta1-42 oligomer-mediated neurotoxicity *in vitro* as efficiently as the whole IgG molecule. The perceived advantages of using small Fab and scFv engineered antibody formats which lack the effector function include more efficient passage across the blood-brain barrier and minimizing the risk of triggering inflammatory side reactions. Furthermore, besides scFv and single-domain antibodies retain the binding specificity of full-length antibodies, they can be expressed as single genes and intracellularly in mammalian cells as intrabodies, with the potential for alteration of the folding, interactions, modifications, or subcellular localization of their targets; *see for review, e.g.*, Miller and Messer, Molecular Therapy 12 (2005), 394–401.

In a different approach Muller *et al.*, Expert Opin. Biol. Ther. (2005), 237-241, describe a technology platform, so-called 'SuperAntibody Technology', which is said to enable antibodies to be shuttled into living cells without harming them. Such cell-penetrating antibodies open new diagnostic and therapeutic windows. The term 'TransMabs' has been coined for these antibodies.

In a further embodiment, co-administration or sequential administration of other antibodies useful for treating a disease, disorder, or symptoms related to the occurrence of mutated and/or aggregated HTT may be desirable. In one embodiment, the additional antibody is comprised in the pharmaceutical composition of the present invention. Examples of antibodies which can be used to treat a subject include, but are not limited to, antibodies targeting CD33, SGLT2, IL-6, and IL-1.

In a further embodiment, co-administration or sequential administration of other agents useful for treating a disease, disorder, or symptoms related to mutated and/or aggregated HTT, may be desirable. In one embodiment, the additional agent is comprised in the pharmaceutical composition of the present invention. Examples of agents which can be used to treat a subject include, but are not limited to: VMAT2 inhibitors targeting involuntary muscle movements

such as Xenazine<sup>TM</sup>, anti-inflammatory agents such as diflusal, corticosteroids, 2-(2,6-dichloranilino) phenylacetic acid (diclofenac), iso-butyl-propanoic-phenolic acid (ibuprofen); diuretics, Epigallocatechin gallate, Melphalan hydrochloride, dexamethasone, Bortezomib, Bortezomib-Melphalan, Bortezomib-dexamethasone, Melphalan-dexamethasone, Bortezomib-Melphalan- dexamethasone; antidepressants, antipsychotic drugs, neuroleptics, antidementia (e.g. the NMDA-receptor antagonist memantine), acetylcholinesterase inhibitors (e.g. Donepezil, HCI, Rivastigmine, Galantamine), glutamat-antagonists and other nootropics blood pressure medication (e.g. Dihydralazin, Methyldopa), cytostatics, glucocorticoides, angiotensin-converting-enzyme (ACE) inhibitors; anti-inflammatory agents or any combination thereof.

A therapeutically effective dose or amount refers to that amount of the active ingredient sufficient to ameliorate the symptoms or condition. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) and LD<sub>50</sub> (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD<sub>50</sub>/ED<sub>50</sub>.

From the foregoing, it is evident that the present invention encompasses any use of an HTT-binding molecule and/or fragments thereof comprising at least one CDR of the above described antibody, in particular for diagnosing and/or treatment of a disease or disorder related to mutated and/or aggregated HTT species and/or fragments thereof as mentioned above, such as HD and/or HTT amyloidosis. Preferably, said binding molecule is an antibody of the present invention or an immunoglobulin chain thereof. In addition, the present invention relates to anti-idiotypic antibodies of any one of the mentioned antibodies described hereinbefore. These are antibodies or other binding molecules which bind to the unique antigenic peptide sequence located on an antibody's variable region near the antigen-binding site and are useful, e.g., for the detection of anti-HTT antibodies in a sample obtained from a subject. In one embodiment thus, the present invention provides an antibody as defined hereinabove and below or a HTT-binding molecule having substantially the same binding specificities of any one thereof, the polynucleotide, the vector or the cell as defined herein or a pharmaceutical or diagnostic composition comprising any one thereof for use in prophylactic treatment, therapeutic treatment and/or monitoring the progression or a response to treatment of a disease or disorder related to

HTT, preferably wherein the disorder is associated with HTT amyloidosis, such as Huntington's disease (HD).

In another embodiment the present invention relates to a diagnostic composition comprising  
5 any one of the above described HTT-binding molecules, antibodies, antigen-binding fragments, polynucleotides, vectors or cells of the invention and optionally suitable means for detection such as reagents conventionally used in immuno- or nucleic acid-based diagnostic methods. The antibodies of the invention are, for example, suited for use in immunoassays in which they can be utilized in liquid phase or bound to a solid phase carrier. Examples of immunoassays  
10 which can utilize the antibody of the invention are competitive and non-competitive immunoassays in either a direct or indirect format. Examples of such immunoassays are the radioimmunoassay (RIA), the sandwich (immunometric assay), flow cytometry, and the Western blot assay. The antigens and antibodies of the invention can be bound to many different carriers and used to isolate cells specifically bound thereto. Examples of well-known carriers  
15 include glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for the purposes of the invention. There are many different labels and methods of labeling known to those of ordinary skill in the art. Examples of the types of labels which can be used in the present invention  
20 include enzymes, radioisotopes, colloidal metals, fluorescent compounds, chemiluminescent compounds, and bioluminescent compounds; see also the embodiments discussed hereinabove.

By a further embodiment, the HTT-binding molecules, in particular antibodies of the present invention may also be used in a method for the diagnosis of a disease or disorder in an individual  
25 by obtaining a body fluid sample from the tested individual which may be a blood sample, a plasma sample, a serum sample, a lymph sample or any other body fluid sample, such as a saliva or a urine sample and contacting the body fluid sample with an antibody of the instant invention under conditions enabling the formation of antibody-antigen complexes. The level of such complexes is then determined by methods known in the art, a level significantly higher  
30 than that formed in a control sample indicating the disease or disorder in the tested individual. In the same manner, the specific antigen bound by the antibodies of the invention may also be used. Thus, the present invention relates to an *in vitro* immunoassay comprising the binding molecule, *e.g.*, antibody or antigen-binding fragment thereof of the invention.

In a further embodiment of the present invention the HTT-binding molecules, in particular antibodies of the present invention may also be used in a method for the diagnosis of a disease or disorder in an individual by obtaining a biopsy from the tested individual.

5 In this context, the present invention also relates to means specifically designed for this purpose. For example, an antibody-based array may be used, which is for example loaded with antibodies or equivalent antigen-binding molecules of the present invention which specifically recognize HTT. Design of microarray immunoassays is summarized in Kusnezow *et al.*, Mol. Cell Proteomics 5 (2006), 1681-1696. Accordingly, the present invention also relates to microarrays  
10 loaded with HTT-binding molecules identified in accordance with the present invention.

In one embodiment, the present invention relates to a method of diagnosing a disease or disorder related to mutated and/or aggregated HTT species and/or fragments thereof in a subject, the method comprising determining the presence of HTT and/or mutated and/or aggregated HTT  
15 in a sample from the subject to be diagnosed with at least one antibody of the present invention, a HTT-binding fragment thereof or an HTT-binding molecule having substantially the same binding specificities of any one thereof, wherein the presence of pathologically mutated and/or aggregated HTT is indicative for HD and/or HTT amyloidosis and an increase of the level of the pathologically mutated and/or aggregated HTT in comparison to the level of the  
20 physiological HTT is indicative for progression of HD and/or HTT amyloidosis in said subject.

The subject to be diagnosed may be asymptomatic or preclinical for the disease. Preferably, the control subject has a disease associated with mutated and/or aggregated HTT, *e.g.* Huntington's disease (HD), wherein a similarity between the level of pathologically mutated and/or  
25 aggregated HTT and the reference standard indicates that the subject to be diagnosed has a HTT amyloidosis or is at risk to develop a HTT amyloidosis. Alternatively, or in addition as a second control the control subject does not have a HTT amyloidosis, wherein a difference between the level of physiological HTT and/or of mutated and/or aggregated HTT and the reference standard indicates that the subject to be diagnosed has a HTT amyloidosis or is at risk to develop  
30 a HTT amyloidosis. Preferably, the subject to be diagnosed and the control subject(s) are age-matched. The sample to be analyzed may be any body fluid suspected to contain pathologically mutated and/or aggregated HTT, for example a blood, blood plasma, blood serum, urine, peritoneal fluid, saliva or cerebral spinal fluid (CSF). In another aspect of the present invention, the antibodies of the present invention can be used in detection of soluble and aggregated HTT

utilizing *e.g.* a TR-FRET based duplex immunoassay as described in Baldo *et al.*, Chem. Biol. 19(2) (2012), 264-275 which disclosure content, in particular the experimental procedures at pages 273-274, are incorporated herein.

5 Furthermore, it has been described in *e.g.* Ren *et al.*, Nature Cell Biol. 11 (2) (2009), 219-225 that mammalian cells can internalize fibrillar polyglutamine peptide aggregates in culture gaining access to the cytosolic compartment and become co-sequestered in aggresomes together with components of the ubiquitin-proteasome system and cytoplasmic chaperones. These internalized fibrillar aggregates were able to selectively recruit soluble cytoplasmic proteins  
10 and to confer a heritable phenotype upon cells expressing the homologous amyloidogenic protein from a chromosomal locus. Therefore, in one embodiment of the present invention the anti-HTT antibody can reduce extracellular spreading or transneuronal propagation of "toxic" HTT species, as shown by Pecho-Vriesling *et al.* Nat. Neurosci. (2014) doi:10.1038/nn.3761 for huntingtin or other proteins involved in neurodegeneration such as  $\alpha$ -synuclein; see *e.g.* Guo  
15 *et al.*, Nat Med. 20(2) (2014), 130-138.

The level of physiological HTT and/or of pathologically mutated and/or aggregated HTT may be assessed by any suitable method known in the art comprising, *e.g.*, analyzing HTT by one or more techniques chosen from Western blot, immunoprecipitation, enzyme-linked  
20 immunosorbent assay (ELISA), radioimmunoassay (RIA), fluorescent activated cell sorting (FACS), two-dimensional gel electrophoresis, mass spectroscopy (MS), matrix-assisted laser desorption/ionization-time of flight-MS (MALDI-TOF), surface-enhanced laser desorption ionization-time of flight (SELDI-TOF), high performance liquid chromatography (HPLC), fast protein liquid chromatography (FPLC), multidimensional liquid chromatography (LC)  
25 followed by tandem mass spectrometry (MS/MS), and laser densitometry. Preferably, said *in vivo* imaging of HTT comprises scintigraphy, positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging or magnetic resonance imaging (MRI).

30 In one embodiment thus, an antibody of the present invention or a HTT-binding molecule having substantially the same binding specificities of any one thereof, the polynucleotide, the vector or the cell as defined hereinabove or a pharmaceutical or diagnostic composition comprising any one thereof is provided for use in prophylactic treatment, therapeutic treatment, and/or monitoring the progression or a response to treatment of a disease or disorder related to

HTT. In general thus, the present invention also relates to a method of diagnosing or monitoring the progression of a disease or disorder related to HTT (such as HTT amyloidosis) in a subject, the method comprising determining the presence of HTT in a sample from the subject to be diagnosed with at least one antibody of the present invention or a HTT-binding molecule having substantially the same binding specificities of any one thereof, wherein the presence of mutated, misfolded and/or aggregated HTT species or fragments thereof is indicative for the disease or disorder. In one embodiment said method of diagnosing or monitoring the progression of HTT amyloidosis in a subject is provided, the method comprising determining the presence of mutated and/or aggregated HTT and/or fragments thereof in a sample from the subject to be diagnosed with at least one antibody of the present invention or a HTT-binding molecule having substantially the same binding specificities of any one thereof, wherein the presence of mutated and/or aggregated HTT and/or fragment thereof is indicative of presymptomatic, prodromal or clinical HTT amyloidosis an increase of the level of HTT aggregates in comparison to the level of the physiological HTT or in comparison to a reference sample derived from a healthy control subject or a control sample from the same subject is indicative for progression of presymptomatic, prodromal or established HTT amyloidosis. It would be appreciated by any person skilled in the art that in one embodiment said method is used as well for the diagnosing or monitoring the progression of any other disease or disorder from the group of disorders related to HTT as defined hereinabove.

As indicated above, the antibodies of the present invention, fragments thereof and molecules of the same binding specificity as the antibodies and fragments thereof may be used not only *in vitro* but *in vivo* as well, wherein besides diagnostic, therapeutic applications as well may be pursued. In one embodiment thus, the present invention also relates to a HTT binding molecule comprising at least one CDR of an antibody of the present invention for the preparation of a composition for *in vivo* detection of or targeting a therapeutic and/or diagnostic agent to HTT in the human or animal body. Potential therapeutic and/or diagnostic agents may be chosen from the nonexhaustive enumerations of the therapeutic agents useful in treatment HTT amyloidosis and potential labels as indicated hereinbefore. In respect of the *in vivo* imaging, in one preferred embodiment the present invention provides said HTT binding molecule comprising at least one CDR of an antibody of the present invention, wherein said *in vivo* imaging comprises scintigraphy, positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging or magnetic resonance imaging (MRI). In a further embodiment the present invention also provides said HTT-binding molecule

comprising at least one CDR of an antibody of the present invention, or said molecule for the preparation of a composition for the above specified *in vivo* imaging methods, for the use in the method of diagnosing or monitoring the progression of a disease or disorder related to HTT in a subject, as defined hereinabove.

5

## VII. Peptides with aggregation specific HTT epitopes

In a further aspect the present invention relates to peptides having an epitope of a polyP-rich region of HTT specifically recognized by any antibody of the present invention. Preferably, such peptide comprises or consists of an amino acid sequence as indicated in SEQ ID Nos.:  
10 146, 147, 148, 149, 150, 152, 153, 155, 156, 139, 151, 154, 158, 161, 157, 159, 160 as the unique linear epitope recognized by the antibody or a modified sequence thereof in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention, preferably by antibody NI-302.74C11, NI-302.15F9, NI-302.39G12, NI-302.11A4, NI-302.22H9, NI-302.37C12, NI-302.55D8, NI-302.78H12, NI-  
15 302.71F6, NI-302.33C11, NI-302.44D7, NI-302.7A8, NI-302.3D8, NI-302.46C9, NI-302.11H6, NI-302.18A1, NI-302.52C9, and/or NI-302.8F1.

In an additional aspect the present invention relates to peptides having an epitope of the P-rich-region of HTT specifically recognized by any antibody of the present invention. Preferably,  
20 such peptide comprises or consists of an amino acid sequence as indicated in SEQ ID Nos. 140, 141, 142, 143, 200 as the unique linear epitope recognized by the antibody or a modified sequence thereof in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention, preferably by antibody NI-302.63F3, NI-302.31F11, NI-302.2A2, NI302.15D3 and/or NI-302.64E5.

25

Furthermore, in one embodiment the present invention relates to peptides having an epitope of the C-terminal region of HTT specifically recognized by any antibody of the present invention. Preferably, such peptide comprises or consists of an amino acid sequence as indicated in SEQ ID NO: 145 or SEQ ID NO: 202 as the unique linear epitope recognized by the antibody or a  
30 modified sequence thereof in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention, preferably by antibody NI-302.35C1 or NI-302.72F10.



In an additional aspect the present invention relates to peptides having an epitope of the N-terminal-region of HTT specifically recognized by any antibody of the present invention. Preferably, such peptide comprises or consists of an amino acid sequence as indicated in SEQ ID NOs: 144 as the unique linear epitope recognized by the antibody or a modified sequence thereof in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention, preferably by antibody NI-302.15E8.

Furthermore, in one embodiment the present invention relates to peptides having an epitope of the Q/P-rich-region of HTT specifically recognized by any antibody of the present invention. Preferably, such peptide comprises or consists of an amino acid sequence as indicated in SEQ ID NO: 201 as the unique linear epitope recognized by the antibody or a modified sequence thereof in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention, preferably by antibody NI-302.7D8.

In addition, in one embodiment the present invention relates to peptides having an epitope of HTT specifically recognized by any antibody of the present invention, preferably by antibody NI-302.6N9, NI-302.12H2, NI-302.8M1 and/or NI-302.4A6 in which one or more amino acids are substituted, deleted and/or added, wherein the peptide is recognized by any antibody of the present invention.

In one embodiment of this invention such a peptide may be used for diagnosing or monitoring a disease or disorder related to mutated, misfolded and/or aggregated HTT species and/or fragments thereof in a subject, such as HD and/or HTT amyloidosis comprising a step of determining the presence of an antibody that binds to a peptide in a biological sample of said subject, and being used for diagnosis of such a disease in said subject by measuring the levels of antibodies which recognize the above described peptide of the present invention and comparing the measurements to the levels which are found in healthy subjects of comparable age and gender. Thus in one embodiment the present invention relates to a method for diagnosing HTT amyloidosis indicative of presymptomatic or clinical HD in a subject, comprising a step of determining the presence of an antibody that binds to a peptide as defined above in a biological sample of said subject. According to this method, an elevated level of measured antibodies specific for said peptide of the present invention is indicative for

diagnosing in said subject presymptomatic or clinical HD or for diagnosing in said subject any other disease or disorder from the group of disorders related to HTT as defined hereinabove. The peptide of the present invention may be formulated in an array, a kit and composition, respectively, as described hereinbefore. In this context, the present invention also relates to a  
5 kit useful in the diagnosis or monitoring the progression of HD and/or HTT amyloidosis, said kit comprising at least one antibody of the present invention or a HTT-binding molecule having substantially the same binding specificities of any one thereof, the polynucleotide, the vector or the cell and/or the peptide as respectively defined hereinbefore, optionally with reagents and/or instructions for use.

10 The above disclosure generally describes the present invention. Unless otherwise stated, a term as used herein is given the definition as provided in the Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, 1997, revised 2000 and reprinted 2003, ISBN 0 19 850673 2. Several documents are cited throughout the text of this specification. Full  
15 bibliographic citations may be found at the end of the specification immediately preceding the claims. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application including the background section and manufacturer's specifications, instructions, etc.) are hereby expressly incorporated by reference; however, there is no admission that any document cited is indeed prior art as to  
20 the present invention.

A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only and are not intended to limit the scope of the invention.

## EXAMPLES

### **Example 1: Isolation and identification of anti-HTT antibodies**

Human-derived antibodies targeting HTT and/or mutated and/or aggregated HTT species and/or fragments thereof were identified utilizing the method described in the international  
30 application WO 2008/081008 the disclosure content of which is incorporated herein by reference, with modifications. In particular, wild-type and mutant HTT proteins obtained by recombinant expression were used in both native and mutated-aggregated conformations for the identification of HTT-targeting antibodies. The mutated-aggregated conformations were produced *in vitro*, using a procedure similar to the one described in Example 3.

**Example 2: Determination of antibody sequence**

The amino acid sequences of the variable regions of the above identified anti-HTT antibodies were determined on the basis of their mRNA sequences, see Fig. 1. In brief, living B cells of selected non-immortalized memory B cell cultures were harvested. Subsequently, the mRNAs from cells producing selected anti-HTT antibodies were extracted and converted in cDNA, and the sequences encoding the antibody's variable regions were amplified by PCR, cloned into plasmid vectors and sequenced.

In brief, a combination of primers representing all sequence families of the human immunoglobulin germline repertoire was used for the amplifications of leader peptides, V-segments and J-segments. The first round of amplification was performed using leader peptide-specific primers in 5'-end and constant region-specific primers in 3'-end (Smith *et al.*, Nat Protoc. 4 (2009), 372-384). For heavy chains and kappa light chains, the second round of amplification was performed using V-segment-specific primers at the 5'-end and J-segment-specific primers at the 3'-end. For lambda light chains, the second round amplification was performed using V-segment-specific primers at the 5'-end and a C-region-specific primer at the 3'-end (Marks *et al.*, Mol. Biol. 222 (1991), 581-597; de Haard *et al.*, J. Biol. Chem. 26 (1999), 18218-18230).

Identification of the antibody clone with the desired specificity was performed by re-screening on ELISA upon recombinant expression of complete antibodies. Recombinant expression of complete human IgG1 antibodies was achieved upon insertion of the variable heavy and light chain sequences "in the correct reading frame" into expression vectors that complement the variable region sequence with a sequence encoding a leader peptide at the 5'-end and at the 3'-end with a sequence encoding the appropriate constant domain(s). To that end the primers contained restriction sites designed to facilitate cloning of the variable heavy and light chain sequences into antibody expression vectors. Heavy chain immunoglobulins were expressed by inserting the immunoglobulin heavy chain RT-PCR product in frame into a heavy chain expression vector bearing a signal peptide and the constant domains of human or mouse immunoglobulin gamma 1. Kappa light chain immunoglobulins were expressed by inserting the kappa light chain RT-PCR-product in frame into a light chain expression vector providing a signal peptide and the constant domain of human kappa light chain immunoglobulin. Lambda light chain immunoglobulins were expressed by inserting the lambda light chain RT-PCR-

product in frame into a lambda light chain expression vector providing a signal peptide and the constant domain of human or mouse lambda light chain immunoglobulin.

Functional recombinant monoclonal antibodies were obtained upon co-transfection into HEK  
5 293 or CHO cells (or any other appropriate recipient cell line of human or mouse origin) of an  
Ig-heavy-chain expression vector and a kappa or lambda Ig-light-chain expression vector.  
Recombinant human monoclonal antibody was subsequently purified from the conditioned  
medium using a standard Protein A column purification. Recombinant human monoclonal  
antibody can produced in unlimited quantities using either transiently or stably transfected cells.  
10 Cell lines producing recombinant human monoclonal antibody can be established either by  
using the Ig-expression vectors directly or by re-cloning of Ig-variable regions into different  
expression vectors. Derivatives such as F(ab), F(ab)<sub>2</sub> and scFv can also be generated from these  
Ig-variable regions. The framework and complementarity determining regions were determined  
by comparison with reference antibody sequences available in databases such as Abysis  
15 (<http://www.bioinf.org.uk/abysis/>) and <http://www.imgt.org/>, and annotated using the Kabat  
numbering scheme (<http://www.bioinf.org.uk/abs/>).

### **Example 3: Expression of HTT exon 1 proteins**

#### Methods

20 Recombinant huntingtin exon1 proteins GST-HttExon1Q21 (GST-HD21), GST-HttExon1Q35  
(GSTHD35), and GST-HttExon1Q49 (GST-HD49) expression and purification pGEX-6P-1  
expression vector (GE Healthcare) encoding Exon1 of human huntingtin with polyQ length of  
21, 35 or 49 CAG repeats, respectively (compare Fig. 2A) fused with a PreScission cleavage  
site to an N-terminal Glutathione S-transferases (GST)-tag were expressed in *E. coli* strain  
25 BL21. Overnight bacterial cultures (37°C, 220rpm) were diluted 1:25 and expression was  
induced at an Absorption 600 of 0.5-0.6 for 4 hrs by addition of 1 mM IPTG (Sigma I1284)  
and further incubation at 36°C, 220 rpm. Cultures were grown in LB medium containing 100  
µg/ml ampicillin at 37°C, for overnight cultures in addition with 1% glucose. Recombinant  
GST-HttExon1 proteins were purified by binding to glutathione agarose (Sigma G4510).  
30 Briefly, the bacteria pellet was resuspended in 20-40ml of cold buffer 1 (50mM NaH<sub>2</sub>PO<sub>4</sub>,  
5 mM Tris, 150 mM NaCl, 1 mM EDTA pH8, 5mg/ml final lysozyme, protease inhibitor  
complete (Roche)) were incubated for 60 min on ice, ultrasonicated, Triton-X100 added (0.1%  
final) and centrifuged for 90 min at 14'000g after incubation on ice for 5 min. Glutathione  
agarose was added to the supernatant, incubated for 2 hrs at 4°C, spun down for 10 min at 1000g

and washed 2x with cold PBS after removal of the supernatant. Elution was performed for 5 min in 1 ml buffer 1 with 10mM reduced glutathione pH 9. This step was repeated 5 to 15 times until no further protein was eluted. The pooled supernatants were dialyzed against buffer (50mM tris pH7.4, 150 mM NaCl, 1 mM EDTA, 1% glycerol) over night (10 kD MWCO, Pierce) and aliquots were stored at -80°C.

#### SDS-PAGE analysis

Purified recombinant GST-HttEx1 proteins were resolved by gradient SDS-PAGE (NuPAGE Bis-Tris 4-12%; Invitrogen, Basel, Switzerland) followed by staining with Coomassie brilliant blue or electroblotting on nitrocellulose membranes. Blots were incubated with primary antibodies Mab 5492 (Chemicon N-terminal aa1-82 epitope, P-rich domain) or NI-302.37C12 followed by a goat antimouse IgG secondary antibody conjugated with HRP or donkey anti-human IgG secondary antibody conjugated with HRP. Blots were developed using ECL and ImageQuant LAS 4000 detection (GE Healthcare, Switzerland).

As shown in Fig. 2B the different recombinant GST-HttEx1 proteins were successfully expressed and purified as demonstrated by Coomassie staining after SDS-PAGE.

#### **Example 4: Characterization of aggregation state by dot blot and filter retardation**

To characterize HD21, HD35 and HD49 protein aggregation kinetics filter retardation and dot-blot analyses were performed.

Therefore, at the beginning an aggregation reaction was performed as follows: Recombinant GST-HttExon1 proteins can be expressed and purified as a fusion protein. As soon as the GST tag is cleaved off from the fusion protein by the PreScission Protease (PP) the aggregation reaction of the huntingtin Exon1 protein starts immediately. Before the start of reactions the GST-HttExon1 proteins were centrifuged at 100'000g for 30 minutes. The cleared protein solution were diluted to 2µM protein concentration in cold aggregation buffer (0.05 M Tris/HCL pH 7, 0.15 M NaCl, 1 mM EDTA) and 1 mM DTT and PreScission Protease (GE Healthcare) were added. The reaction was incubated at room temperature with rotating at 300rpm and the aggregation reactions were stopped by snap freezing at -80°C after the indicated time intervals. Aliquots of HD21, HD35 and HD49 aggregation reactions were subsequently removed after 1, 3, 5, 7 and 24 hrs of incubation time, respectively, snap frozen on dry ice and stored at -80°C.

For the dot blot analysis samples were thawed on ice, diluted and transferred onto a nitrocellulose transfer membrane with a filter device applying vacuum in the chamber below the membrane. To that end, the membrane was equilibrated with PBS, mounted in the chamber and washed with 100µl PBS per well. The samples were loaded and completely sucked through the membrane followed by 3 washes with PBS. The device was dissembled and the membrane was briefly air-dried for 15 min at room temperature, blocked for 1 hour at room temperature with blocking buffer (3% BSA, 0.1% Tween 20 in PBS buffer) and incubated with polyclonal HD-1 antibody (1:10'000, kind gift of Prof. E. Wanker, MDC, Berlin). After washing, the membrane was incubated for 1 h at RT with an anti-rabbit IgG antibody coupled to HRP and blots were developed using ECL and ImageQuant LAS 4000 detection (GE Healthcare, Switzerland).

As evident from the dot blot shown in Fig. 2C, left side, polyclonal HD-1 antibody detected HD21, HD35 and HD49 proteins irrespective of their aggregation state.

For filter retardation assays samples were thawed on ice, diluted in denaturation buffer (4% SDS, 100 mM DTT) and transferred through a cellulose acetate membrane with a pore size of 0.2µm using a vacuum chamber. To that end, the membrane was equilibrated in 0.1% SDS in PBS, mounted on the vacuum chamber and the wells were washed with 0.1% SDS. The samples were added, filtered through the membrane by vacuum and washed 3 times with 0.1% SDS. The membrane was then removed from the chamber, briefly air-dried, blocked for 1h at RT in blocking buffer (5% milk, 0.1% Tween 20 in PBS buffer), incubated with polyclonal HD-1 antibody (1:5'000, Scherzinger *et al.*, Cell 90 (1997), 549–558) and processed further as described above.

In the filter retardation assay, the first aggregates retained by the membrane were detected for HD35 after 24 hours of incubation. HD49 proteins with an extended polyQ tract form insoluble aggregated as early as 3 hrs after cleavage of the GST tag, see Fig. 2C right side (FRA).

#### **Example 5: Characterization of Huntingtin Exon1 aggregates**

To verify and characterize HD35 and HD49 Exon1 aggregate formation electron microscopy (EM) was performed. In brief, HD49 aggregation reactions after 1, 3 and 24 hrs, respectively or samples from HD35 after 24 hrs were analyzed by electron microscopy. Samples were adsorbed onto glow-discharged carboncoated copper grids. Excess sample was removed by

blotting on filter paper. Grids were stained with 2% (w/v) uranyl acetate for 1 min and excess uranyl acetate was washed with distilled deionized water. Grids were air-dried and imaged using a Philips CM100 transmission electron microscope with an acceleration voltage of 100 kV.

5

EM analysis of the HD35 aggregation reaction revealed larger aggregates visible by EM resembling protofibrillar structures after 24 hrs of incubation (Fig. 2D [E]). HD49 displayed a more rapid aggregation kinetics with fibrils being detectable already after 1 hour of incubation (Fig. 2D [F]) and increasing in size and number with aggregation time (Fig. 2D [C, D, G, H]).

10 These observations were consistent with the results obtained in the filter retardation assays where aggregates larger than 0.2µm are retained on the cellulose acetate membrane and confirm the successful preparation of huntingtin exon 1 aggregates; see also Example 4.

**Example 6: Binding affinity of anti-polyP domain NI-302.33C11 antibody utilizing direct ELISA and EC<sub>50</sub>**

15

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.33C11 to soluble and aggregated huntingtin Exon1 proteins with 21 or 49 polyQ repeats direct ELISA was performed. In brief, 96 well microplates (Corning) were coated with either GST-HD21, GST-HD49 or aggregated HD21 or HD49 at a concentration of 20 5 µg/ml in coating buffer (15 mM Na<sub>2</sub>CO<sub>3</sub>, 35 mM NaHCO<sub>3</sub>, pH 9.42). Nonspecific binding sites were blocked for 1 h at RT with PBS/0.1% Tween®-20 containing 2% BSA (Sigma-Aldrich, Buchs, Switzerland). Primary antibodies were diluted to the indicated concentrations and incubated 1 h at RT. Binding was determined using either a donkey anti-human IgG Fcγ-specific antibody conjugated with HRP or a goat anti-mouse IgG (H+L)-specific antibody 25 conjugated with HRP, followed by measurement of HRP activity in a standard colorimetric assay. Subsequently, EC<sub>50</sub> values were estimated by a non-linear regression using GraphPad Prism software (San Diego, USA).

25

The EC<sub>50</sub> of human-derived HTT antibody NI-302.33C11 for aggregated and soluble HTT exon 30 1 proteins with 21 or 49 poly Q repeats was determined by direct ELISA with coating of the different preparations at 5 µg/ml concentration. As shown in Fig. 3A and B antibody NI-302.33C11 bound with similar high affinity to all four species including the pathologically aggregated HTT Exon1 HD49 with an EC<sub>50</sub> of approximately 100 pM.

30

**Example 7: Binding selectivity of anti-HTT antibodies utilizing dot blot and filter retardation assay**

To characterize recombinant human-derived HTT antibody NI-302.33C11 to soluble and aggregated huntingtin Exon1 proteins with 21, 35 or 49 polyQ repeats filter retardation assay and dot-blot were performed. For this reason, aliquots of HD21, HD35 and HD49 aggregation reactions as described in Example 4 were removed after 1, 3, 5, 7 and 24 hrs of incubation time, snap frozen on dry ice and stored at -80°C and a dot blot was performed as described in Example 4. Filter retardation assay was also performed as described in Example 4, with the exception that the membrane was incubated with NI-302.33C11 (1 µg/ml).

It could be shown that on the dot blot (Fig. 3C, left side), antibody NI-302.33C11 preferentially detects proteins of huntingtin with expanded polyQ tracts (HD49>>HD35>HD21). Furthermore, the signal intensity increased with increasing incubation times of the aggregation reactions of HD35 and HD49.

This is also true for the results shown in the filter retardation analysis (Fig. 3C, right side), which showed that NI-302.33C11 detects HD35 and HD49 aggregates that were retained on the 0.2 µm pore size membrane. These findings based on spotted protein preparations suggested that antibody NI-302.33C11 has a preference for aggregated HTT conformations with pathogenic polyQ expansions.

**Example 8: Binding specificity and selectivity of anti-HTT antibodies to unrelated aggregating protein targets utilizing direct ELISA**

To determine the binding specificity antibody NI-302.33C11 recombinant antibody binding to the polyP-region of HTT and not to unrelated aggregating protein targets direct ELISA was performed on 96 well microplates (Corning) coated with different target proteins at a concentration of 1-10 µg/ml in coating buffer (15 mM Na<sub>2</sub>CO<sub>3</sub>, 35 mM NaHCO<sub>3</sub>, pH 9.42). Non-specific binding sites were blocked for 1 h at RT with PBS/0.1% Tween®-20 containing 2% BSA (Sigma-Aldrich, Buchs, Switzerland). NI-302.33C11 antibody was diluted to the indicated concentrations and incubated 1 h at RT. Binding was determined using donkey anti-human IgG Fcγ-specific antibody conjugated with HRP followed by measurement of HRP activity in a standard colorimetric assay. Signals for target protein were calculated in fold increase above median.



It could be shown that human-derived NI-302.33C11 binds specifically to HTT, *i.e.* aggregated HD49, with absent binding to the other unrelated protein targets including prominent amyloid-forming proteins, see Fig. 16A.

5    **Example 9:    Assessment of the binding epitope of the HTT antibody NI-302.33C11**

To map the huntingtin (HTT) epitope recognized by the NI-302.33C11 human-derived antibody epitope mapping by peptide scanning analysis with synthetic peptides was performed.

In brief, scans of overlapping peptides were used for epitope mapping. The sequence of human HTT Exon 1 sequence was synthesized as a total of 16 linear 15-meric peptides with 10 aa  
10    overlap between individual peptides (JPT Peptide Technologies, Berlin, Germany) and spotted onto nitrocellulose membranes. The membrane was activated for 5 min in methanol and then washed at RT in TBS for 10 min. Non-specific binding sites were blocked for 2 hours at room temperature with Roti®-Block (Carl Roth GmbH+Co. KG, Karlsruhe, Germany). Human NI-302.33C11 antibody (1 µg/ml) was incubated for 3 hrs at RT in Roti®-Block. Binding of  
15    primary antibody was determined using HRP conjugated donkey-anti human IgG secondary antibody. Blots were developed using ECL and ImageQuant LAS 4000 detection (GE Healthcare, Switzerland).

As shown in Fig. 4, prominent binding of NI-302.33C11 was observed to peptides number 7,  
20    8, 9, 13 and 14 indicating that the epitope recognized by this antibody is localized in the polyP repeat domain of huntingtin. The NI-302.33C11 binding epitope is therefore predicted to be localized within HTT amino acids 35-PPPPPPPP-42 (SEQ ID No.: 139) and amino acids 63-PPPPPPPPPP-72 (SEQ ID No.: 162).

25    **Example 10:    Epitope mapping by direct ELISA binding to different Exon1 peptides of the HTT antibody NI-302.33C11**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.33C11 to BSA-coupled peptide fragments of the huntingtin Exon 1 direct ELISA with BSA-coupled Htt Exon1 domain peptides was performed.

30

In brief, 96 well microplates (Corning) were coated with BSA-coupled synthetic peptides (Schafer-N, Denmark) of the N-terminal amino acid 1-19 (MATLEKLMKAFESLKSFQQ, SEQ ID No.: 93), the P-rich domain sequence (PPQLPQPPQAQPLLQPQPP, SEQ ID No.: 94), the polyP repeat sequence (PPPPPPPPPP, SEQ ID No.: 95) or the 14 C-terminal amino

acids (PPGPAVAEEPLHRP, SEQ ID No.: 96) or with the full lengths GST-HD49 Exon 1 protein at 5µg/ml in coating buffer (15 mM Na<sub>2</sub>CO<sub>3</sub>, 35 mM NaHCO<sub>3</sub>, pH 9.42). Non-specific binding sites were blocked for 1 h at RT with PBS/0.1% Tween®-20 containing 2% BSA (Sigma-Aldrich, Buchs, Switzerland). Primary antibodies were diluted to the indicated concentrations and incubated 1 h at RT. Binding was determined using donkey anti-human IgG Fcγ-specific antibody conjugated with HRP, followed by measurement of HRP activity in a standard colorimetric assay and the EC<sub>50</sub> values were estimated by a non-linear regression using GraphPad Prism software (San Diego, USA).

As shown in Fig. 5 NI-302.33C11 bound with high affinity to the BSA-coupled polyP peptide as well as to full-length GST-HD49 with an equivalent EC<sub>50</sub> of 30 pM. This confirms the epitope mapping to the polyP sequence as shown in Example 9.

#### **Example 11: Assessment of the purity and integrity of recombinant human NI-302.33C11 anti-polyP domain antibody**

To assess the purity and integrity of recombinant human NI-302.33C11 anti-polyP domain lead antibody human NI-302.33C11 anti-polyP domain antibody was expressed by transient transfection of CHO-S cells and purified by protein A affinity purification on an Äkta system. After PD-10 column desalting the antibody was formulated in PBS. Subsequently SDS-PAGE analysis was performed, wherein two and 10 µg of purified recombinant human NI-302.33C11 anti-polyP domain antibody were resolved under reducing conditions by gradient SDS-PAGE (NuPAGE 4-12% Bis-Tris gel; Invitrogen) followed by Coomassie staining (SimplyBlue SafeStain, Invitrogen).

The SDS-PAGE analysis under reducing conditions of the recombinant human NI-302 anti-polyP domain lead antibody revealed two major bands corresponding to the antibody heavy and light chains at the expected size as shown in Fig. 6, while no significant contaminations or proteolytic degradation products were detected.

#### **Example 12: Characterization of HTT antibody NI-302.33C11 in human HTT transgenic mice**

To assess the binding of NI-302.33C11 antibody to huntingtin pathology in human HTT transgenic mouse brain tissues immunohistochemistry was performed. The B6.Cg-Tg(HDexon1)61Gpb/J transgenic mouse line (Mangiarini *et al.*, Cell 87 (1996), 493-506) is a

well characterized mouse model for Huntington's Disease (HD). Starting at around 9 weeks of age, this animal model develops a progressive pathology characterized by intranuclear inclusions of huntingtin reminiscent of human Huntington's disease (Naver *et al.*, Neuroscience 122 (2003), 1049-1057). Hemibrains of these B6.Cg-Tg(HDexon1)61Gpb/J transgenic mice at a progressed stage of disease (270 days) were fixed in phosphate-buffered 4% paraformaldehyde solution, paraffin-embedded, and 5- $\mu$ m sections were prepared. After formic acid and citrate buffer pretreatment, sections were incubated with 1, 5 or 50 nM human NI-302.33C11 anti-HTT antibody followed by incubation with biotinylated donkey-anti-human secondary antibody (Jackson ImmunoResearch; 1:250). Antibody signal was amplified with the Vectastain ABC kit (Vector Laboratories) and detected with diaminobenzidine (Pierce).

As shown in Fig. 27 human-derived polyP domain antibody NI-302.33C11 revealed a very prominent staining of neuronal intranuclear inclusion pathology already at the lowest 1 nM concentration (Fig. 27 [E-H]) consistent with the high affinity binding to huntingtin aggregates as determined by ELISA and dot blot analyses. At a concentration of 5 nM or higher, the antibody stained in addition entire medium spiny neurons and produced a more generalized diffuse staining which was also detectable on nontransgenic brain sections. A certain degree of cross-reactivity cannot be excluded as the polyp epitope targeted by NI-302.33C11 was present also in numerous unrelated proteins (Fig. 27 [F-H]).

### **Example 13: Characterization of binding affinity and selectivity of anti-P-rich domain NI-302.63F3 antibody utilizing direct ELISA and EC<sub>50</sub>**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.63F3 to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA and EC<sub>50</sub> determination was performed as described in Example 6, *supra*.

It could be shown that NI-302.63F3 binds with similar high affinity to all four species including the aggregated HTT Exon1 HD49 with an EC<sub>50</sub> of approximately 200 to 400 pM Fig. 7 A and B. Accordingly, the human-derived HTT anti-P-rich domain antibody NI-302.63F3 targets an epitope exposed in aggregated as well as in an uncut, more linear structure of HTT Exon1 protein with high-affinity in the subnanomolar range.

Additionally, to characterize the binding of recombinant human-derived HTT antibody NI-302.63F3 to soluble and aggregated HTT Exon1 proteins with 21, 35 or 49 polyQ repeats using

filter retardation assay and dot blot as described in Example 7, *supra*, with the small modification that the incubation was performed with 1 µg/ml of NI-302.63F3 antibody.

On the dot blot, antibody NI-302.63F3 most prominently detected the HD49 protein with an expanded polyQ tract (Fig. 7C, left side). In the filter retardation analysis NI-302.63F3 detected HD35 and HD49 aggregates that were retained on the 0.2 µm pore size membrane (Fig. 7C, right side). These findings based on spotted protein preparations demonstrate that antibody NI-302.63F3 recognizes aggregated HTT conformations with pathogenic polyQ expansions.

Furthermore, to determine the binding of NI-302.63F3 recombinant antibody to unrelated aggregating protein targets, direct ELISA was performed as described in Example 8, *supra*. As shown in Fig. 16B human-derived NI-302.63F3 bound specifically to HTT while a binding to unrelated proteins could not be shown.

#### **Example 14: Assessment of the binding epitope of the HTT antibody NI-302.63F3**

To map the huntingtin epitope recognized by the NI-302.63F3 human-derived antibody epitope mapping with synthetic peptides was performed as described above in Example 9.

As shown in Fig. 8, prominent binding of NI-302.63F3 was observed to peptides number 10 and 11 with a weak signal on peptide 8 and 9 indicating that the epitope recognized by this antibody is localized in the P-rich domain (between the polyP repeat regions) of HTT. The NI-302.63F3 binding epitope was therefore predicted to be localized within HTT amino acid sequence 43-(PPPQL)PQPPPQAQPL-57 (SEQ ID Nos.: 161 and 140).

#### **Example 15: Epitope mapping by direct ELISA binding to different Exon1 peptides of the HTT antibody NI-302.63F3**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.63F3 to BSA-coupled peptide fragments of the huntingtin Exon 1 direct ELISA with BSA-coupled Htt Exon1 domain peptides and EC<sub>50</sub> determination were performed as described in Example 10.

As shown in Fig. 9 NI-302.63F3 binds with high affinity to the BSA-coupled P-rich domain peptide as well as to full-length GST-HD49 with a similar EC<sub>50</sub> of 200 to 300 pM. This confirms the epitope mapping to the P-rich domain sequence as shown in Example 14.

**Example 16: Assessment of the purity and integrity of recombinant human NI-302.63F3 anti-P-rich domain antibody**

To assess the purity and integrity of recombinant human NI-302.63F3 anti-proline-rich domain antibody SDS-PAGE analysis was performed as already described in Example 11, *supra*.

5

SDS-PAGE analysis under reducing conditions of the recombinant human NI-302.63F3 anti-P-rich domain antibody revealed two major bands corresponding to the antibody heavy and light chains at the expected size. No significant contaminations or proteolytic degradation products were detected as shown in Fig. 10.

10

**Example 17: Characterization of HTT antibody NI-302.63F3 in human HTT transgenic mice**

The assessment of the binding of NI-302.63F3 anti-P-rich domain antibody to HTT pathology in human HTT transgenic mouse brain tissues was assessed as described in Example 12, *supra* with the difference that the incubation of the sections was performed with 1 or 50 nM of the anti-P-rich domain antibody.

15

As shown in Fig. 28 [E-F] the human-derived NI-302.63F3 anti-P-rich domain antibody revealed a prominent and highly specific staining of neuronal intranuclear inclusion pathology at 1 and 50 nM concentration in the striatum and cortex of R6/1 transgenic animals consistent with the high affinity binding to HTT aggregates as determined by ELISA and dot blot analysis. However as shown in Fig. 28 [F] at a concentration of 50 nM the antibody NI-302.63F3 stained additionally weakly the entire nucleus of the medium spiny neurons.

20

**Example 18: Characterization of binding affinity and selectivity of anti-C-terminal domain antibodies NI-302.35C1 and NI-302.72F10 utilizing direct ELISA and EC<sub>50</sub>**

25

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibodies NI-302.35C1 and NI-302.72F10 to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA and EC<sub>50</sub> determination was performed as described in Example 6, *supra*.

30

It could be shown that NI-302.35C1 binds with high affinity to all four species including the aggregated HTT Exon1 HD49 with an EC<sub>50</sub> of approximately 2.7 nM; see Fig. 11 A and B.

Similarly, NI-302.72F10 binds to all four species albeit with a different affinity than NI-302.35C1 (aggregated HD21>>GST-HD21>>aggregated HD49>>GST-HD49) (Fig. 31 C) which may be explained with the different epitopes recognized by both antibodies (Fig. 20).

5 Accordingly, the human-derived HTT anti-C-terminal domain antibodies NI-302.35C1 and NI-302.72F10 target an epitope exposed in aggregated as well as in soluble forms of HTT with low nanomolar affinity.

10 Additionally, to characterize the binding of recombinant human-derived HTT antibodies NI-302.35C1 and NI-302.72F10 to soluble and aggregated HTT Exon1 proteins with 21, 35 or 49 polyQ repeats filter retardation assay and dot blot as described in Example 7, *supra*, was performed.

15 On the dot blot, antibody NI-302.35C1 preferentially detected constructs of HTT with expanded polyQ tracts (HD49>HD35>>HD21, Fig. 11C, left side). Furthermore, the signal intensity increases with increasing incubation times of the aggregation reactions of HD35 and HD49. Similarly, antibody NI-302.72F10 detected constructs of HTT with expanded polyQ tracts albeit with a different preference (HD35>>HD49>HD21) whereas the signal intensity increases with increasing incubation times of the aggregation reactions of HD35 only (Fig. 32 C).

20 In the filter retardation analysis NI-302.35C1 detected HD35 and HD49 aggregates that were retained on the 0.2 µm pore size membrane (Fig. 11 C, right side) whereas NI-302.72F10 detected HD35 aggregates only (Fig. 32 C, right side). These findings based on membrane bound protein preparations suggested that antibodies NI-302.35C1 and NI-302.72F10  
25 preferentially targets aggregated HTT conformations with pathogenic polyQ expansions.

Furthermore, to determine the binding of NI-302.35C1 and NI-302.72F10 recombinant antibodies to unrelated aggregating protein targets, direct ELISA was performed as described in Example 8, *supra*. As shown in Fig. 16 C human-derived NI-302.35C1 as well as shown in  
30 Fig. 33 C human-derived NI-302.72F10 bound specifically to HTT while a binding to unrelated proteins could not be shown.

**Example 19: Assessment of the binding epitope of the HTT antibody NI-302.35C1**

To map the huntingtin epitope recognized by the NI-302.35C1 human-derived antibody epitope mapping with synthetic peptides was performed as described above in Example 9.

- 5 Determination of NI-302.35C1 antibody binding epitope by scan of overlapping peptides did not result in specific signal. Therefore, processing this antibody in the way it was done for the other HTT NI-302 antibodies did not results in any specific signal on the individual peptides for unknown reasons. The epitope was successfully mapped to a C-terminal peptide by coupling it to BSA, see also Example 20.

10

**Example 20: Epitope mapping by direct ELISA binding to different Exon1 peptides of the C-terminal domain HTT antibody NI-302.35C1**

- To determine the half maximal effective concentration ( $EC_{50}$ ) of recombinant human-derived HTT antibody NI-302.35C1 to BSA-coupled peptide fragments of the HTT Exon 1 direct  
15 ELISA with BSA-coupled Htt Exon1 domain peptides and  $EC_{50}$  determination were performed as described in Example 10.

- As shown in Fig. 12 NI-302.35C1 binds with high affinity to the BSA-coupled C-terminal peptide as well as to full-length GST-HD49 with an  $EC_{50}$  value of approximately 0.7 nM and  
20 3.2 nM, respectively. This locates the epitope to the C-terminal region of HTT Exon1 sequence (71- PPGPAVAEEPLHRP-85, SEQ ID No: 96). If the same C-terminal peptide was coated directly to the plate only weak binding was observed ( $EC_{50} > 100$ nM, data not shown) suggesting that the presentation of the peptide coupled to BSA increases the binding to the epitope and might be an explanation why the epitope mapping by peptide scanning analysis as  
25 shown in Example 20 did not work.

**Example 21: Assessment of the purity and integrity of recombinant human NI-302.35C1 anti-P-rich domain antibody**

- To assess the purity and integrity of recombinant human NI-302.35C1 anti-C-terminal domain  
30 antibody SDS-PAGE analysis was performed as already described in Example 11, *supra*.

SDS-PAGE analysis under reducing conditions of the recombinant human NI-302.35C1 anti-C-terminal domain antibody revealed two major bands corresponding to the antibody heavy

and light chains at the expected size, while no significant contaminations or proteolytic degradation products were detected (Fig. 13).

**Example 22: Characterization of HTT antibody NI-302.35C1 in human HTT transgenic mice**

The assessment of the binding of NI-302.35C1 anti-C-terminal domain antibody to HTT pathology in human HTT transgenic mouse brain tissues was assessed as described in Example 12, *supra* with the difference that the incubation of the sections was performed with 5 or 50 nM of the anti-C-terminal domain antibody.

As shown in Fig. 29 [E-F] the human-derived NI-302.35C1 anti-C-terminal domain antibody revealed a prominent staining of neuronal intranuclear inclusion pathology at 5 and 50 nM concentration in striatum of R6/1 transgenic animals consistent with the high affinity binding to HTT aggregates as determined by ELISA and dot-blot analyses.

**Example 23: Assessment of the effects of human-derived antibodies targeting HTT on spine density in hippocampal slice cultures**

Antibody Expression and Purification

Human-derived antibodies targeting distinct domains in HTT exon 1 were expressed by transient transfection of CHO-S cells and purified by protein A affinity purification on the Äkta system. After PD-10 column desalting the antibodies were formulated in PBS. Endotoxin levels were confirmed to be <10 EU/ml.

Hippocampal slice culture

Organotypic hippocampal slice cultures were prepared and cultured according to Stoppini *et al.*, J Neurosci Methods. (1991) 37(2):173-82. In short, 6- to 8-d-old B6CBA-Tg(HDexon1)62Gpb/1J transgenic and nontransgenic littermates were decapitated, brains were removed, and both hippocampi were isolated and cut into 400-µm thick slices. This method yields thin slices which remain 1-4 cell layers thick and are characterized by a well preserved organotypic organization. Slices were cultured on Millicell culture plate inserts (0.4 µm, Millipore) in six-well plates containing 1 ml of culture medium (46% minimum essential medium Eagle with HEPES modification, 25% basal medium with Earle's modification, 25% heat-inactivated horse serum, 2 mM glutamine, 0.6% glucose, pH 7.2). Culture plates were kept at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. Slices were kept in culture for 7 d



before the experiments. Culture medium was exchanged every second or third day. On day 7 antibodies were added at a concentration of 10 µg/ml. On day 10 *in vitro* slice cultures were infected with Sindbis virus using a droplet method (Shahani *et al.*, J Neurosci. 31 (2006), 6103–6114). For spine analysis, cultures were fixed at day 4 post infection (14 days *in vitro*). Slices were left attached to the culture plate membrane to preserve hippocampal structure and rinsed with PBS. Slices were then fixed with 4% paraformaldehyde in PBS containing 4% sucrose for 2 h at 4°C. For each dendrite a picture was taken and spines were analyzed over a length of 30–45 µm. Eight to 13 slices per group from a total of 12 transgenic animals were quantified for each antibody treatment. Data represent the mean ± SEM. \* $p < 0.05$  (MWU), #  $p = 0.05$ .

The quantification of dendritic spine density in hippocampal slice cultures of Tg(HDexon1)62Gpb/1J transgenic mice (Fig. 17 B, D) revealed a significant reduction by 53% compared to non-transgenic littermates (Fig. 17 A, C, E) using hippocampal slices of postnatal day 6 animals after 14 days *in vitro* with the experimental design described above. Upon addition of human-derived NI-302 antibodies at concentration of 10 µg/ml for seven days a significant attenuation of spine density loss was observed for antibodies NI-302.31F11 (Fig. 17 F,  $p < 0.05$ , t-test) and NI-302.63F3 ( $p = 0.05$ , t-test), whereas antibody NI-302.33C11 and NI-302.35C1 did not show a clear effect under the conditions tested.

The significant reduction of spine density compared to non-transgenic littermate in displayed in hippocampal slice cultures of Tg(HDexon1)62Gpb/1J transgenic mice led to the suggestion that this is a suitable model for *in vitro* testing of HTT candidate antibodies for their activity towards interference with HTT toxicity. In this model, antibodies NI-302.63F3 and NI-302.11F11 that both targeted the P-rich domain within HTT exon 1 were able to improve spine density compared to an isotype control antibody. This suggests that these antibodies can attenuate the toxic effects on spine density driven by expression of pathological poly-Q-expanded HTT.

#### **Example 24: Penetration of NI-302 antibodies in the brain of R6/1 animal model**

To test the penetration of the anti-HTT antibodies of the present invention a transgenic mice model was utilized. In particular, Tg(HDexon1)61Gpb/J transgenic mice harbor a 1.9 kb transgene which was isolated from a phage genomic clone derived from an Huntington's disease (HD) patient and contained the 5' end of the human huntingtin (HTT) gene. It was composed of approximately 1 kb of 5' UTR sequences, exon 1 (carrying expanded CAG repeats of ~130

units) and the first 262 bp of intron 1. This construct was microinjected into single cell CBAxC57BL/6 embryos. Male founder R6 was bred to CBAxC57BL/6 females, producing several founder lines. Mice from founder line R6/1 have the transgene integrated as a single intact copy which is ubiquitously expressed. Transgenic mice on a mixed CBAxC57BL/6 genetic background were backcrossed to C57BL/6J for more than 12 to generate the congenic strain B6.Cg-Tg(HDexon1)61Gpb/J.

R6/1 transgenic mice exhibit a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures, as well as nonmovement disorder components, including unusual vocalization. They urinate frequently and exhibit loss of body weight and muscle bulk through the course of the disease. Neurologically they develop neuronal intranuclear inclusions (NII) which contain both the HTT and ubiquitin proteins. These NII have also been identified in human HD patients. The age of onset of HD symptoms is reported to occur between 15 and 21 weeks for this 6/1 line.

The study animals displayed the following properties and were identified by classical ear marking:

Strain: Hemizygous B6.Cg-Tg(HDexon1)61Gpb/J (Mangiarini *et al.*, Cell, 87 (1996), 493-506)

Source: Jackson Laboratory, Maine, USA

Sex: Males and females

Age start: 230 to 260 days

Cohorts: NI-302.31F11 Total: 3 males

NI-302.35C1 Total: 3 males

Vehicle Total: 3 males

For the spinal cord homogenization B6.Cg-Tg(HDexon1)61Gpb/J transgenic mice were deeply anesthetized and transcardially perfused with cold phosphate-buffered saline through the left ventricle by mean of a peristaltic pump. The brain was dissected out and snap frozen on dry ice.

The tissue samples were homogenized in 1:10 w/v DEA-Buffer (50mM NaCl, 0.2% DEA, protease inhibitor complete, Roche Diagnostics) with a hand-sonicator (Sartorius, Labsonic M). Samples were centrifuged for 30 minutes at 100'000 x g at 4°C and aliquots of the supernatant were stored at -80°C before analysis.

In the following human IgG drug level sandwich ELISA the human NI-302.35C1, NI-302.11F11 antibody plasma levels were determined using the corresponding recombinant antibody of known concentration as standard. 96 well microplates (Corning) were coated with donkey anti human IgG (709-005-149, Jackson ImmunoResearch) at 1 µg/ml in 50mM carbonate coating buffer pH 9.6. Non-specific binding sites were blocked for 1 hr at RT with PBS/0.1% Tween®-20 containing 2% BSA (Sigma, Buchs, Switzerland). Plasma samples were diluted 1:20'000 and 1:100'000, brain homogenates were diluted 1:5 and 1:50 and both were incubated 1 hr at RT together with the standard dilution curves. Binding was determined using the detection antibody anti human HRP (709-036-098, Jackson ImmunoResearch), followed by measurement of HRP activity in a standard colorimetric assay. Concentrations of plasma and spinal cord samples were calculated based on the individual standard curve. Values shown in table 6-1 are average values of 2 independent ELISA experiments.

Plasma and brain samples were obtained 2 days after a single intraperitoneal injection of 50 mg/kg of antibodies NI-302.31F11, NI-302.35C1 in R6/1 transgenic mice. Antibody levels in plasma and brain homogenates were determined by human sandwich IgG ELISA (Fig. 18 A and B). The ratio of brain versus plasma drug levels was determined at  $0.13 \pm 0.02\%$  and  $0.21 \pm 0.06\%$  for human-derived antibodies NI-302.31F11 and NI-302.35C1, respectively. These results suggest a 48h brain penetration of the tested NI-302 antibodies in the expected range in HTT transgenic mice.

#### **Example 25: Characterization of binding affinity and specificity of further antibodies identified in accordance with the present invention**

To determine the half maximal effective concentration ( $EC_{50}$ ) of further identified recombinant human-derived HTT antibodies to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA with coating of the different preparations at 5 µg/ml concentration and  $EC_{50}$  determination was performed as described in Example 6, *supra*.

The determined  $EC_{50}$  for the different HTT species are shown in Fig. 19 as well as Fig. 31 (A, D-F) and summarized in Fig. 20. Most human-derived antibodies bound with high affinity at subnanomolar or low nanomolar  $EC_{50}$ . Some candidates such as NI-302.37C12, NI-302.55D8, NI-302.11A4, NI-302.22H9 or NI-302.64E5 seemed to have preferred binding to uncut GST-HTT protein, other antibodies such as NI-302.74C11, NI-302.71F6, NI-302.4A6, NI-302.12H2 or NI-302-8M1 showed high affinity binding with similar  $EC_{50}$ -values to all HTT preparation

in the ELISA assay. NI-302.15F9 showed about a 5-fold preference of HD49 vs. HD21 with EC<sub>50</sub> values in the range of 5 to 35nM. Antibody 33C11 served as control in this experiment (Fig. 32 G).

5 Therefore, a panel of high affinity recombinant HTT specific human antibodies was cloned from memory B-cells derived from healthy elderly human donor cohorts and recombinantly expressed and characterized. Additionally, a screening campaign for additional backup antibodies was initiated in a cohort of selected presymptomatic patients with Huntington's disease (HD) carrying different lengths CAG repeat expansions.

10

To further characterize the binding of the identified recombinant human-derived HTT NI-302 antibodies to soluble and aggregated HTT Exon1 proteins with 21, 35 or 49 polyQ repeats filter retardation assay utilizing 0.2 µg/ml primary antibody and dot-blot analysis utilizing 1 µg/ml primary antibody were performed as described in Example 7, *supra*.

15

As shown in Fig. 21 and Fig. 32 (A, G), on the dot blot (Fig. left side, DotBlot) most of the antibodies characterized showed a preference for detection of HTT proteins with expanded polyQ tracts (HD49>>HD35>HD21). Furthermore, the signal intensity increased with increasing incubation times of the aggregation reactions of HD35 and HD49 in particular for antibodies NI-302.15F9, NI-302.71F6 (Fig. 21, first row of blots) and NI-302-64E5 (Fig. 32 A, left side). In the filter retardation analysis NI-302.15F9, NI-302.71F6 (Fig. 21, right side, FRA) and NI-302-64E5 (Fig. 32 A, right side) detected SDS stable HD35 and HD49 aggregates that were retained on the 0.2 µm pore size membrane whereas other antibodies such as NI-302.44D7 and NI-302.37C12 (Fig. 21, second row of blots) or NI-302.4A6, NI-302.12H2 and NI-302.8M1 (Fig. 32 D, E, F) did not bind to aggregates on the filter. Antibody 33C11 served as control in this experiment (Fig. 32 G). These findings based on spotted protein preparations suggest that several of the cloned NI-302 antibodies show a preference for aggregated HTT conformations with pathogenic polyQ expansions.

30 Additionally, the binding specificity of the identified antibodies to unrelated proteins, in particular to proteins forming aggregates was assessed by direct ELISA (Fig. 22 and Fig. 33 A, D-F) as already described in Example 8, *supra*. The results showed that most of the human-derived NI-302 antibodies tested bind specifically to HTT with absent binding to the other unrelated proteins tested.

**Example 26: Assessment of the binding and epitope mapping of human-derived HTT antibodies**

To map the HTT epitope recognized by the newly identified human-derived antibodies epitope mapping with synthetic peptides was performed as described above in Example 9 (Fig. 23 and Fig. 35 A, D-F). Additionally, the half maximal effective concentration ( $EC_{50}$ ) of the HTT antibodies to BSA-coupled peptide fragments of the HTT Exon 1 by direct ELISA with BSA-coupled Htt Exon1 domain peptides was determined as well as  $EC_{50}$  determination were performed as described in Example 10.

**Example 27: Assessment of the binding of HTT antibodies in human HTT transgenic mice**

The characterization of the binding of the identified antibodies to HTT pathology in human HTT transgenic mouse brain tissues was assessed as described in Example 12, *supra* with the difference that the incubation of the sections was performed with 5 nM ffig.3M (74C11, 39C12, 11A4, 22H9, 78H12, 37C12, 7D8, 72F10) or 50 nM concentrations (15F9, 71F6, 55D8, 44D7, 7A8, 64E5) of the anti-HTT antibodies. As shown in Fig. 24 the identified human-derived anti-HTT antibodies revealed a prominent and highly specific staining of neuronal intranuclear inclusion pathology in the striatum and cortex of R6/1 transgenic animals, as also shown for the antibodies NI-302.33C11, NI-302.63F3, and NI-302.35C1, described above. These findings are consistent with the high affinity binding to HTT aggregates as determined by ELISA and dot blot analysis in Example 26.

**Example 28: Basic characterization of transgenic mouse model R6/1 of Huntington's disease (HD)**

Tg(HDexon1)61Gpb/J transgenic mice harbor a 1.9 kb transgene which was isolated from a phage genomic clone derived from an HD patient and contained the 5' end of the human huntingtin (HTT) gene. It was composed of approximately 1 kb of 5' UTR sequences, exon 1 (carrying expanded CAG repeats of ~130 units) and the first 262 bp of intron 1. This construct was microinjected into single cell CBAC57BL/6 embryos. Male founder R6 was bred to CBAC57BL/6 females, producing several founder lines (Mangiarini *et al.*, Cell 87 (1996), 493–506). Mice from founder line R6/1 have the transgene integrated as a single intact copy which is ubiquitously expressed. Transgenic mice on a mixed CBAC57BL/6 genetic background were backcrossed to C57BL/6J for more than 12 to generate the congenic strain

B6.Cg-Tg(HDexon1)61Gpb/J. R6/1 transgenic mice exhibit a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures, as well as nonmovement disorder components, including unusual vocalization. They urinate frequently and exhibit loss of body weight and muscle bulk through the course of the disease. Neurologically they develop neuronal intranuclear inclusions (NII) which contain both the HTT and ubiquitin proteins. These NII have also been identified in human HD patients. The age of onset of HD symptoms is reported to occur between 15 and 21 weeks for this 6/1 line (Naver *et al*, Neuroscience 122 (2003), 1049-1057; Hodges *et al*, Genes Brain Behav. 7(3) (2008), 288-299).

R6/1 transgenic mice obtained from Jackson Laboratories were expanded and longitudinally characterized with respect to behavior phenotype, longitudinal development of body weight, total brain weight, histopathological analysis and survival, as shown in Fig. 25. The findings obtained by in large were in line with the published data and identified this mouse line as a suitable preclinical model for efficacy studies with human-derived NI-302 antibodies targeting aggregated HTT.

#### **Example 29: Basic characterization of transgenic mouse model N171-82Q of HD**

The B6C3-Tg(HD82Gln)81Dbo/J (N171-82Q) transgenic mouse line (Schilling *et al.*, Hum Mol Genet. 8(3) (1999), 397-407) is a well characterized mouse model for HD. B6C3-Tg(HD82Gln)81Dbo/J (N171- 82Q) transgenic mice expresses an N-terminally truncated human HTT cDNA that encodes 82 glutamines and encompasses the first 171 amino acids. The altered HTT cDNA is under control of a mouse prion protein promoter. Expression is observed in neurons of the central nervous system. Mice expressing this transgene appear normal at birth through 1-2 months. However, the mice fail to gain weight, develop tremors, hypokinesia and lack coordination. They exhibit an abnormal gait and frequent hind limb clasping. Their life expectancy is 5-6 months. Studies using HTT antibodies indicated diffuse nuclear labeling and numerous immunoreactive nuclear inclusions in multiple neuron populations. Additionally neuritic damage was evident.

N171-82Q transgenic mice obtained from Jackson Laboratories were expanded and longitudinally characterized with respect to behavior phenotype, longitudinal development of body weight, total brain weight at endstage, histopathological analysis and survival (Fig. 26). These findings by in large were in line with published data and identified this mouse line

additionally to the mouse line described in Example 29, as a suitable preclinical model for efficacy studies with human-derived NI-302 antibodies targeting aggregated HTT.

**Example 30: Assessment of neuronal inclusion staining in Huntington's disease (HD) patients**

To assess the staining of neuronal inclusions by the identified antibodies of the present invention in patients immunohistochemical analysis was performed. The assessment of the binding of identified antibodies to HTT pathology in human brain tissues was assessed as described in Example 12, *supra* with the difference that the incubation of the sections was performed with 50 nM of NI-302.33C11, 50 nM of NI-302.63F3 or 100 nM of NI-302.35C1 antibody.

As shown in Fig. 27 the immunohistochemical analysis with the polyP-region binding antibody NI-302.33C11 showed a staining of neuronal intranuclear inclusions in cortical neurons of Huntington Disease patients (Fig. 27 A-D) at 50 nM and in striatal neurons of 270 day old, late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals at 1 (E) and 5 nM (F) concentration, while no staining was detected in non-transgenic littermates (G), when the primary antibody was omitted during the staining (H) or if tissue of non-Huntington Disease controls was stained with 50 nM of NI-302.33C11. The P-rich-domain antibody NI-302.63F3 (Fig. 28) and anti-C-terminal domain antibody NI-302.35C1 (Fig. 29) showed within the immunohistochemical analysis with 50 nM of NI-302.63F3 or 100 nM of NI-302.35C1 a staining of neuronal intranuclear inclusions (A-C) and staining of some neurites (D) of cortical neurons of four different Huntington Disease patients (A-D). A staining could also be observed in the striatal neurons of 270 day old, late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals at 1 (E) and 50 nM (F) concentration. No staining was detected in non-transgenic littermates (G), if primary antibody was omitted during the staining (H) or if tissue of non-Huntington Disease controls was stained with 50 nM of NI-302.63F3 or 100 nM of NI-302.35C1, respectively.

In contrast to the specific anti-HTT antibodies of the present invention, immunohistochemical analysis with the commercially available anti-polyQ antibody Mab1574 (1:2000, Chemicon) showed additional staining of tissue, *i.e.* a more general nuclear and cytoplasmic staining and staining of some neurites (Fig. 30 A, D) of cortical neurons of four different Huntington Disease

patients and in striatal neurons of presymptomatic, 150 day old (Fig. 30 E) and 270 day old (Fig. 30 F), late disease stage B6.Cg-Tg(HDexon1)61Gpb/J transgenic animals.

**Example 31: Characterization of binding affinity and selectivity of anti-poly Q/P domain  
NI-302.7D8 antibody utilizing direct ELISA and EC<sub>50</sub>**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.7D8 to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA and EC<sub>50</sub> determination was performed as described in Example 6, *supra*.

It could be shown that NI-302.7D8 binds with similar high affinity to soluble GST-HD21 and aggregated HD21 with an EC<sub>50</sub> of approximately 50 to 100 nM albeit showing a preference to the elongated more pathogenic form of aggregated HD49 and soluble GST-HD49 with an EC<sub>50</sub> of 17 and 6 nM respectively (Fig. 31 B)

Accordingly, the human-derived HTT anti-poly Q/P domain antibody NI-302.7D8 targets an epitope exposed in aggregated as well as in an uncut, more linear structure of HTT Exon1 protein with high-affinity in the low nanomolar range.

Additionally, to characterize the binding of recombinant human-derived HTT antibody NI-302.7D8 to soluble and aggregated HTT Exon1 proteins with 21, 35 or 49 polyQ repeats using filter retardation assay and dot blot at a concentration of 1 µg/ml as described in Example 7, *supra*.

It could be shown that on the dot blot (Fig. 32 B, left side), antibody NI-302.7D8 equally good detected proteins of huntingtin with expanded polyQ tracts (HD49=HD35=HD21). In the filter retardation analysis (Fig. 32 B, right side, FRA) NI-302.7D8 did not bind to SDS stable HD21, HD35 or HD49 aggregates on the filter membrane.

Furthermore, to determine the binding of NI-302.7D8 recombinant antibody to unrelated aggregating protein targets, direct ELISA was performed as described in Example 8, *supra*. As shown in Fig. 33 B human-derived NI-302.7D8 bound specifically to HTT while a binding to unrelated proteins could not be shown.



**Example 32: Assessment of the binding epitope of the HTT antibodies NI-302-64E5, NI-302.7D8 and NI-302.72F10**

To map the huntingtin epitope recognized by the NI-302-64E5, NI-302.7D8 and NI-302.72F10 human-derived antibody epitope mapping with synthetic peptides was performed as described  
5 above in Example 9.

Figure 35 A shows a prominent binding of NI-302-64E5 to peptides number 10 to 12 indicating that the epitope recognized by this antibody is localized in the P-rich repeat domain of huntingtin. The NI-302.64E5 binding epitope is therefore predicted to be localized within HTT  
10 amino acids 48-PQPPPQAQPL-58 (SEQ ID No.: 200). As shown in Fig. 35 B, prominent binding of NI-302.7D8 was observed to peptides number 6 to 8 indicating that the epitope recognized by this antibody is localized in the polyQ/polyP repeat domain of huntingtin. The NI-302.7D8 binding epitope is therefore predicted to be localized within HTT amino acids 28-  
15 QQQQQQPPPP-37 (SEQ ID No.: 201). In contrast, prominent binding of NI-302.72F10 was observed to peptides number 15 and 16 indicating that the epitope recognized by this antibody is localized at the anti-N-terminal domain of HTT (Fig. 35 C). The NI-302.72F10 binding epitope was therefore predicted to be localized within HTT amino acids 70-  
PPPGPAVAEEPLH-82 (SEQ ID No.: 202).

**Example 32: Characterization of binding affinity and selectivity of anti-N-terminal domain antibody NI-302.15E8 utilizing direct ELISA and EC<sub>50</sub>**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.15E8 to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA and EC<sub>50</sub> determination was performed as described in Example 6, *supra*.

It could be shown that NI-302.15E8 binds with higher affinity to non-aggregated GST-HD49 and GST-HD21 and less affinity to aggregated HD49 and HD21, see Fig. 14 A and B. Accordingly, the human-derived HTT anti-N-terminal domain antibody NI-302.15E8 target an epitope exposed in both aggregated as well as in soluble forms of HTT, albeit with a higher  
30 affinity to soluble forms of HTT.

**Example 33: Epitope mapping by direct ELISA binding to different Exon1 peptides of the HTT antibody NI-302.15E8**

To determine the half maximal effective concentration (EC<sub>50</sub>) of recombinant human-derived HTT antibody NI-302.15E8 to BSA-coupled peptide fragments of the huntingtin Exon 1 direct ELISA with BSA-coupled Htt Exon1 domain peptides and EC<sub>50</sub> determination were performed  
5 as described in Example 10.

As shown in Fig. 15 NI-302.15E8 binds with high affinity to the first 19 BSA-coupled amino acids at the N-terminus as well as to full-length GST-HD49 with an EC<sub>50</sub> of approx. 0.1 or 15,  
10 respectively.

**Example 34: Impact of HTT antibody NI-302.35C1 on behavioral deficits in human HTT transgenic mice**

An Elevated Plus Maze test to measure anxiety-like behavior and a Pole test to measure motor  
15 performance and coordination in human HTT mice were performed to study the anti-HTT antibody NI-302.35C1 *in vivo*.

Groups and Treatment

For the behavioral analysis two groups of mice with n=24 (12/12 male/female) B6.Cg-Tg(HDexon1)61Gpb/J transgenic (tg) mice as described in Example 12 and one group of wild  
20 type (wt) mice were used. The groups of transgenic mice received intraperitoneal treatment of either 30mg/kg mouse chimeric NI-302.35C1 or vehicle starting at an age for 6-7 weeks until end stage phenotype of the mice between 7 to 9 months of age and the wild type mice were injected with the same volume of vehicle. The Elevated-Plus-Maze and pole test behavioral  
25 tests were performed at an age of 16 and 18 weeks of age respectively.

Elevated Plus Maze test

The Elevated Plus Maze test was performed according to Naver *et al.*, Neuroscience 122 (2003), 1049-1057. The maze was elevated 50 cm above the floor. Four maze arms (30 cm x 5  
30 cm) originated from a central platform forming a cross. Two of the arms located opposite each other were enclosed by 15 cm high walls (closed arms) while the other arms did not have any kind of screening (open arms). The test were performed at the beginning of the dark phase of the animals and the illumination on the open arm was in the range of 40lux. Each mouse was placed in the center of the Plus Maze facing an open arm. The experiment lasted for 5 min and

was recorded with a videotracking system (VideoMot Software, TSE Systems). Between the sessions, the maze was rinsed with water and dried with a paper towel. Subsequently the number of entries made into open and closed arms as well as the time spent in open and closed compartments were evaluated. An entry was defined as all four paws in one arm. The number of entries into the open arms and the time spent in the open arms are used as indices of open space-induced anxiety in mice.

#### Pole test

The pole test is used widely to assess basal ganglia-related movement disorders in mice; see, *e.g.* Matsuura *et al.* J. Neurosci. 73 (1997), 45-48; Sedelis *et al.* Behav Brain Res. 125 (2001), 109-125, Fernagut *et al.*, Neuroscience 116 (2003), 1123-1130. Briefly, animals were placed head-up on top of a vertical wooden pole 50 cm long (1 cm in diameter). The base of the pole was placed in the home cage. When placed on the pole, animals orient themselves downward and descend the length of the pole back into their home cage. On the test day, animals received three trials, and the total time to descend (t-total) were measured. The results of the third trial of the day is shown in Fig. 24 B.

As shown in Fig. 34 A NI-302.35C1 treated R6/1 animals spend less time in the open arms, entered the open arms less frequently and did less unprotected head dips on the open arm compared to vehicle treated R6/1 animals. Hence the NI-302.35C1 treated R6/1 mice displayed a more anxious phenotype, comparable to the non-transgenic littermates. Furthermore, as shown in Fig. 24 B NI-302.35C1 treated R6/1 animal showed an improved performance in the pole test compared to vehicle treated R6/1 animals reaching levels similar to non-transgenic animals. In summary, the antibody NI-302.35C1 of the present invention has a beneficial impact on behavioral performance and motor-related tasks in human HTT transgenic mice.

#### **Example 35: Sequence alignment of HTT antibodies**

The determination of percent identity or similarity was performed with the standard parameters of the BLASTn program as described in section "Definitions" of the present invention. As shown in Fig. 36 all antibodies of the present invention are rich of tyrosines in the CDRs.

#### **Example 36: Generation of bispecific anti-HTT antibodies**

The generation of bispecific antibodies can be performed as generally described in Brennan; see *supra*. Starting material for producing bispecific antibodies are intact IgG anti-HTT

antibodies of the present invention recognizing either a polyP-region, a polyQ/polyP-region, the P-rich-region, the C terminal-region or the N-terminal region of HTT exon 1 protein as described in the Examples and summarized in Figure 20. The antibodies are treated with pepsin for three hours at 37 ° C treated in acetate buffer pH 4.0, to cleave the Fc portion of the antibody.

5 The reaction is stopped by increasing the pH to 8 with Tris buffer. Subsequently the solution is filled up with an equal volume of a mixture of 5, 5'-dithiobis-2-nitrobenzoic acid (DTNB) and incubated with thionitrobenzoate (TNB) for 20 hours at room temperature. The molar ratio of the DTNB-TNB mixture is 20:30 being established by incubating a 40 mM DTNB solution with a 10 mM DTT solution for several minutes. After further reduction of the two modified  
10 F(ab') fragments with 0.1 mM DTT for one hour at 25 ° C, the thus obtained F(ab')-TNB and F(ab')-SH fragments are hybridized to a bispecific F(ab')<sub>2</sub>-fragment for 1 h at 25 ° C. Bispecific F(ab')<sub>2</sub>-fragments were purified via gel filtration (Superdex 200 column).

**Example 37: Characterization of binding affinity and selectivity of bispecific anti-HTT  
15 antibodies utilizing direct ELISA and EC<sub>50</sub>**

To determine the half maximal effective concentration (EC<sub>50</sub>) of bispecific HTT antibodies to soluble and aggregated HTT Exon1 proteins with 21 or 49 polyQ repeats direct ELISA and EC<sub>50</sub> determination is performed as described in Example 6, *supra*. The bispecific HTT antibodies bind with high affinity to all four species including the aggregated HTT Exon1  
20 HD49, equally targeted their respective epitopes exposed in aggregated as well as in soluble forms of HTT with low nanomolar affinity. Additionally, to characterize the binding of bispecific HTT antibodies to soluble and aggregated HTT Exon1 proteins with 21, 35 or 49 polyQ repeats filter retardation assay and dot blot as described in Example 7, *supra*, are performed. On the dot blot, bispecific HTT antibodies preferentially detect constructs of HTT  
25 with expanded polyQ tracts. Furthermore, the signal intensity increases with increasing incubation times of the aggregation reactions of HD35 and HD49. In the filter retardation analysis bispecific HTT antibodies detect HD35 and HD49 aggregates that are retained on the 0.2 µm pore size membrane. Based on their dual specificity to HTT and the previous findings for the binding of the individual antibodies on membrane bound protein preparations it is  
30 expected that bispecific HTT antibodies preferentially target aggregated HTT conformations with pathogenic polyQ expansions. Furthermore, to determine the binding of bispecific anti-HTT antibodies to unrelated aggregating protein targets, direct ELISA is performed as described in Example 8, *supra*. In this context, bispecific anti-HTT antibodies bind specifically to HTT while a binding to unrelated proteins may not be shown.

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 integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated human-derived monoclonal anti-huntingtin (HTT) antibody or an HTT-binding fragment, synthetic or biotechnological derivative thereof, which comprises variable domains of both the light ( $V_L$ ) and heavy ( $V_H$ ) chain and a constant domain, wherein the antibody comprises in its variable region the six complementarity determining regions (CDRs) of the  $V_H$  and  $V_L$  variable region amino acid sequence of any one of antibodies NI-302.63F3, NI-302.31F11, NI-302.2A2, NI-302.15D3 or NI-302.64E5 depicted in
  - (i)  $V_H$  sequence (SEQ ID NOs: 5, 13, 17, 135, 164, 166); and
  - (ii)  $V_L$  sequence (SEQ ID NOs: 7, 15, 19, 137, 168), respectively.
2. The antibody of claim 1, wherein the antibody comprises in its variable region an amino acid sequence of the  $V_H$  and  $V_L$  region of any one of antibodies NI-302.63F3, NI-302.31F11, NI-302.2A2, NI-302.15D3 or NI-302.64E5 depicted in
  - (i)  $V_H$  sequence (SEQ ID NOs: 5, 13, 17, 135, 164, 166); and
  - (ii)  $V_L$  sequence (SEQ ID NOs: 7, 15, 19, 137, 168), respectively, or a  $V_H$  and  $V_L$  region thereof comprising one or two amino acid substitutions.
3. The antibody of claim 1 or claim 2, which is of the IgG type.
4. The antibody of any one of claims 1 to 3, wherein the light chain is kappa ( $\kappa$ ).
5. The antibody of any one of claims 1 to 4, which recognizes an epitope in the amino acid sequence of exon 1 of the HTT gene, preferably an epitope in the P-rich-region.
6. The antibody of any one of claims 1 to 5, which is capable of binding a peptide comprising the epitope and/or aggregated forms of HTT exon 1.
7. The antibody of any one of claims 1 to 6 or an HTT-binding fragment, synthetic or biotechnological derivative thereof which specifically binds an epitope in the P-rich-region which comprises the amino acid sequence PQPPPQAQPL (SEQ ID No. 140), PPPQLPQPPP (SEQ ID No. 141), QAQPLLPQPQPPPPP (SEQ ID No. 142), or PPPQLPQPPPQAQPL (SEQ ID No. 143).

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8. The antibody of any one of claims 1 to 7 or an HTT-binding fragment, synthetic or biotechnological derivative thereof, wherein the antibody or antigen binding fragment thereof further comprises a polypeptide sequence which is heterologous to the V<sub>H</sub> and V<sub>L</sub> region or the six CDRs, preferably wherein polypeptide sequence comprises a human constant domain, preferably of the IgG type, most preferably of the IgG1 class or isotype.
9. The antibody of any one of claims 1 to 8, wherein the antibody has a binding affinity corresponding to an EC<sub>50</sub> (half maximal effective concentration) value of  $\leq 20$  nM, preferably  $\leq 10$  nM and most preferably  $\leq 1$  nM for binding HD49 and an EC<sub>50</sub> value of  $\leq 40$  nM, preferably  $\leq 10$  nM and most preferably  $\leq 1$  nM for binding HD21.
10. The antibody of any one of claims 1 to 9 which is a chimeric murine-human or a murinized antibody and/or an antibody or HTT-binding molecule which competes with an antibody of any one of claims 1 to 5 for specific binding to HTT.
11. One or more polynucleotide(s) encoding at least the binding domain or variable region of the heavy and light chain of the antibody of any one of claims 1 to 10 which is (are) operatively linked to a heterologous promoter region, preferably wherein the polynucleotide(s) is (are) cDNA.
12. One or more vector(s) comprising the polynucleotide(s) of claim 11.
13. A host cell comprising the polynucleotide(s) of claim 11 or the vector(s) of claim 12.
14. A method for preparing an anti-HTT antibody, a biotechnological derivative, or immunoglobulin chain(s) thereof, said method comprising
- (a) culturing the cell of claim 13 and
  - (b) isolating the antibody or immunoglobulin chain(s) thereof from the culture.
15. An isolated antibody or immunoglobulin chain(s) thereof encoded by the polynucleotide(s) of claim 11, the vector(s) of claim 12 or obtained by the method of claim 14.

16. The antibody of any one of claims 1 to 10 or 15, which is a bispecific antibody.
17. The antibody of claim 16, which recognizes two different epitopes on a protein encoded by exon 1 of the HTT gene.
18. The antibody of any one of claims 1 to 10 or 15 to 17, which is
  - (i) detectably labeled, preferably wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal; or
  - (ii) attached to a drug.
19. A composition comprising the antibody of any one of claims 1 to 10 or 15 to 18, the vector(s) of claim 12, or the cell of claim 13, preferably wherein the composition is
  - (a) a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier, optionally further comprising an additional agent useful for treating diseases and/or symptoms associated with HTT amyloidosis, preferably wherein the composition is a vaccine;
  - (b) a diagnostic composition, preferably which comprises reagents conventionally used in immuno or nucleic acid based diagnostic methods.
20. A kit useful in the diagnosis or monitoring of disorders associated with HTT amyloidosis, said kit comprising at least one antibody of any one of claims 1 to 10 or 15 to 18, optionally with reagents and/or instructions for use.
21. A method of treating a disease and/or symptoms associated with HTT amyloidosis or for *in vivo* detection of or targeting a therapeutic and/or diagnostic agent to HTT in the human or animal body comprising administering to a subject in need thereof a therapeutically or diagnostically effective amount of an anti-HTT antibody or an HTT-binding fragment, synthetic or biotechnological derivative thereof, which comprises a variable light (V<sub>L</sub>) and heavy (V<sub>H</sub>) chain, and a constant domain for use in treating a disease and/or symptoms associated with HTT amyloidosis or for *in vivo* detection of or targeting a therapeutic and/or diagnostic agent to HTT in the human or animal body, wherein the anti-HTT antibody is an antibody of any one claims 1 to 10 or 15 to 18.



- 5
22. Use of an antibody of any one of claims 1 to 10 or 15 to 18 in the manufacture of a medicament for treating a disease and/or symptoms associated with HTT amyloidosis.
  23. Use of an antibody of any one of claims 1 to 10 or 15 to 18 in the manufacture of a preparation for in vivo detection of or targeting a therapeutic and/or diagnostic agent to HTT in the human or animal body.

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2015295441**(A) NI-302.33C11 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVESGGGVVQPGNSLRSLSCAASGFRFSDDFGMHWVRQAPGKGLEWLALIWIYDGGYKYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDN SKNTMFLQMNSLRAEDTAVYYCATHLEYCSRTTCYLGHWGQGLTLTVSS

**NI-302.33C11 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQLTQSPSFLSASVGDVTFTFCRASQGISDYLAWFQQKPGIAPKLLIYAAASTLQTGVPSRFSGSGSGT  
 -----CDR3-----FR4-----  
 EFTLTIRSLQSEDFGTYYCQQLKTPYTFGQGTKVEIK

**(B) NI-302.63F3 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 QVQLVQSGSAFKKPGTSVKVSCKASGYTFETSRSMNWVRQAPGQGLEYMGWINTNTGNRTYVQAFGRFV  
 -----CDR3-----FR4-----  
 FSLDTSVSTAYLQISNLKTEDTAVYYCARGAGGGYWFDSWGQGLTLTVSS

**NI-302.63F3 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQMTQSPDSLAVSLGERATINCKSNQSLFYSSNNNNYLAWYQHKSGQPPKLLVYWGSTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISSLQAEDVAIYYCHQYHNPYTFGQGTKLEIK

**(C) NI-302.35C1 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVESGGNLVQPGGSLRLSCTASGFTFSITALSWVRQAPEKGPQWVSAITGNAYGTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDN AKNTLYLQMNGLRAEDTAIYYCVKGIASDSSGYSAFWGPGLTLTVSS

**NI-302.35C1 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPATLSLSPGERATLSRASQSVNDQFAWYQQKPGQAPRLLIYDASRRAPGIPDRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISSELPEDFAIYYCQHRYTWLYTFGQGTRLEIK

Fig. 1

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**(D) NI-302.31F11 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3--  
 EVQLVESGGGLIQPGGSLRLSCAASGFTVSSTYMSWVRQAPGKGLECVSVIFSGADTYADSVKGRFTV  
 -----CDR3-----FR4-----  
 SRDNSKNTLFLQMNSLRVEDTATYYCVRHYYGSDLPSEFWGQGLTVTVSS

**NI-302.31F11 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPSLSPVAPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGKPPQLLVYLGSDRASGVPDRFSG  
 -----CDR3-----FR4-----  
 SGSGKDFTLNISRVEAEDVGYYCMQGLQSPWTFGQGTKLEIK

**(E) NI-302.2A2 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3--  
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYWMNWVRQAPGKGLEWVANIKPDGSDKYYVDSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNAKNSLYLQMNSLRDEDTAVYYCARGDGSGWNVYWGQGLTVTVSS

**NI-302.2A2 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3--  
 DIQMTQSPDSLAVSLGERATINCKSSQSLLYTSKNKDSKNYLGWYQQKPGQPPELLIYWASTRESGVPD  
 -----CDR3-----FR4-----  
 RFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTTPQFGGGTKVEIK

**(F) NI-302.6N9 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3--  
 EVQLVESGGDLVQPGGSLRLSCVVS~~GFTFSS~~YAMTWVRQAPGKGLAWVSTISATGGSTFYTDSVRGRFT  
 -----CDR3-----FR4-----  
 ISRDNSKNTLYLQMNSLRD~~DDTAIYYC~~VDLFGVDTSYYGMDVWGQGT~~TVTVSS~~

**NI-302.6N9 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPGTLSLSPGERATLSCRPSQSVSGRYVAWYQQKPGQAPRLLFYAASNRAIGIPDRFSGSGSG  
 -----CDR3-----FR4-----  
 TDFTLTISRLEPEDFAVYYCQHYGASSYTFGPGTKVDIK

Fig. 1 (continued)

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**(G) NI-302.74C11 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3-----  
 EVQLVQSGTEVQKPGASVKVSKASGYSFTGYFLHWVRQAPGQGLEWMGWINPNSGDTNYAEKFRGRII  
 -----CDR3-----FR4-----  
 MTRDTSVSTAHMELSSLRFDDTALYYCTREAPDPAETDVWGQGTITVTVSS

**NI-302.74C11 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSVLTQPPSVSVSPGQTARITCSGDAVPKQYIYWYQQKPGQAPILVIYKDTQRPSTGIPERFSGSNSGTT  
 -----CDR3-----FR4-----  
 VTLTITGVQADDEGDYYCQADSSATWVFGGGTKLTVL

**(H) NI-302.15F9 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR  
 EVQLVESGGGLVTPGGSRLSCEASGFLFKNSSMNWVRQTPGKGLEWVSSIDTSATNYKYYADSVKGRF  
 3-----CDR3-----FR4-----  
 TISRDDATNSLYLQMNSLRADDTATYYCARGYYTPRDFDYWGQGTITVTVSS

**NI-302.15F9 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPQTLVSLGQAASISCRSSQSLLYRDNNTYLNWFHQRPQGSPRRLIYRASDRDSGVPDRFSG  
 -----CDR3-----FR4-----  
 GGSGTDFTLKISGVEAEDVGTYTCMQGTHWPRTFGQGTKVEIK

**(I) NI-302.39G12 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3-  
 EVQLVQSGGGLVHPWGSRLSCLASGFSVSNYAITWVRRAPGKGLQYISVIYRDGRITYYGDSVGRFTI  
 -----CDR3-----FR4-----  
 SRDDSKNTLYLQMNSLRFDATAVYYCARAHGQYYYGVDVWGQGTITVTVSS

**NI-302.39G12 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPPLSLVSPGEPASISCRSSQSLLSNGYNYLDWYRQKPGQSPQLLIYLSNRPSTGVPDRFSA  
 -----CDR3-----FR4-----  
 SGSGTEFTLQISRVEAEDVGYYTCMSLQTFTFGGGTKVDIK

Fig. 1 (continued)

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**(J) NI-302.11A4 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3-  
 EVQLVESGGGLIQPGGSLRLSCAASGFPVSSSYMSWVRQAPGEGLEWVSVLYRDGDTYYADSVQGRFTI  
 -----CDR3-----FR4-----  
 SRDNSQNTFYLQMNSLKAEDTAVYYCAGDRRSSHYYYGMDVWGQGTITVTVSS

**NI-302.11A4 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVMTQSPGTLSLSPGERATLSCRASQSVSSSYFAWYQQKPGQAPRLLIYGTSSRRATAIPDRFSGSGSG  
 -----CDR3-----FR4-----  
 TDFTLTISRLEPEDFAVYYCQQYGSSWTFGPGTKVEIK

**(K) NI-302.22H9 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3-  
 EVQLVESGGGLVHPWGSRLVSCAASGFVSNSYAITWVRQAPGKGLYISVIYRDGRITYYGDSVGRFTI  
 -----CDR3-----FR4-----  
 SRDDSKNTIYLQMNSLRFEDTAVYYCARAHGQYYYGVDVWGQGTITVTVSS

**NI-302.22H9 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPLSLSVSPGEPASISCRSSQSLLSNGYNYLDWYRQKPGQSPQLLIYLNNSNRASGVDPDRFSG  
 -----CDR3-----FR4-----  
 SSGSGTEFTLTISRVEAEDVGVYYCMQSLQTFTFGGGTKVEIK

**(L) NI-302.44D7 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGIGYSDTSTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 VSRDISKNTLYLQMNSLRAEDTAVYYCAKGTRDYYGMDVWGQGTMTVTVSS

**NI-302.44D7 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTSYPSWYQQTPGRAPRTLIYSTNTRSSGVPDRFSGSIL  
 -----CDR3-----FR4-----  
 GNKAALTITGAQADDESYYCVLFMSGIGVFGGGTRLTIVL

Fig. 1 (continued)

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**(M) NI-302.37C12 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3---  
 EVQLVESGGGLVQPGGSLRLSCVASALTVTNSQMTWVRRAPGRGLEWVSVIYTSGSAYYADSVKGRFTI  
 -----CDR3-----FR4-----  
 SRDNSKNTVFLQMNSLRVEDTAVYYCAKGPSAYYYGLDLWGQGTITVTVSS

**NI-302.37C12 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPLSLPVTTPGEPASISCRSSQSLLSNGYNYLDWYLQKPGQSPQLLIYLGSTRASGVPDRFSG  
 -----CDR3---FR4-----  
 SSGTDFTLKISRVEAEDVGVYYCMQGLQTYTFGQGTKLEIK

**(N) NI-302.55D8 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----  
 QVQLVQSGSEVKKPGASVKVSCKASGYTFTDYIHWVRQAPGQGLEWMGRINPNNGGTNYAQNFQGWVT  
 --FR3-----CDR3-----FR4-----  
 MTRDTSISTAYMELSRLRSDDTAVYYCARVGGELLREGGYHYMDVWGKGTITVTVSS

**NI-302.55D8 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSVLTQPPSVSGAPGQRTISCTGNSSNIGAGYDVHWYQLPGTAPKLLIFDNTNRPSGVPDRFSGSKS  
 -----CDR3-----FR4-----  
 GTSASLAITGLQAEDEANYHCQSYDNSLSGSWVFGGGTKLTVL

**(O) NI-302.7A8 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 EVQLVESGGGSVQPGGSLRLSCVASGFIFRNSWMTWVRQDPGKGLEWVANIKEDGSRTYYVDSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNAKNSLYLQMNSLRAEDTAVYYCARGDYNISGIYYFPGDYWGQGTITVTVSS

**NI-302.7A8 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPLSLPVTLGQPASISCRSSQSLVSDGNTYLNWFQQRPQGQSPRRLIYKVSNRDSGVPDRFSG  
 -----CDR3-----FR4-----  
 SSGTDFTLRISRVEAEDVGIYYCMQGTHWPGTFGQGTKVEIK

Fig. 1 (continued)

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**(P) NI-302.78H12 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 QVQLQESGPGLVKPSSETLSLTCLVSSYSISNGYYWGWRQPPGKGLEWIGSIYHNGNTYYNP<sup>SLKSRVI</sup>  
 -----CDR3-----FR4-----  
 ISVDTSKNQFSLKLRSVTAADTAVYYCAMP<sup>SATYYYGSGTQFHA</sup>FDVWGQGT<sup>TVTVSS</sup>

**NI-302.78H12 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSALTQPRSVSGSPGQSVTISCTGT<sup>SRDVGNYNYVSWYQQHPGEV</sup>PKLI<sup>IYDV</sup>SERPSGVPDRFSGSKS  
 -----CDR3-----FR4-----  
 GNTASLTISGLQAEDEADYYCCSYAGSYTFEVFGGGTKLTVL

**(Q) NI-302.71F6 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3--  
 QVQLQQWGAGLLKPSSETLSLTCAVYGGSLSGYYWSWIRQPPGKGLEWIGEVNHSGGTNLNSSLKSRV<sup>II</sup>  
 -----CDR3-----FR4-----  
 SVDKSKKQFSLKLSSVTAADTAMYFCARGYSYDPKYYFDSWSQGT<sup>LTVTVSS</sup>

**NI-302.71F6 VL (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSALTQPASVSGSPGQAITISCTGTSSDIGSYDFVSWYQQDPGKAPKV<sup>IIYGVNKR</sup>PSGVS<sup>NR</sup>FSGSKS  
 -----CDR3-----FR4-----  
 GNTASLTISGLQADDEADYYCCSYAGSTTWVFGGGTKLTVL

**(R) NI-302.11H6 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVQSGAVMKKPGDSVRVSCRASTYSFSTYSFTWVRQVPQG<sup>LEWMGWISAYNGHTNYVDS</sup>FQGR<sup>LT</sup>  
 -----CDR3-----FR4-----  
 LTTDTSASTAYMELRSLRSDDTAIYYCAAVDTT<sup>YYYYGMDV</sup>WGQGT<sup>LTVTVSS</sup>

**NI-302.11H6 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QTVVTQEPTFSVSPGGTVTLT<sup>CALRFGSVSSSYPSWFQQT</sup>PGQAPRTLIY<sup>STNTRSSG</sup>VPARFSGSIL  
 -----CDR3-----FR4-----  
 GNKAALTIAGAQANDEADYYCVLYMGSIGIVFGGGTKLTVL

Fig. 1 (continued)

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**(S) NI-302.3D8 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVQSGGGLVQPGGSLRLSCEASGFIFKTYAMSWVRQLPGRGLEWVSAISATGGSTFYAESVKGRLT  
 -----CDR3-----FR4-----  
 ISRD TAKNTVYLQMNNLRAEDTAMYYCAKGSTAVYLEFDSWGQGLTVTVSS

**NI-302.3D8 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQMTQSPSSLSASVGDRVLTLCRASQDIRNFLAWIQQKPGKPPKSLIYAASTLQSGVPSRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISLHPEDFATYYCQQFYNYPPPTFGQGTKVEIK

**(T) NI-302.18A1 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR  
 QLQLQESGPGLVKPSSEALSLTCTVSGGSITTDYYYWGWIRQSPGKGLEWVGTIYFGGATYYNPSLRNRV  
 3-----CDR3-----FR4-----  
 SISVDTSNTRLISLRLISLSAADTAVYYCARVGYLDRSGLLVGQGLTVTVSS

**NI-302.18A1 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPPLSVPTPGEPASISCRSSQSLLHNNGYNYLDWYLKKPGQSPQLLIYLGSTRASGVDPDRFSA  
 -----CDR3-----FR4-----  
 SSGGTDFTEISRVEAEDVGVYYCMQALQTPPTFGRGTKVEIK

**(U) NI-302.8F1 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----F  
 EVQLVESGGGLVKPGGSLTISCAASGFTFSNAWMNWVRQAPGKGLEWVGHI RTQAEGGTSDYAAPVKGR  
 R3-----CDR3-----FR4-----  
 FTISRDDSKNTLYLQMNSLKTEDTAVYYCIPPPYYYYYGLDVWGQGLTVTVSS

**NI-302.8F1 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSALTQPASVSGSPGQSITISCTGASSDVGTYDLVSWYQQHPGKAPKLIIYE VNKRPSGVSYRFSASKS  
 -----CDR3-----FR4-----  
 ANTASLTISGLQAEDEAEYYCCSYAGYSTVFGGGTKLTVL

Fig. 1 (continued)



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**(V) NI-302.52C9 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3-  
 EVQLVQSGGGLVQPGGSLRLSCAGSGFTVSDTYMSWVRQAPGKGLEWVSGIHAGGETYYADSVKGRFTI  
 -----CDR3-----FR4-----  
 SRDNSKNTLYLQMNRLTPEDTAVFYCARHYYGNDDDTDYWGQGLTVTVSS

**NI-302.52C9 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DVVMTQSPSLSPVTPGEPASISCRSSQSLLHSNGYNYLDWYVQKPGQSPQLLIYLGSTRASGVPDRFSG  
 -----CDR3-----FR4-----  
 SSGGTDFTLKISRVEAEDVGVIYCLQAQQIPWTFGQGTKVEIK

**(W) NI-302.46C9 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR  
 QVQLQESGPGLVKPSQTLSTCTVSGASVSSGAYYWSWIRQPAKRLIEWIGRVYPTWSTNYPNPSLESRV  
 3-----CDR3-----FR4-----  
 TISLDTSNNQFSLKLTSLTAADTAVYYCAREAPGDYDAAPLAYWGQGLTVTVSS

**NI-302.46C9 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQMTQSPSSLSASVGDRTITCRASQYISHYLNWYRQKPGKAPQLVIYAASSLQSEVPSRFSGSGSGP  
 -----CDR3-----FR4-----  
 EFTLTISLQPEDFATYYCQQSYTTPRTFGQGTKLEIK

**(X) NI-302.64E5 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----F  
 EVQLVETGGGLVKPGGSLRLSCAASGFTFDQAWMSWVRQVPGKGLEWVGRIKTKTEGEATDYAAPVRGR  
 R3-----CDR3-----FR4-----  
 FTISRDDSEDTVFLQMNSLKTEDTALYYCTSTIGVLAAAVDVYWGQGLTVTVSS

**NI-302.64E5 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQLTQSPDSLAVSLGERATMTCKSSQSLFYSYNNENYLAWYQQRPGQPPKLLIYWASTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGGTDFTLTISLQAEADVYYCQYYSTPQTFGQGTKVDIK

Fig. 1 (continued)

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**(Y) NI-302.7D8 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 QVQLVQSGSELKKPGASVKVSCKASGYNFNNYAINWLRQAPQGLEWMGWINTITGHPTYAQGFKGRFV  
 -----CDR3-----FR4-----  
 FSLDTSVSTAYLQISSLKPEDTAVYYCARTYSNYGEFDYWGQGLTVTVSS

**NI-302.7D8 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSALTQPASVSGSRGQSITISCTGTSSDVGSYNLVSWYQQYPGKAPKLIIHEGSERPSGVSNRFSGSKS  
 -----CDR3-----FR4-----  
 GNTASLTISGLQAEDEADYYCCSYAGTTTFVLFGGGTKLTVL

**(Z) NI-302.72F10 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 EVQLVETGGGFVQPGGSLRLSCAASGFNFGSYAMSWVRQAPGKGLEWVSDISGIGSNTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNSDNTLYLDMSSLRAEDTARYYCAKDRKRSGWYEQWGQGLTVTVSS

**NI-302.72F10 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVMTQSPATLTLSLSPGERATLSCRASQSISAYLGWYQQKPGQAPRLIYDASIRATGIPDRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISSELPEDSAVYYCHQRSKWPLTFGGGTKVEIK

**(AA) NI-302.4A6 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSAYAMSWVRQAPGKGLEWVSTISGSGGSTYYADSVKGRFS  
 -----CDR3-----FR4-----  
 ISRDNSKNTLYLQMNSLRAEDTAVYFCAKVTTELYGANSYYYYMDVWGKGTTTVTVSS

**NI-302.4A6 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPGTLSLSPGERATLSCRASQSVVSRYLAWYQQKPGQAPRLIYGASSRATGIPDRFSGSGSG  
 -----CDR3-----FR4-----  
 TDFTLTISRLEPEDFAMYYCQLYGNSQTFGGGTKVEIK

Fig. 1 (continued)

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**(AB) NI-302.12H2 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVQSGGGLVQPGGSLRLSCEASGFTFSNYAMGWVRQAPGKGLEWVSVISGTGGSTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNSMNTLYLQMNSPRADDTAVYYCAKDLRKISGPLYYYGMDVWGQGTITVTVSS

**NI-302.12H2 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPGTLSSLSPGERATLSCRASQSVSSGYLAWYQQKPGQAPRLLIYGASTRATGIPDRFSGSGSG  
 -----CDR3-----FR4-----  
 TDFTLTISRLEPEDFAVYYCQHYGASSYTFGQGTKLEIK

**(AC) NI-302.8M1 VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVQSGAEVKKPGASVKVSCKASGYTFTIYYMHWVRQAPQGLEWMGGISPSGAHTMYAQNFQGRVT  
 -----CDR3-----FR4-----  
 VTRDTSTSTVYMELSSLRSEDVAVYYCARGSTVTNYPFDYWGQGTITVTVSS

**NI-302.8M1 VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQMTQSPSSLSASVGDRTITCRASQDISNYLAWYQQKPGKVPKLLIFAASTLQSGVPSRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISLQPEDVATYYCQNYNSGPPPPFGPGTKVDIK

**(AD) NI-302.33C11-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 QVQLVESGGGVVQPGNSLRLSCAASGFRFSDFGMHWRQAPGKGLEWLALIWDGGYKYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNSKNTMFLQMNSLRAEDTAVYYCATHLEYCSRTTCYLGHWGQGTITVTVSS

**NI-302.33C11-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIQLTQSPSFLSASVGDVTFVTCRASQGISDYLAWFQQKPGIAPKLLIYAASTLQTVPSRFSGSGSGT  
 -----CDR3-----FR4-----  
 EFTLTIRSLQSEDFGTYYCQQLKTYPTYTFGQGTKLEIK

Fig. 1 (continued)

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**(AE) NI-307.63F3-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPDSLAVSLGERATINCKSNQSLFYSSNNNNYLAWYQHKSGQPPKLLVYWGSTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISSLQAEDVAIYYCHQYYHNPYTFGQGTKLEIK

**NI-307.63F3-PIMC-NS VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPDSLAVSLGERATINCKSSQSLFYSSNNNNYLAWYQHKSGQPPKLLVYWGSTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISSLQAEDVAIYYCHQYYHNPYTFGQGTKLEIK

**NI-307.63F3-PIMC-SG VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPDSLAVSLGERATINCKSNQGLFYSSNNNNYLAWYQHKSGQPPKLLVYWGSTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISSLQAEDVAIYYCHQYYHNPYTFGQGTKLEIK

**NI-307.63F3-PIMC-NQ VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPDSLAVSLGERATINCKSQSLFYSSNNNNYLAWYQHKSGQPPKLLVYWGSTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISSLQAEDVAIYYCHQYYHNPYTFGQGTKLEIK

**(AF) NI-302.35C1-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPATLSLSPGERATLSCRASQSDVNQFAWYQQKPGQAPRLLIYDASRRAPGIPDRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISLEPEDFAIYYCQHRYTWLYTFGQGTKLEIK

Fig. 1 (continued)

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**(AG) NI-302.31F11-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSP<sup>1</sup>LSLPVAPGEPASISCRSSQSL<sup>2</sup>LYSNGYNYLDWYLQKPGKPPQLLVYL<sup>3</sup>GS<sup>4</sup>DRASGVPDRFSG  
 -----CDR3-----FR4-----  
 SGSGKDFTLNISRVEAEDVG<sup>5</sup>VYYCMQGLQSPWTFGQGTKVEIK

**(AH) NI-302.2A2-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPDSLAVSLGERATINCKSSQSL<sup>2</sup>LYTSKNKDSKNYLGWYQQKPGQPPKLLIYWASTRESGVPD  
 -----CDR3-----FR4-----  
 RFSGSGSGTDFTLT<sup>3</sup>ISSLAEDVAVYYCQQYYTTPQFGGGTKVEIK

**(AJ) NI-302.74C11-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-----FR2-----CDR2-----FR3-----  
 QVQLVQSGTEVQKPGASVKVSKASGYSFTGYFLHWVRQAPGQGLEWMGWINPNSGDTNYAEKFRGRII  
 -----CDR3-----FR4-----  
 MTRDTSVSTAHMELSSLRFD<sup>3</sup>D<sup>4</sup>TALYYCTREAPDPAETDVGQGT<sup>5</sup>TVTVSS

**NI-302.74C11-PIMC VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 SYELTQPPSVSVSPGQTARITCSGDAVPKQYIYWYQQKPGQAPILVIYKDTQRP<sup>3</sup>SGIPERFSGSNSGTT  
 -----CDR3-----FR4-----  
 VTLTITGVQADDEGDYYCQ<sup>4</sup>SADSSATWVFGGGTKLTVL

**(AK) NI-302.39G12-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-----FR2-----CDR2-----FR3-----  
 EVQLVESGGGLVHPWGSLRLSCAASGFSVSNYAITWVRRAPGKGLQYISVIYRDGR<sup>3</sup>TYYGDSVRGRFTI  
 -----CDR3-----FR4-----  
 SRDDSKNTLYLQMNSLRFD<sup>4</sup>TAVYYCARAHGQYYYGVDVWGQGT<sup>5</sup>TVTVSS

Fig. 1 (continued)

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**NI-302.39G12-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPLSLSVSPGEPASISCRSSQSLLSNGYNYLDWYRQKPGQSPQLLIYLSSNRPSGVPDRFSA  
 -----CDR3---FR4-----  
 SSGSGTEFTLQISRVEAEDVGVIYCMQSLQTFTFGGGTKVEIK

**(AL) NI-302.11A4-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPGTLSSLSPGERATLSCRASQSVSSSYFAWYQQKPGQAPRLLIYGTSSRRATAIPDRFSGSGSG  
 -----CDR3---FR4-----  
 TDFTLTISRLEPEDFAVYYCQYQSSWTFGPGTKVEIK

**(AM) NI-302.22H9-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 DIVMTQSPLSLSVSPGEPASISCRSSQSLLSNGYNYLDWYRQKPGQSPQLLIYLNSENRRASGVPDRFSG  
 -----CDR3---FR4-----  
 SSGSGTEFTLTISRVEAEDVGVIYCMQSLQTFTFGGGTKVEIK

**(AN) NI-302.44D7-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGIGYSDTSTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 VSRDISKNTLYLQMNSLRAEDTAVYYCAKGTDRDYGMVDVWGQGTITVTVSS

**(AO) NI-302.78H12-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1--FR2-----CDR2-----FR3  
 QLQLQESGPGLVKPSETLSLTCLVSSYSISNGYYWGWRQPPGKLEWIGSIYHNGNTYYNP<sup>1</sup>SLKSRVI  
 -----CDR3-----FR4-----  
 ISVDTSKNQFSLKLRSVTAADTAVYYCAMP<sup>2</sup>SATYYYGSGTQFHAFDVWGQGTMTVTVSS

Fig. 1 (continued)

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**(AP) NI-302.15E8 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR  
 EVQLVESGGGLIQPGGSLRLSCAVSGFTVSSYSMNWVRQAPGKGLEWVSYTSSSRSNTKKYADSVKGRF  
 3-----CDR3-----FR4-----  
 TISRDNARNSLYLQMNSLRDEDTAVYYCARAGDFGELLTGEGYYGMDVWGQGT<sup>1</sup>TVTVSS

**NI-302.15E8 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 SYELTQPPSVSVSPGQTATITCSGDELGDKYVGWYQQKPGQSPLLVIYQDAKRPSGIPERFSGSNSGNT  
 -----CDR3-----FR4-----  
 ATLTI<sup>1</sup>SGTQAMDEADYYCQAWDSGTMVFGGGTRLTVL

**(AQ) NI-302.15D3 VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----FR3  
 EVQLVESGGDLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRI<sup>1</sup>SDNGSSKTYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNAKNTLYLQMNSLRAEDTAVYYCAILGGYCSSTSCRPF<sup>1</sup>DNWGQGT<sup>1</sup>LVTVSS

**(AR) NI-302.15D3 VL (variable light chain sequence VL)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 QSALTQPASVSGSPGQSITISCTGTSSDVG<sup>1</sup>VYNYVSWYQQHPGKAPKLMI<sup>1</sup>FDVSNRPSGISNRFS<sup>1</sup>SGSKS  
 -----CDR3-----FR4-----  
 GNTASLTISGLQAEDEADYYCSSYTSSDTWVFGGGTKLTIL

**(AS) NI-302.64E5-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-FR2-----CDR2-----F  
 EVQLVESGGGLVKPGGSLRLSCAASGFTFDQAWMSWVRQVPKGLEWVGRIKTKTEGEATDYAAPVRGR  
 R3-----CDR3-----FR4-----  
 FTISRDDSEDTVFLQMNSLKTEDTALYYCTSTGVLAAVDVYWGQGT<sup>1</sup>LVTVSS

Fig. 1 (continued)

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**NI-302.64E5-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3---  
 DIVMTQSPDSLAVSLGERATMTCKSSQSLFYSYNNENYLAWYQQRPGQPPKLLIYWASTRESGVPDRFS  
 -----CDR3-----FR4-----  
 GSGSGTDFTLTISLQAEDVAVYYCQQYYSTPQTFGQGTKVEIK

**(AT) NI-302.72F10-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-----FR2-----CDR2-----FR3  
 EVQLVESGGGFVQPGGSLRLSCAASGFNFGSYAMSWVRQAPGKGLEWVSDISGIGSNTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNSDNTLYLDMSSLRAEDTARYYCAKDRKRSWYEQWGQGLTVTVSS

**NI-302.72F10-PIMC VK (variable light chain sequence VK)**

FR1-----CDR1-----FR2-----CDR2---FR3-----  
 EIVLTQSPATLTLSLSPGERATLSCRASQSISAYLGWYQQKPGQAPRLLIYDASIRATGIPDRFSGSGSGT  
 -----CDR3-----FR4-----  
 DFTLTISLLEPEDSAVYYCHQRSKWPLTFGGGTKVEIK

**(AU) NI-302.12H2-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-----FR2-----CDR2-----FR3  
 EVQLVESGGGLVQPGGSLRLSCEASGFTFSNYAMGWVRQAPGKGLEWVSVISGTGGSTYYADSVKGRFT  
 -----CDR3-----FR4-----  
 ISRDNSMNTLYLQMNSPRADDTA VYYCAKDLRKISGPLYYYGMDVWGQGLTVTVSS

**NI-302.8M1-PIMC VH (variable heavy chain sequence VH)**

FR1-----CDR1-----FR2-----CDR2-----FR3  
 QVQLVQSGAEVKKPGASVKVSCKASGYTFTIYYMHVVRQAPGQGLEWMGGISPSGAHTMYAQNFQGRVT  
 -----CDR3-----FR4-----  
 VTRDTSTSTVYMEISSLRSEDTAVYYCARGSTVTNYPFDYWGQGLTVTVSS

Fig. 1 (continued)



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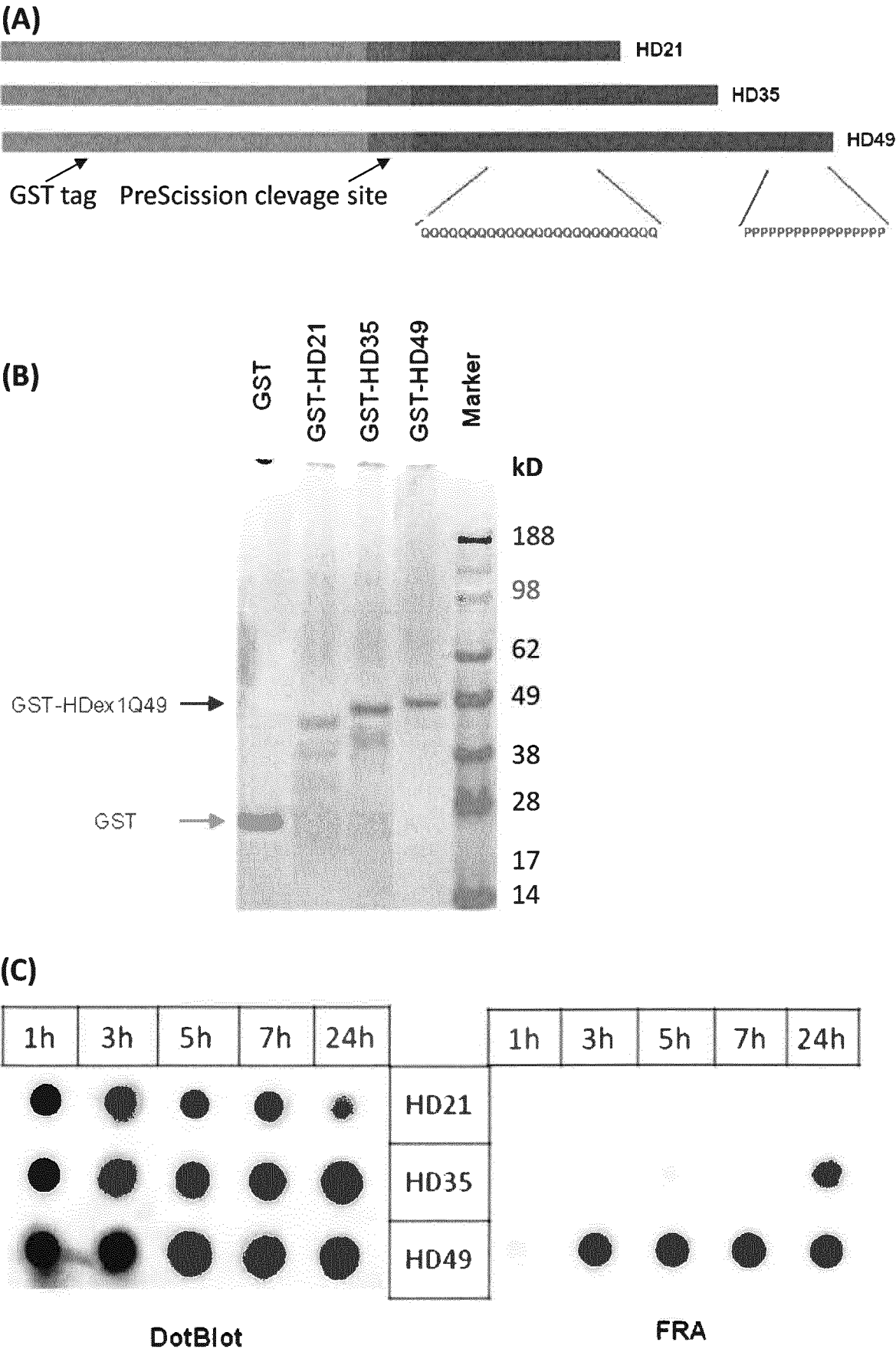


Fig. 2

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(D)

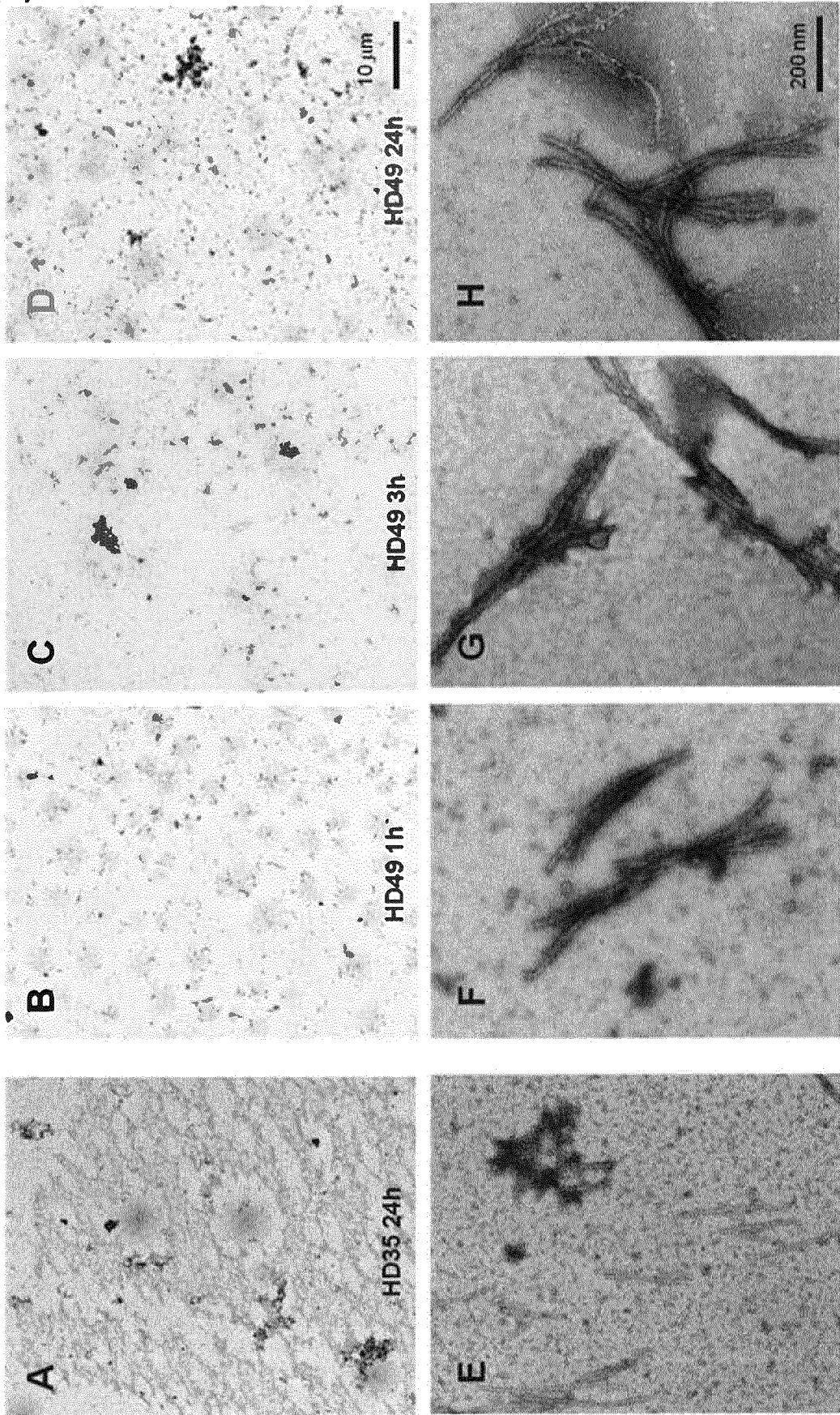


Fig. 2 (continued)

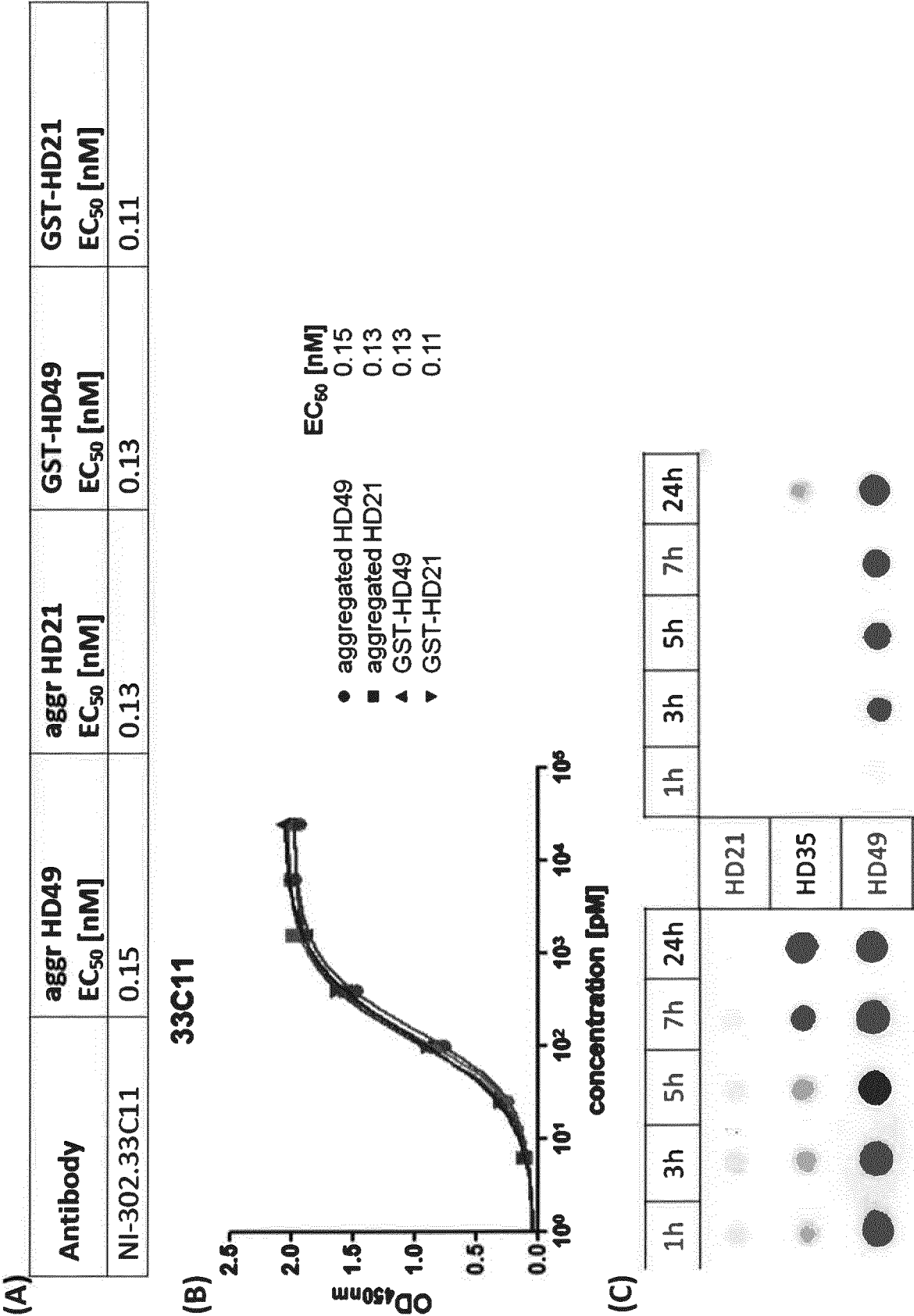
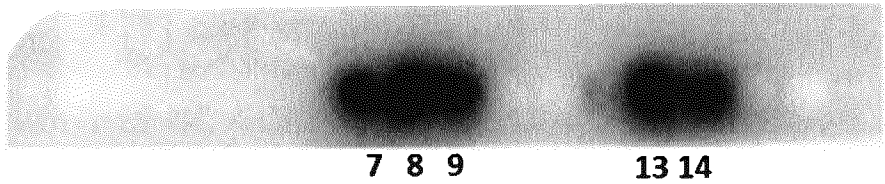


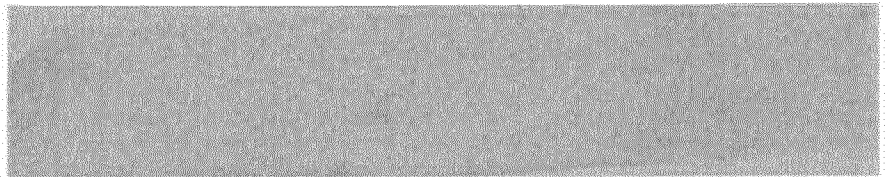
Fig. 3

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33C11 1µg/ml



2nd AB only goat anti-human (H+L) 1:20000



28 30 35 40 42 47 50 52  
7 Q Q Q Q Q Q Q P P P P P P P P  
8 Q Q P P P P P P P P P P P Q L  
9 P P P P P P P P P Q L P Q P P P  
consensus: P P P P P P P P  
58 60 63 67 70 72 75 77  
13 L P Q P Q P P P P P P P P P  
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Fig. 4



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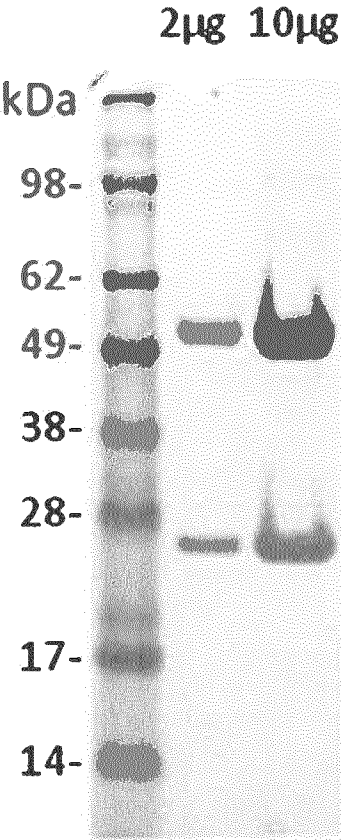


Fig. 6

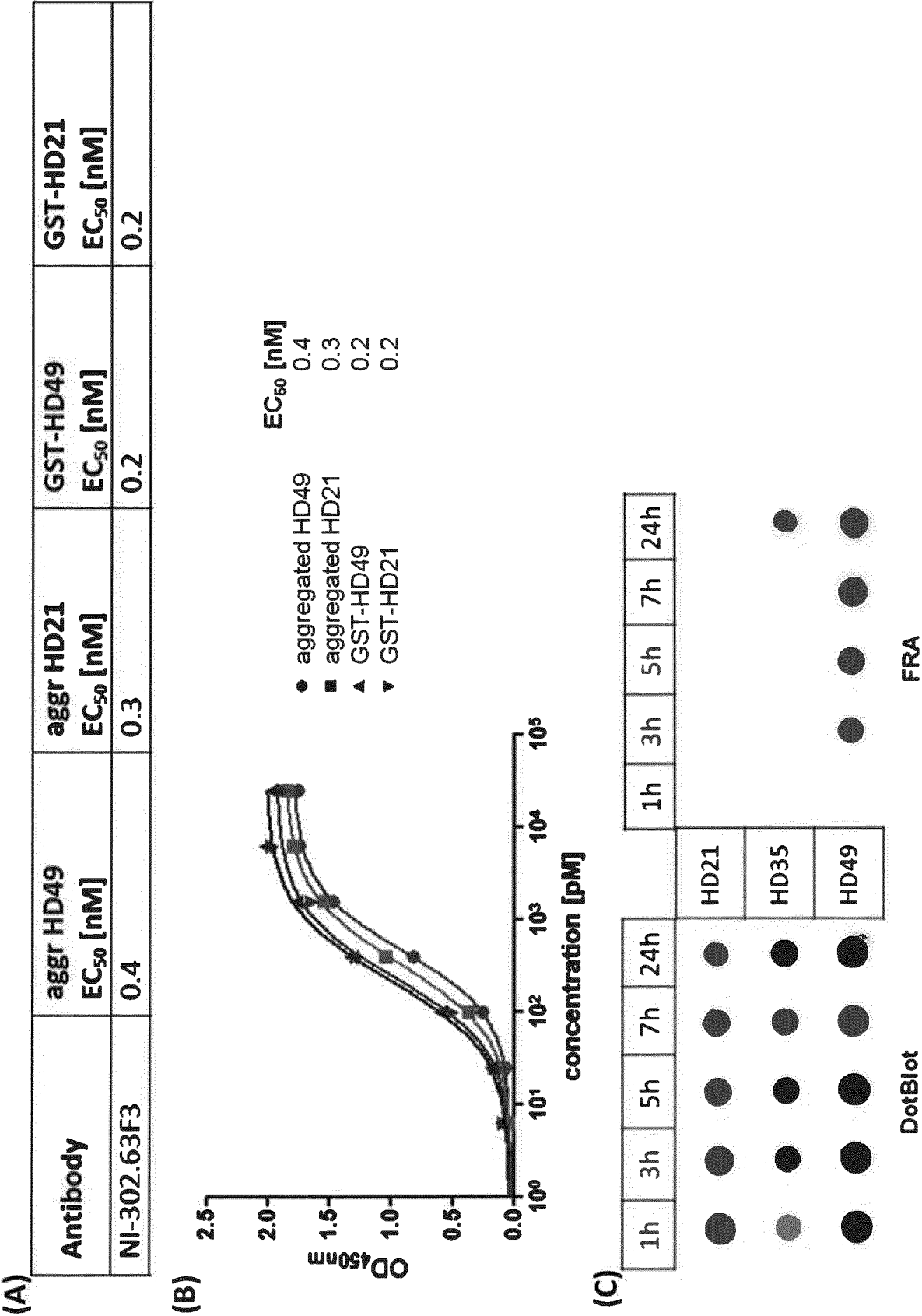
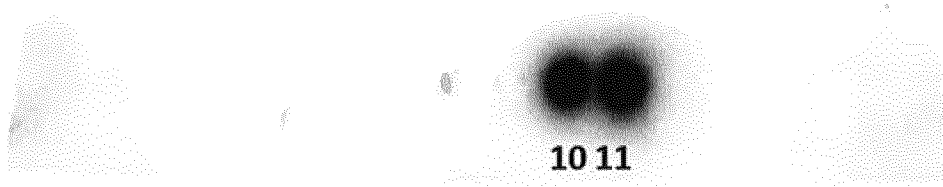


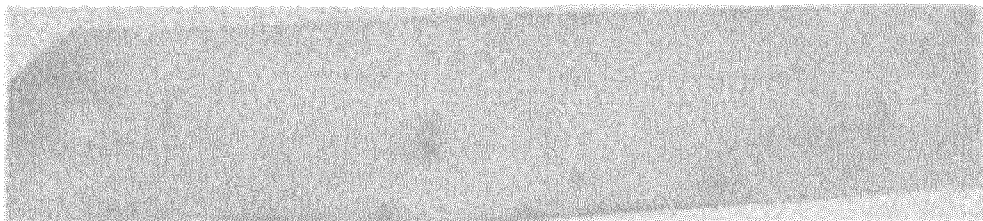
Fig. 7

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63F3 1ug/ml (21 Spot membrane)



2nd AB only goat anti human (H+L)



	43	47	50	52	55	57	60	62												
10	P	P	P	Q	L	P	Q	P	P	P	Q	A	Q	P	L					
11						P	Q	P	P	P	Q	A	Q	P	L	L	P	Q	P	Q
consensus:						P	Q	P	P	P	Q	A	Q	P	L					

Fig. 8





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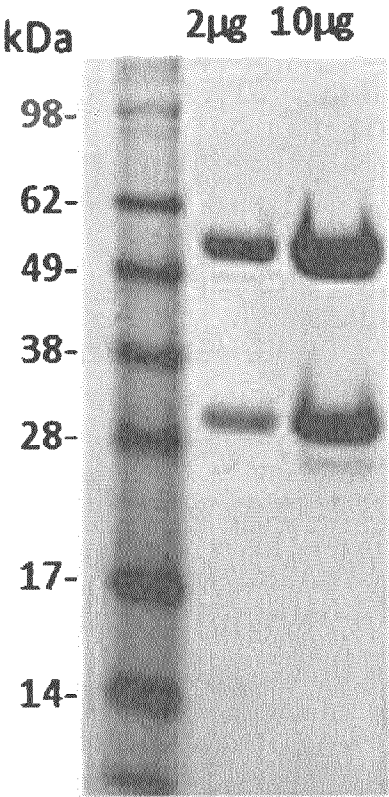


Fig. 10

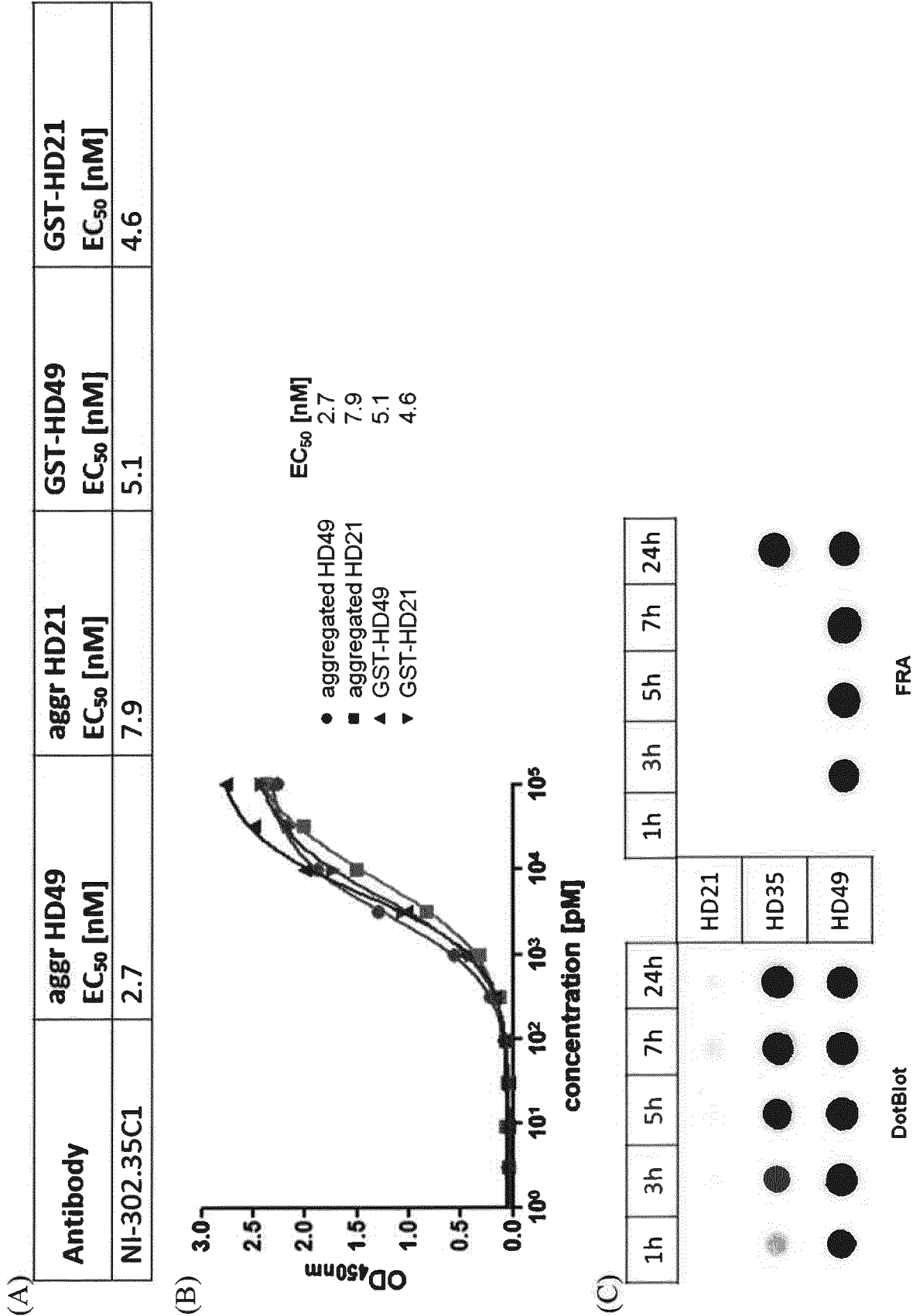
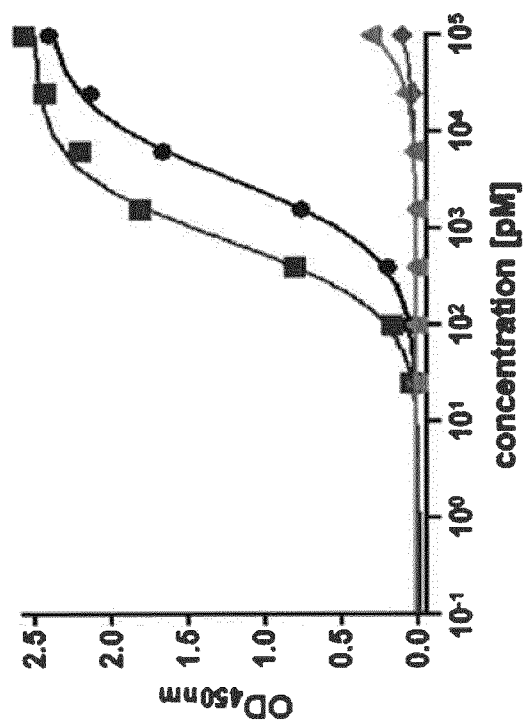


Fig. 11

## Exon 1

[illegible]

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EC50

◆ GST-HD49: 3.2nM  
◆ P-rich peptide: n.a.  
■ C-term peptide 0.7nM  
▲ polyP peptide n.a.

Fig. 12

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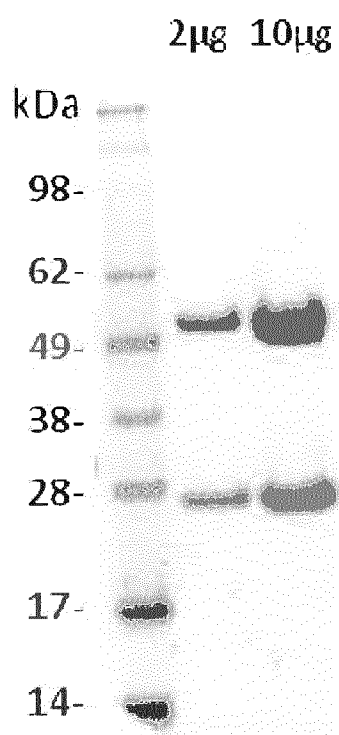
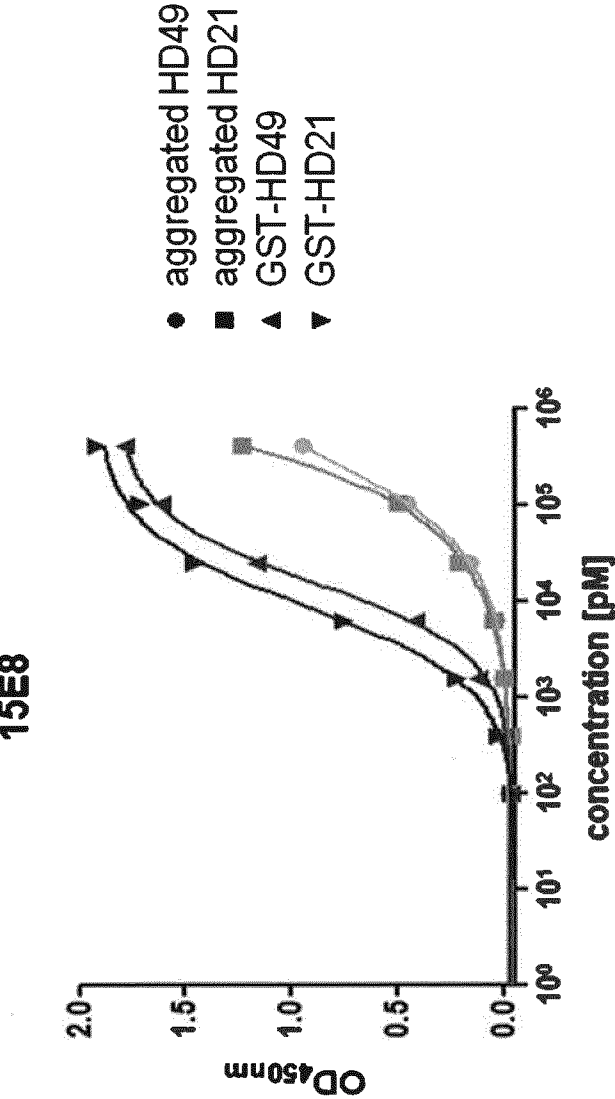


Fig. 13

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Antibody	aggr HD49 EC <sub>50</sub> [nM]	aggr HD21 EC <sub>50</sub> [nM]	GST-HD49 EC <sub>50</sub> [nM]	GST-HD21 EC <sub>50</sub> [nM]
NI302.15E8	>100	>100	15	9.3

(A)



(B)

Fig. 14

## Exon 1

[illegible]

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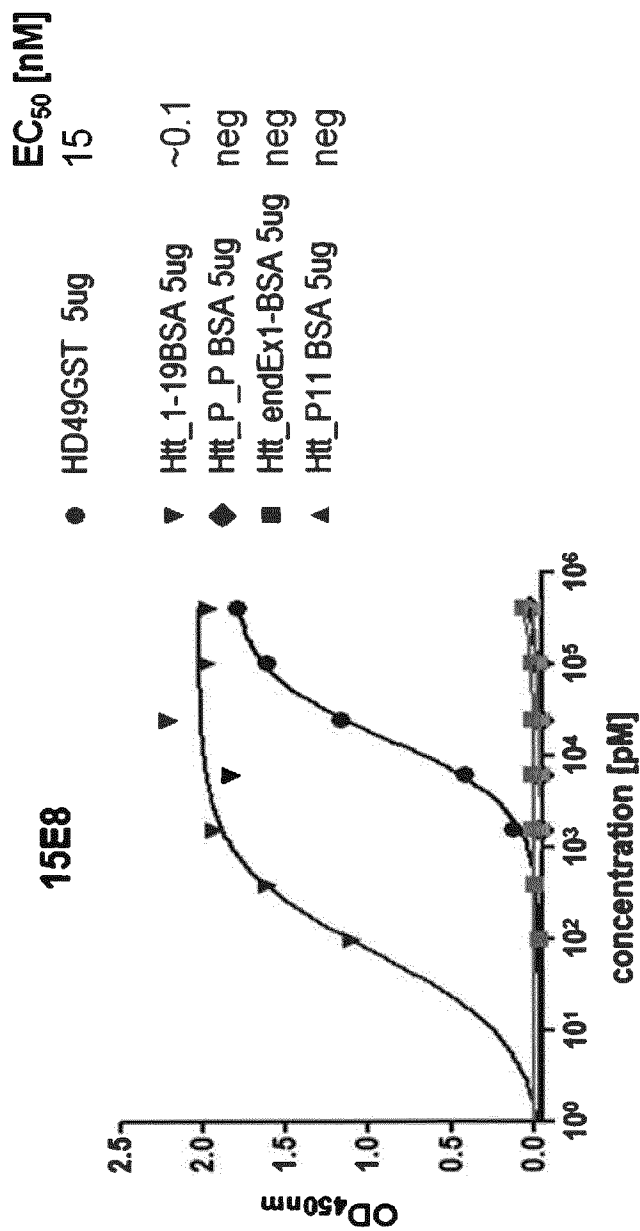


Fig. 15

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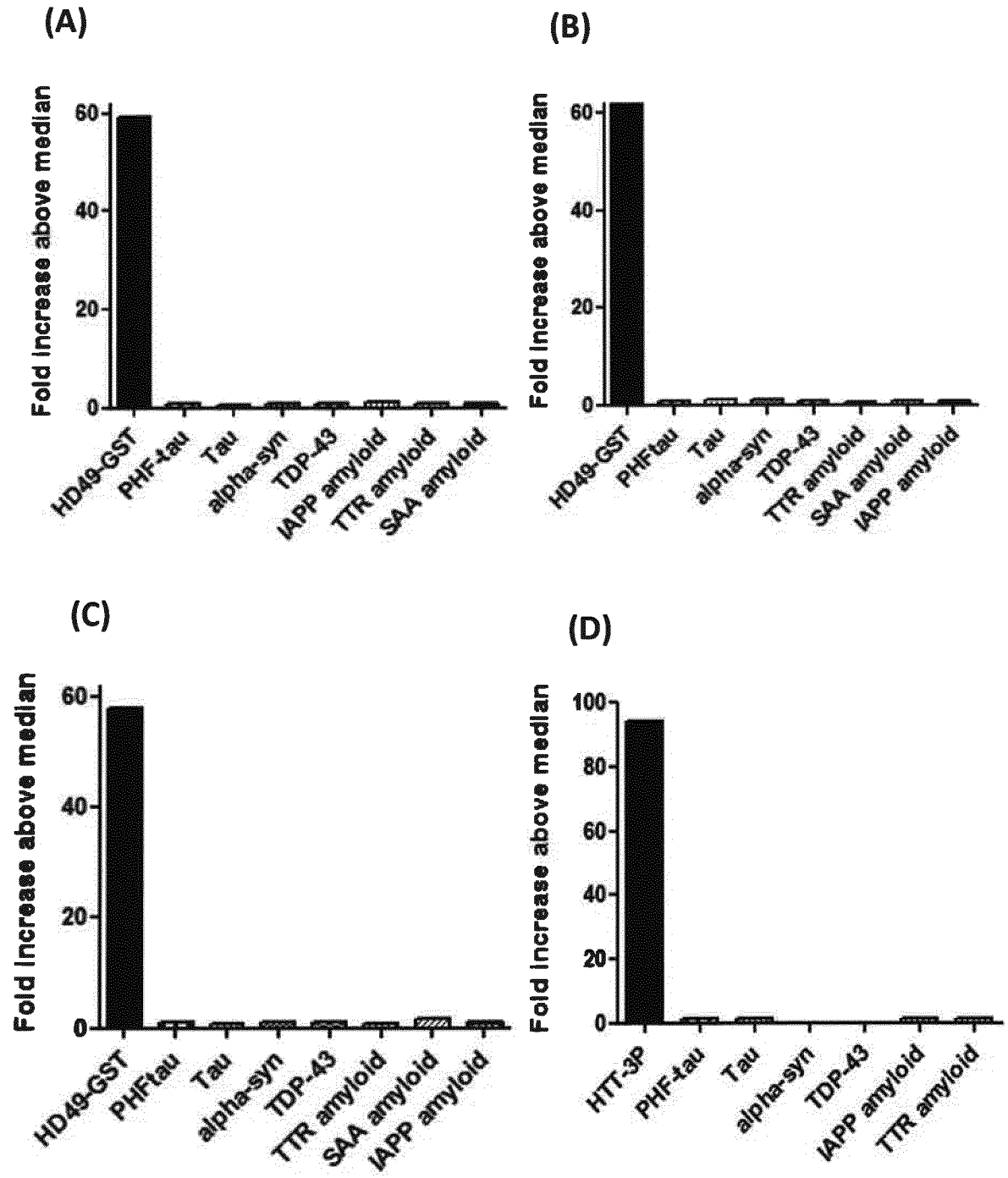


Fig. 16



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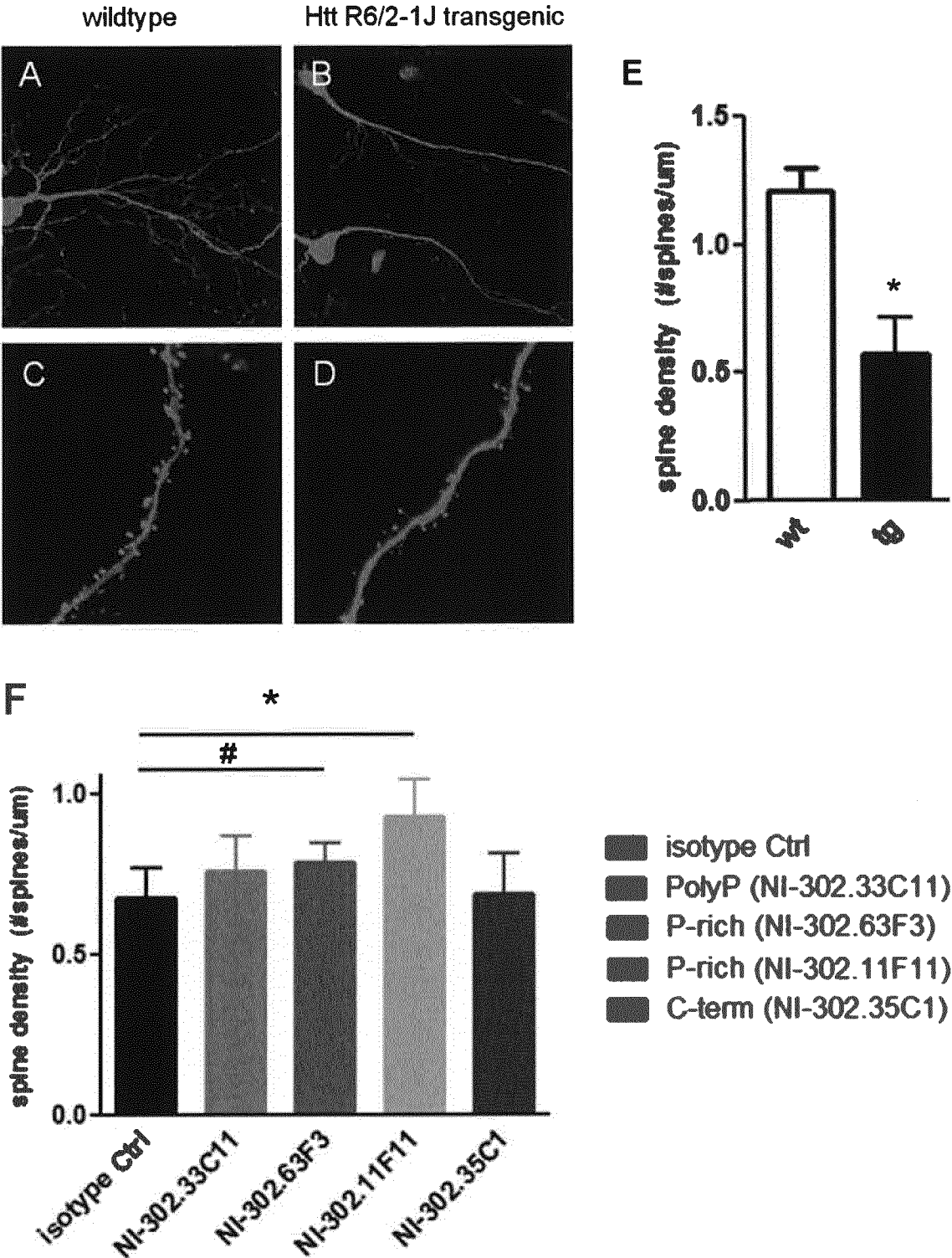
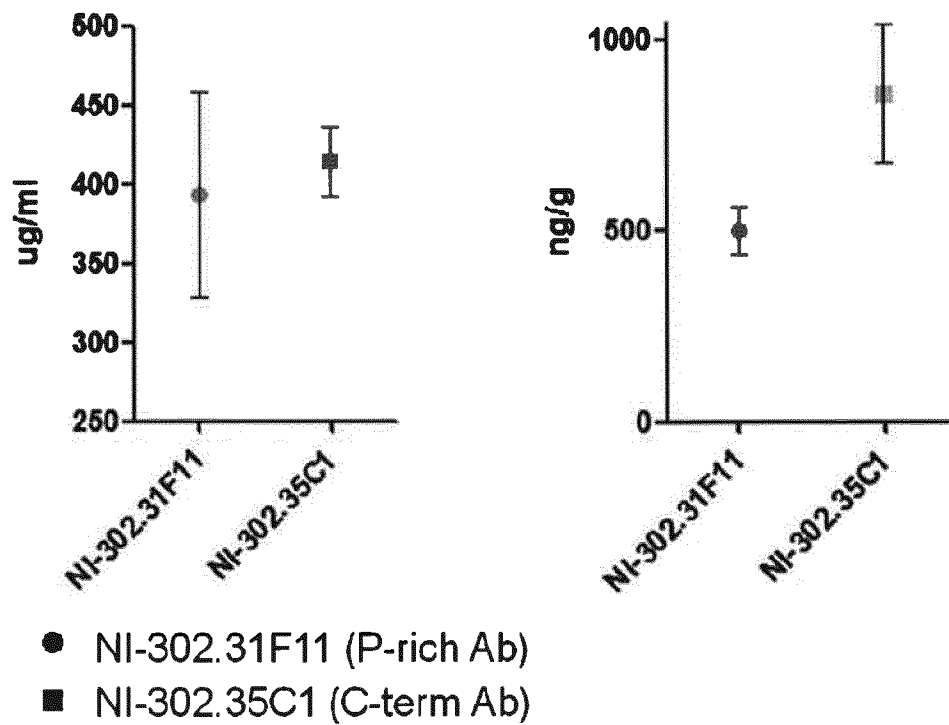


Fig. 17

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(A)



(B)

**Plasma levels**

antibody	Mice			Mean	SD	CV
	$\mu\text{g/ml}$			$\mu\text{g/ml}$	$\mu\text{g/ml}$	%
31F11	265	476	440	394	113	29
35C1	442	431	371	414	38	9

**Brain levels**

antibody	Mice			Mean	SD	CV
	$\text{ng/g}$			$\mu\text{g/ml}$	$\mu\text{g/ml}$	%
31F11	391	504	608	501	109	22
35C1	1222	676	687	861	312	36

**Brain-plasma penetration ratio [%]**

antibody	Mice			Mean	SD	CV
	$\mu\text{g/ml}$			$\mu\text{g/ml}$	$\mu\text{g/ml}$	%
31F11	0.15	0.11	0.14	0.13	0.02	17
35C1	0.28	0.16	0.19	0.21	0.06	30

Fig. 18

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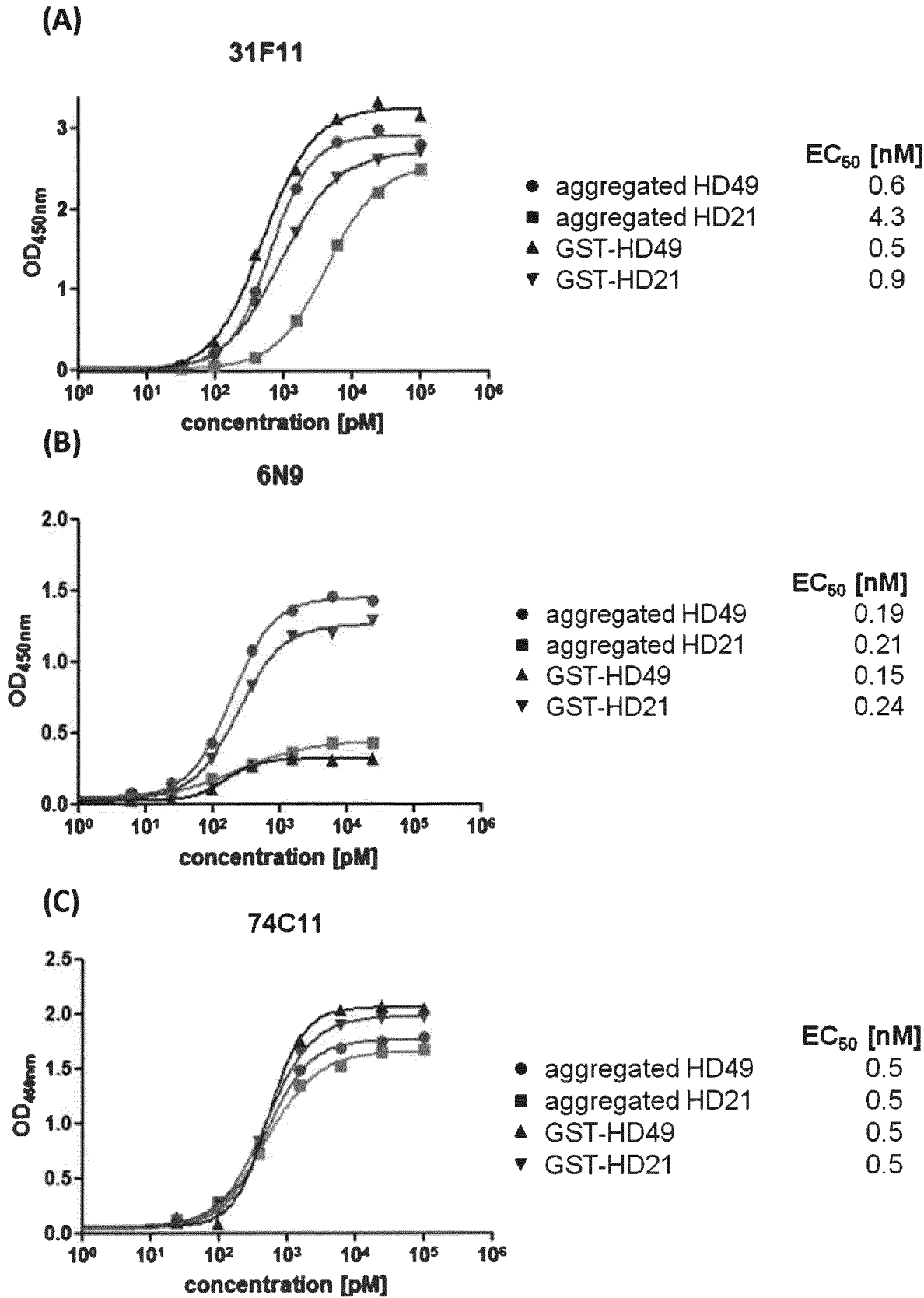


Fig. 19

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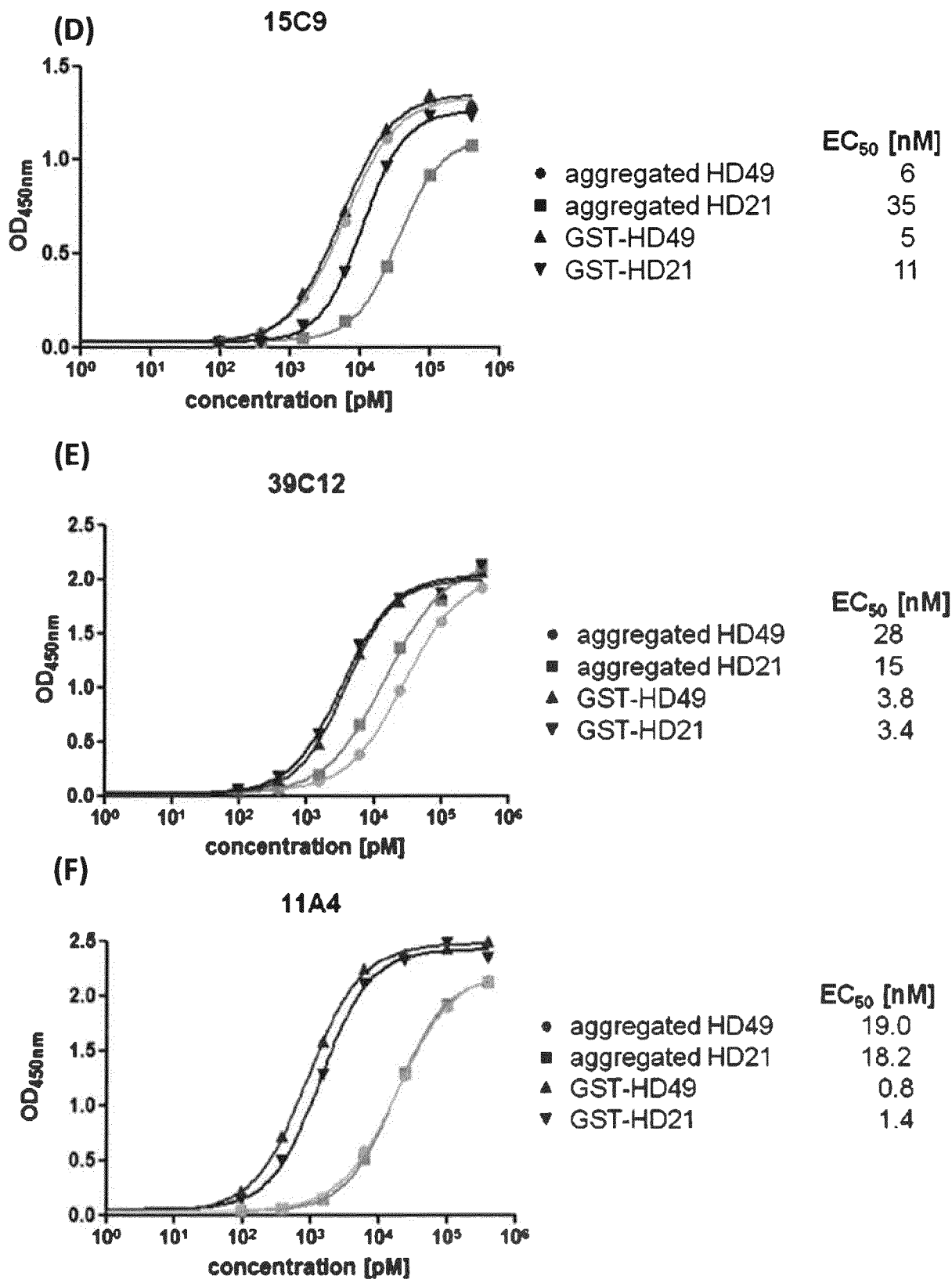


Fig. 19 (continued)

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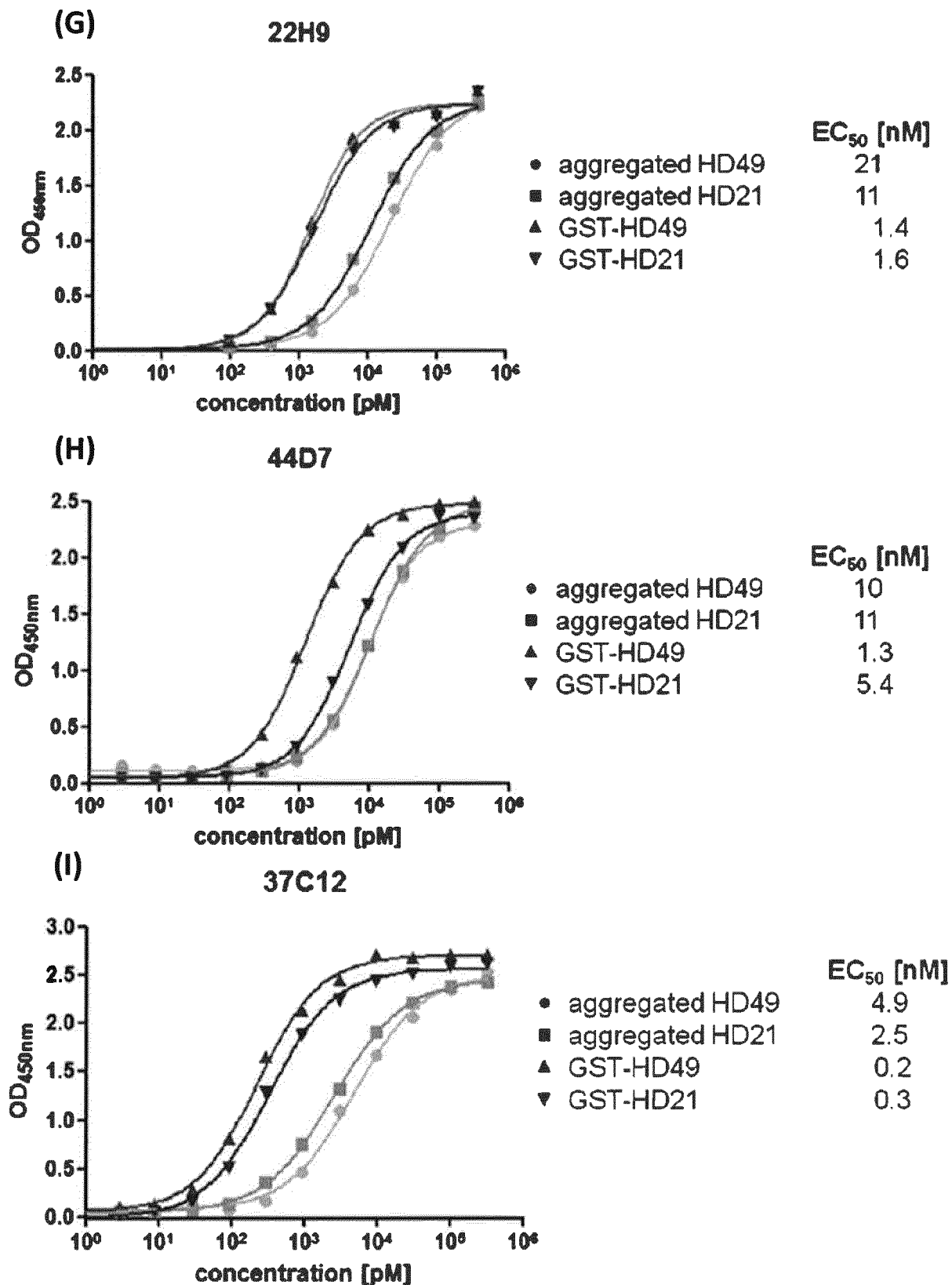


Fig. 19 (continued)

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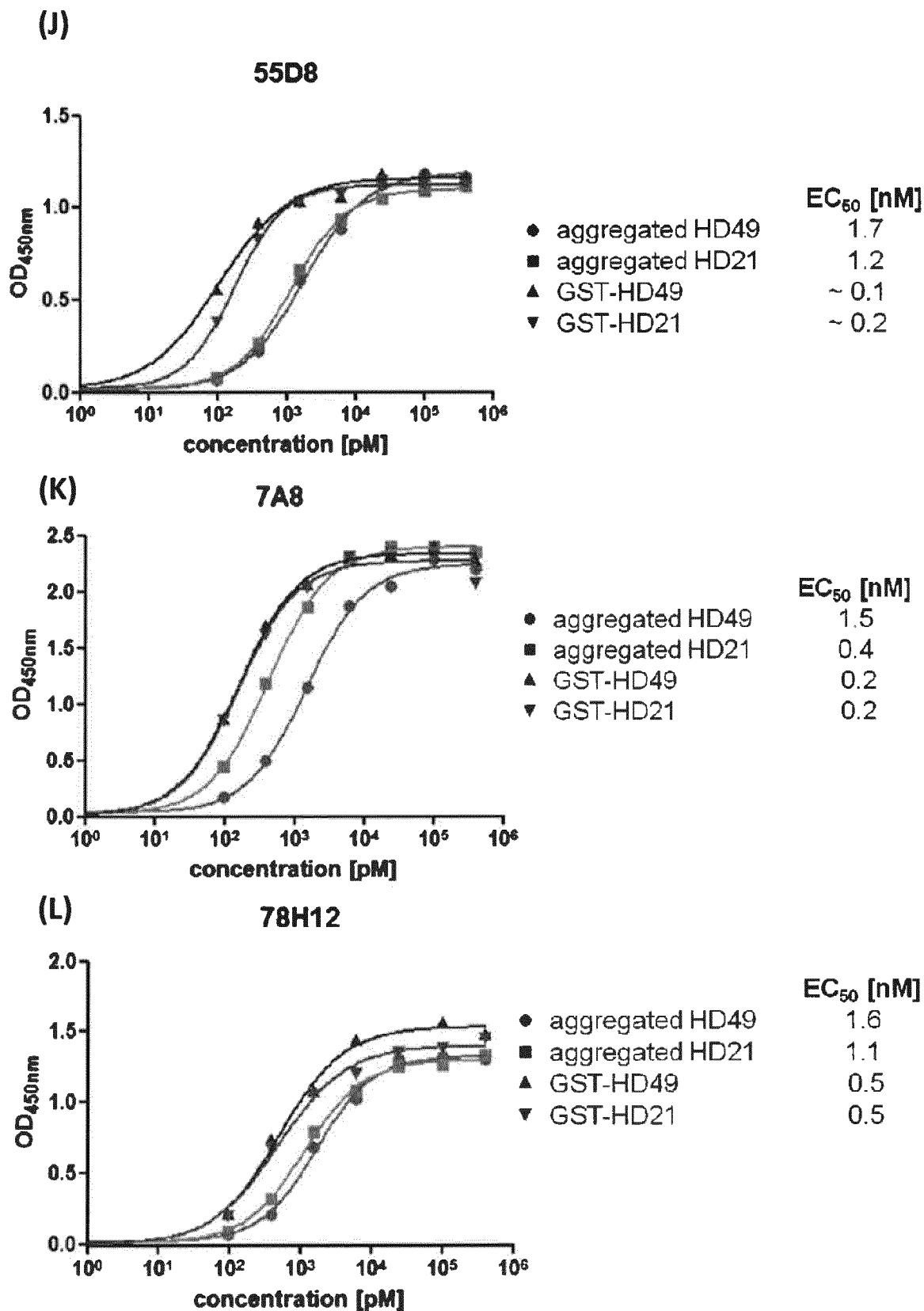


Fig. 19 (continued)

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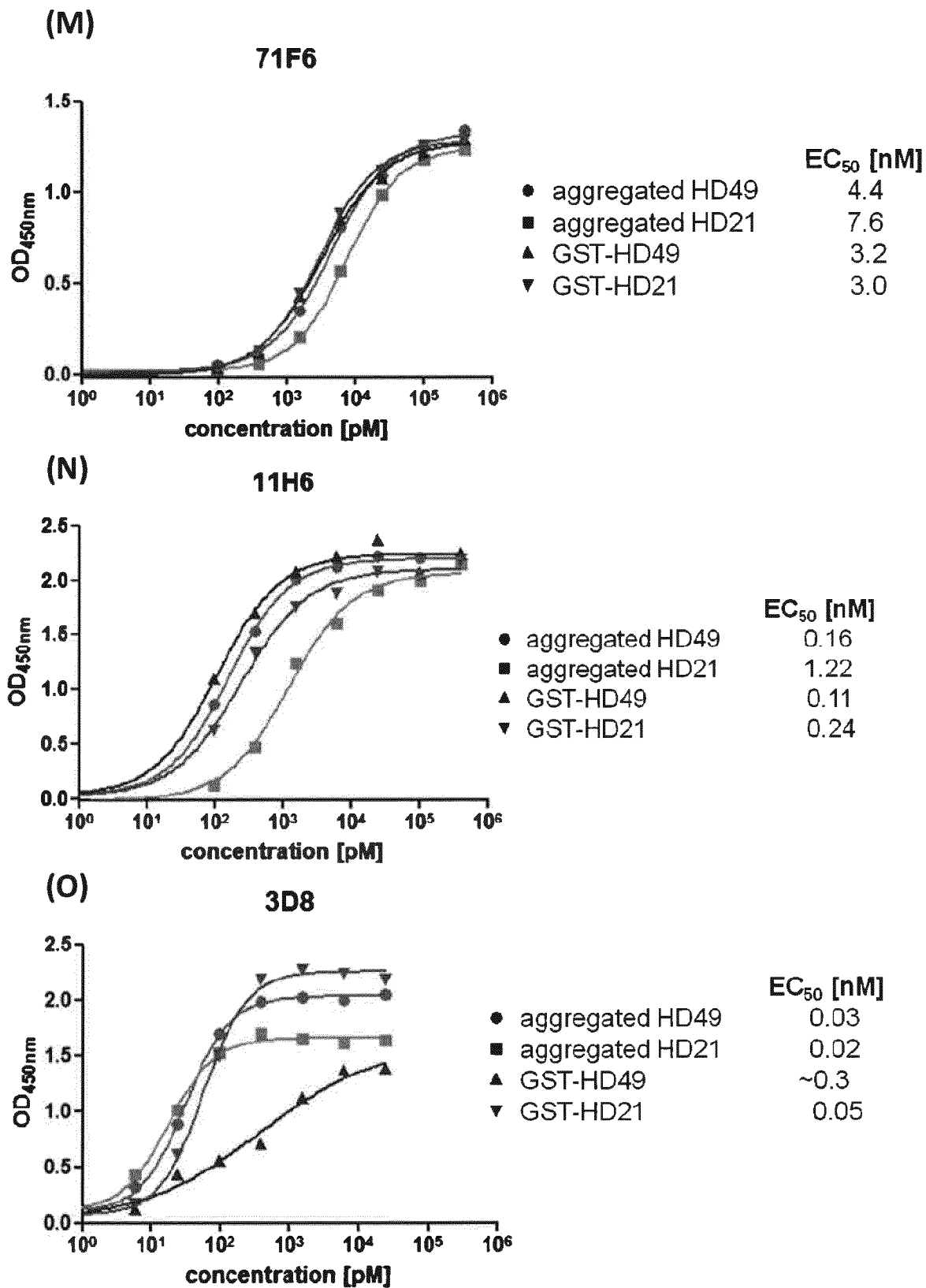
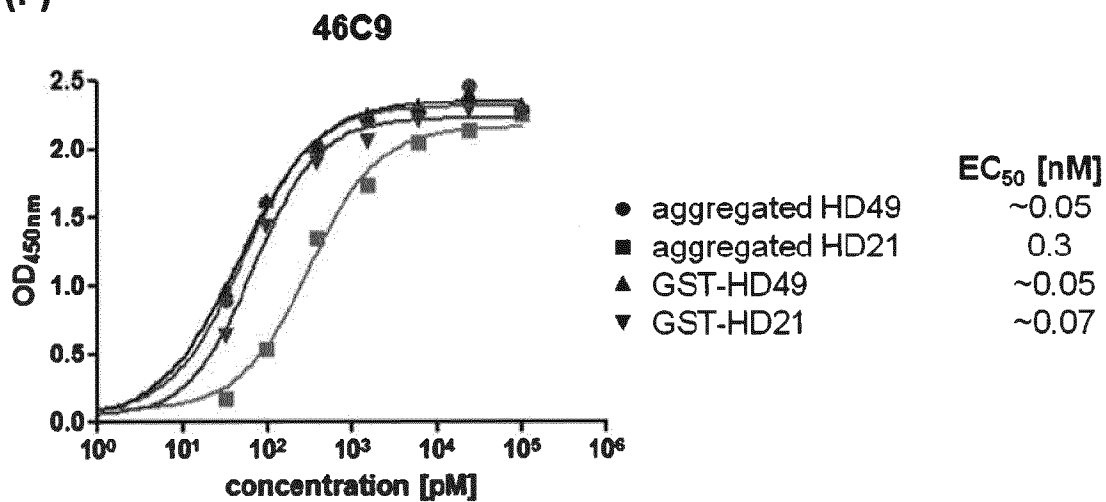


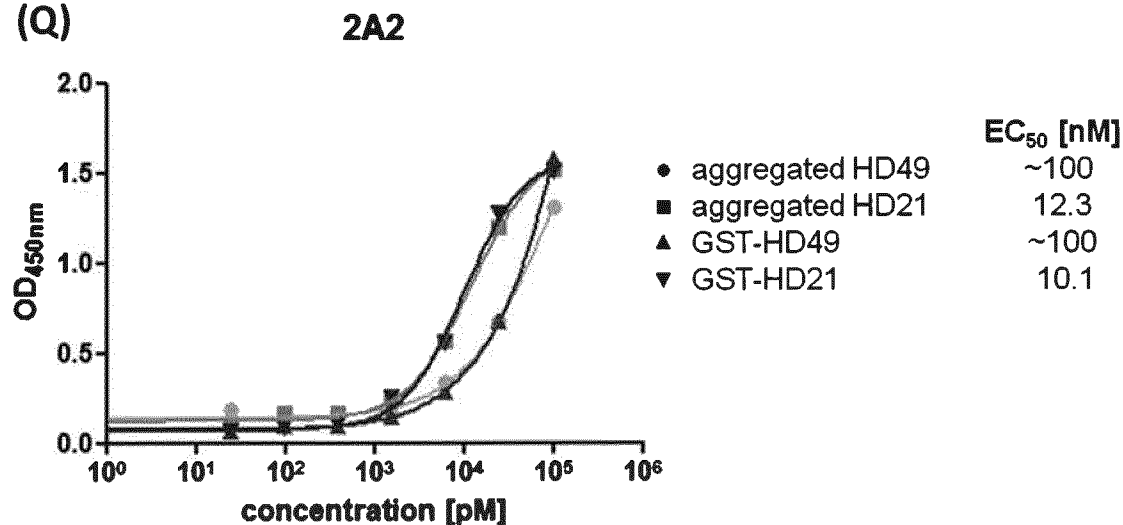
Fig. 19 (continued)

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(P)



(Q)



(R)

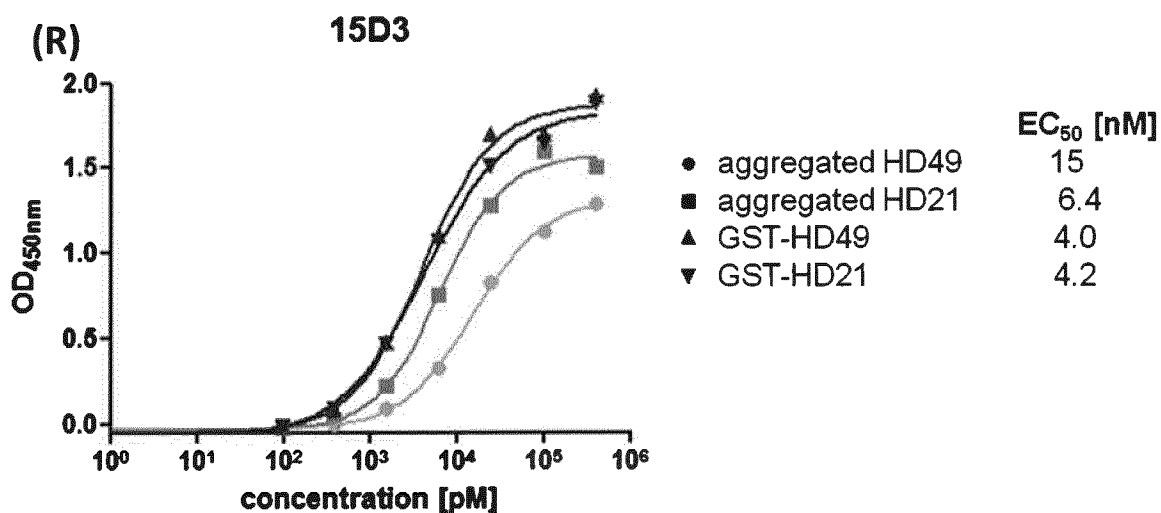


Fig. 19 (continued)



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Antibody	aggr HD49 EC <sub>50</sub> [nM]	aggr HD21 EC <sub>50</sub> [nM]	GST-HD49 EC <sub>50</sub> [nM]	GST-HD21 EC <sub>50</sub> [nM]	peptide EC <sub>50</sub> [nM]	epitope
NI-302.33C11	0.15	0.13	0.13	0.11	0.1 (polyP)	PPPPPPPP
NI-302.63F3	0.4	0.3	0.2	0.2	0.3 (P-rich)	PQPPPPQAQPL (P-rich)
NI-302.31F11	0.6	4.3	0.5	0.9	0.5 (P-rich)	PPPQLPQPPP (P-rich)
NI-302.2A2	>100	12.3	>100	10.1	1.4 (P-rich)	QAQPLLPQPPPPPP (P-rich)
NI-302.15D3	15	6.4	4.0	4.2	1.2 (P-rich)	PPPQLPQPPPPQAQPL (P-rich)
NI-302.35C1	2.7	7.9	5.1	4.6	0.7 (endEx1)	PPGPAVAEEPLHRP (endEx1)
NI302.15E8	>100	>100	15	9.3	0.1 (N-term)	KAFESLKSFQQ (N-term)
NI-302.64E5	1.6	0.7	0.05	1.4	0.1 (P-rich)	PQPPPPQAQPL (P-rich)
NI-302.7D8	17	>100	6	51	n.d. (Q/P)	QQQQQQQPPP (polyQ/P)
NI-302.72F10	26	4	>100	10	0.1 (endEx1)	PPPGPAVAEEPLH (endEx1)
NI-302.4A6	3	3	6	3	neg.	no signal on linear peptide
NI-302.12H2	0.04	0.05	0.04	0.04	neg.	no signal on linear peptide
NI-302.8M1	0.003	0.002	0.003	0.002	neg.	no signal on linear peptide
NI-302.6N9	0.19	0.21	0.15	0.24	neg.	no signal on linear peptide
NI-302.74C11	0.5	0.5	0.5	0.5	n.d.	PPPPPPPPPP
NI-302.15F9	6	35	5	11	n.d.	PPPPPPPPPP

Fig. 20

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Antibody	aggr HD49 EC50 [nM]	aggr HD21 EC50 [nM]	GST-HD49 EC50 [nM]	GST-HD21 EC50 [nM]	peptide EC50 [nM]	epitope
NI-302.39G12	28	15	3.8	3.4	n.d.	PPPPPPPPPPPP
NI-302.11A4	19	18	0.8	1.4	n.d.	PPPPPPPPPPPP
NI-302.22H9	22	11	1.4	1.6	n.d.	PPPPPPPPPPPP
NI-302.44D7	10	11	1.2	5.4	n.d.	PPPPPPPPPP
NI-302.37C12	4.9	2.5	0.23	0.33	n.d.	PPPPPPPPPPPP
NI-302.55D8	1.7	1.2	0.1	0.2	n.d.	PPPPPPPPPPPP
NI-302.7A8	1.5	0.4	0.2	0.2	n.d.	PPPPPPPPPP
NI-302.78H12	1.6	1.1	0.5	0.5	n.d.	PPPPPPPPPPPP
NI-302.71F6	4.4	7.6	3.2	3.0	n.d.	PPPPPPPPPPPP
NI-302.11H6	0.2	1.2	0.1	0.2	n.d.	PPPPPPPP
NI-302.3D8	0.03	0.02	0.3	0.05	n.d.	PPPPPPPPPP
NI-302.18A1	0.03	0.02	0.07	0.04	n.d.	PPPPPPPP
NI-302.8F1	1.9	1.6	0.4	0.8	n.d.	polyP
NI-302.52C9	30	28	4.9	10.2	n.d.	PPPPPPPP
NI-302.46C9	0.05	0.3	0.05	0.07	n.d.	PPPPPPPPPP

Fig. 20 (continued)

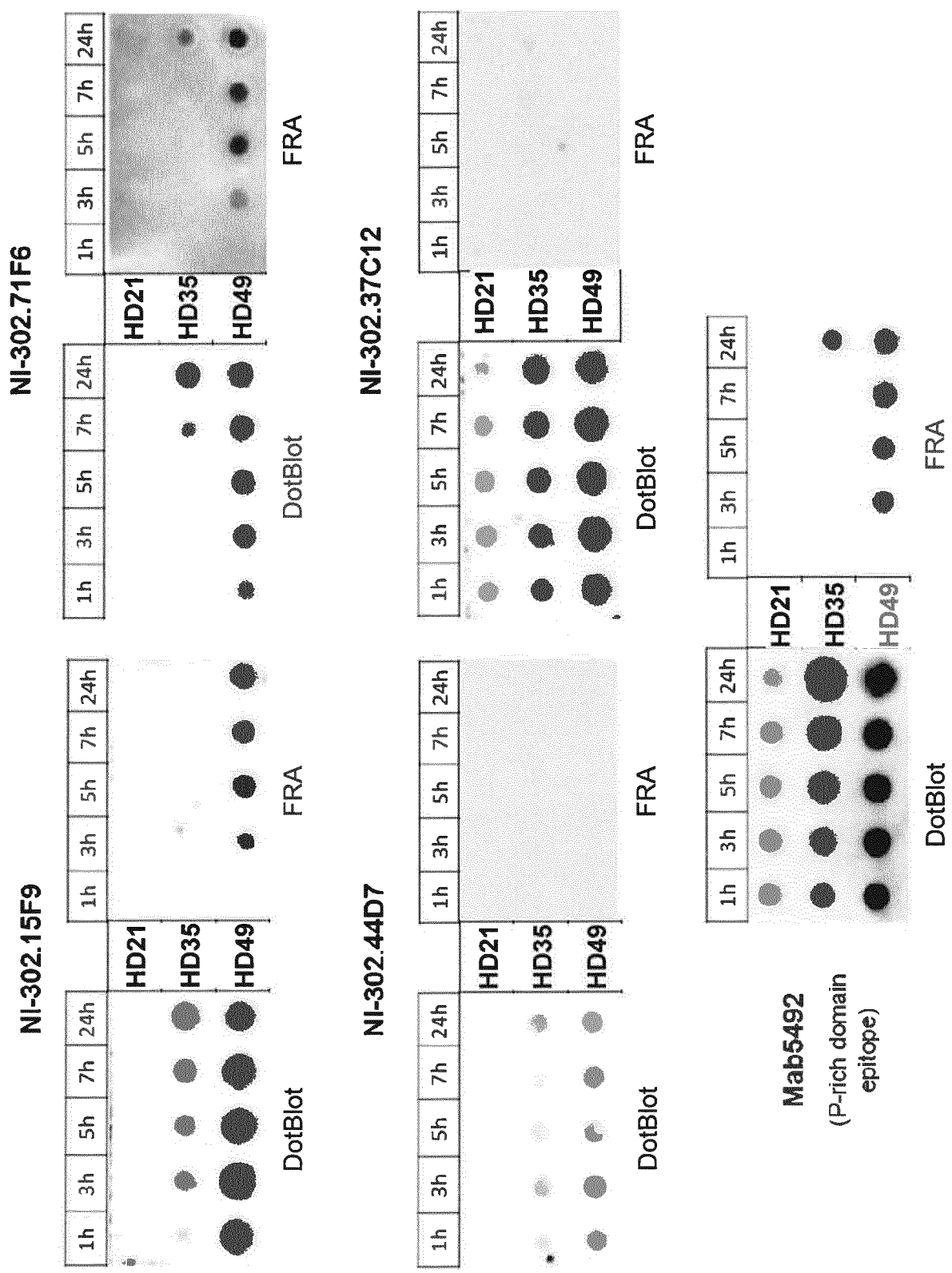


Fig. 21

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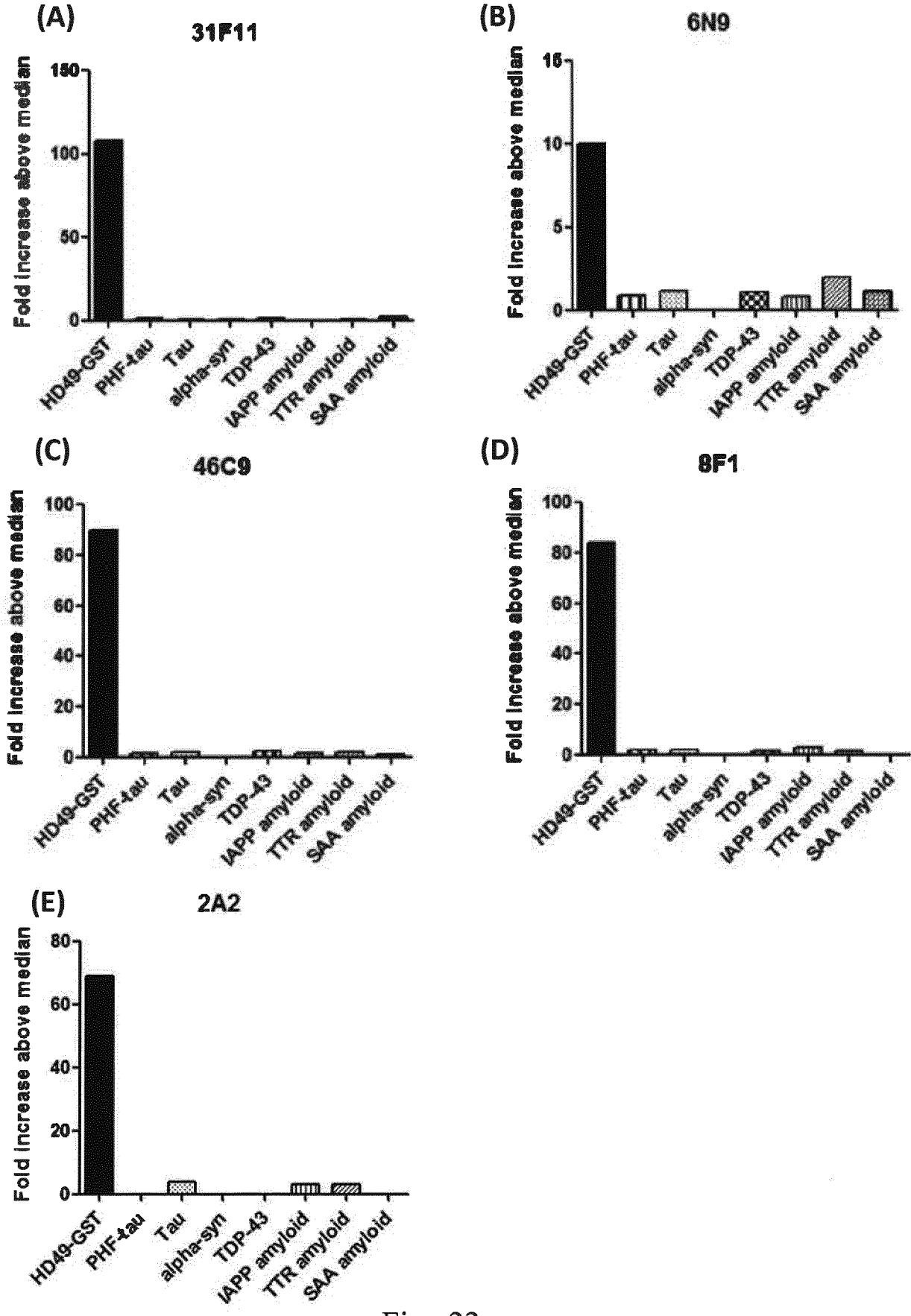


Fig. 22

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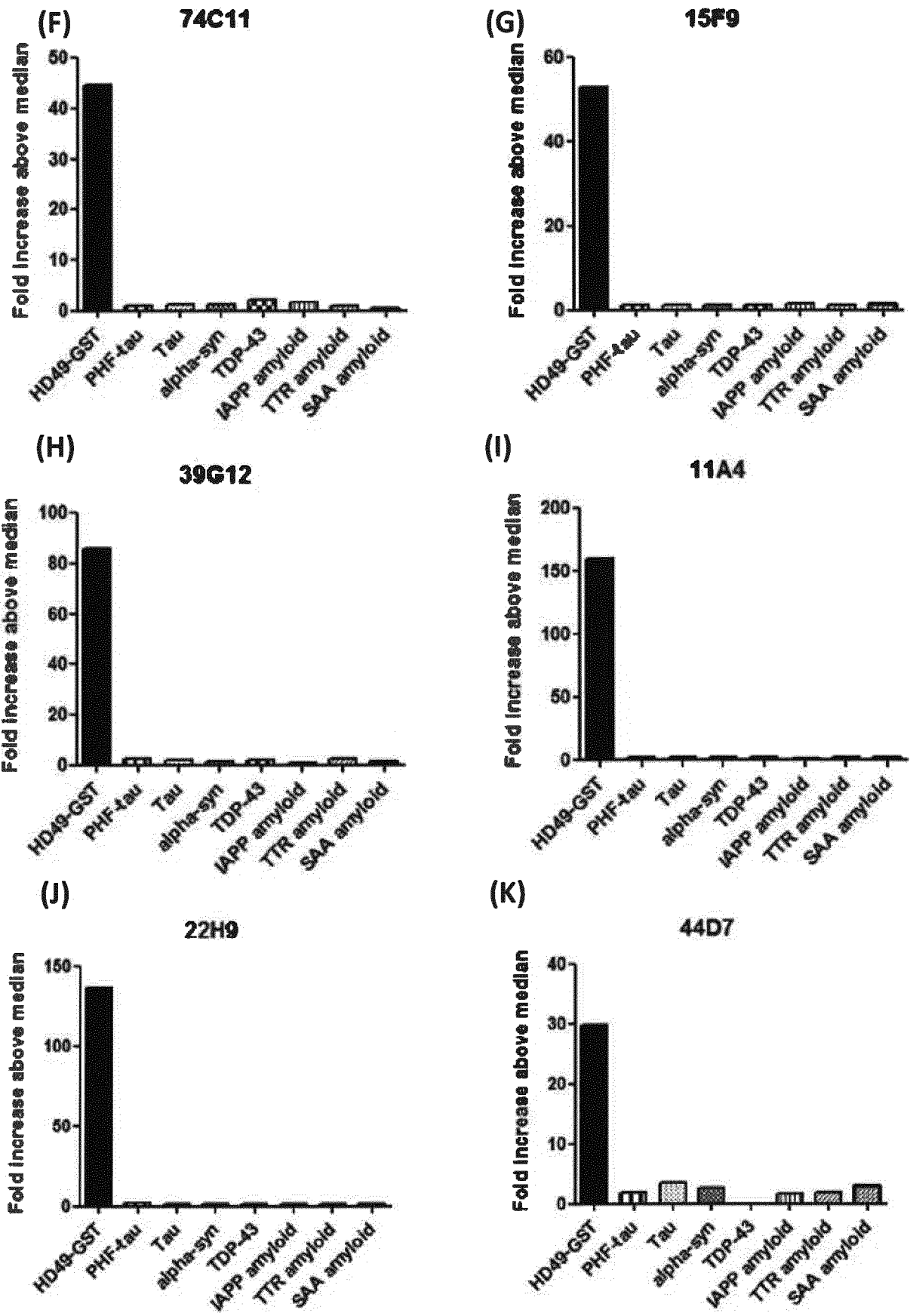


Fig. 22 (continued)

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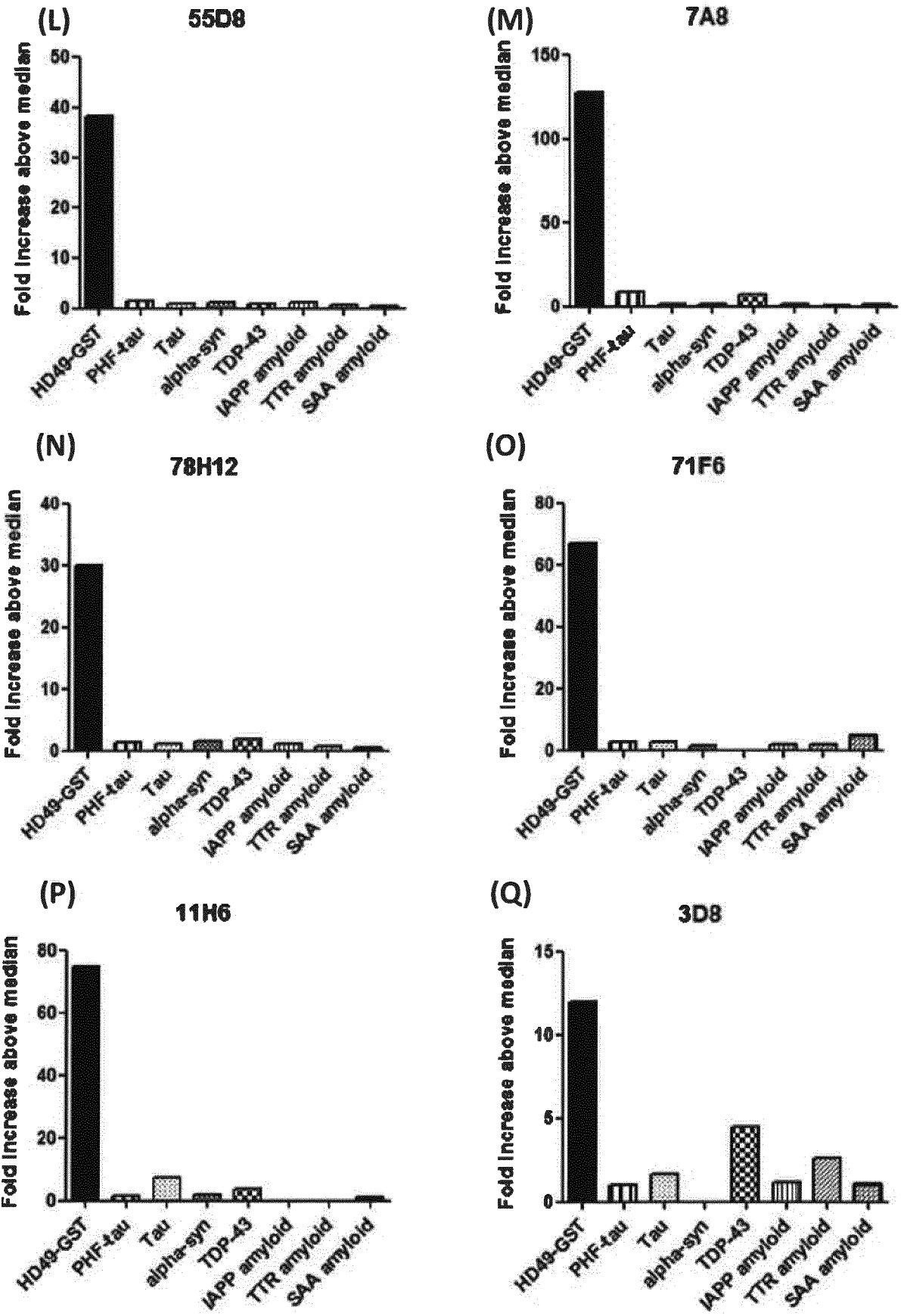
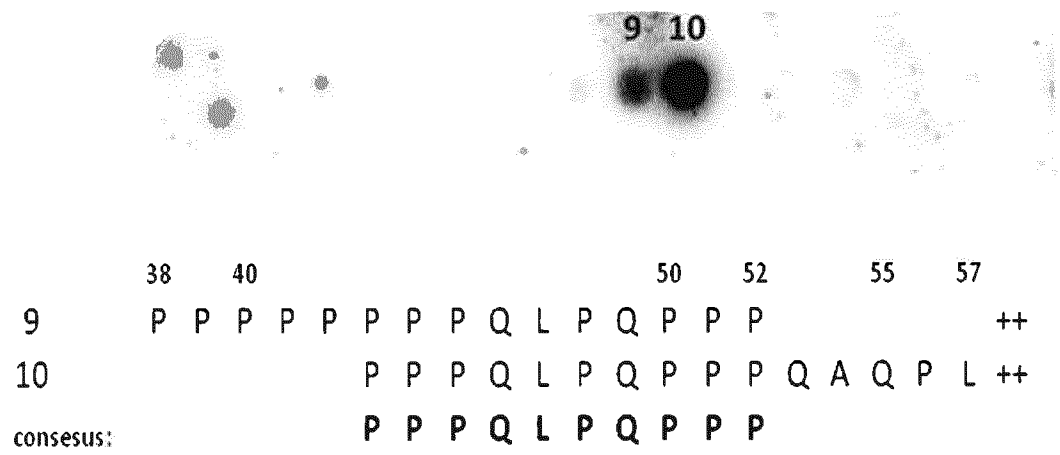


Fig. 22 (continued)

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(A)

NI-302.31F11 1μg/ml (21 Spot membrane)



(B)

NI-302.74C11 1μg/ml (16 Spot membrane)

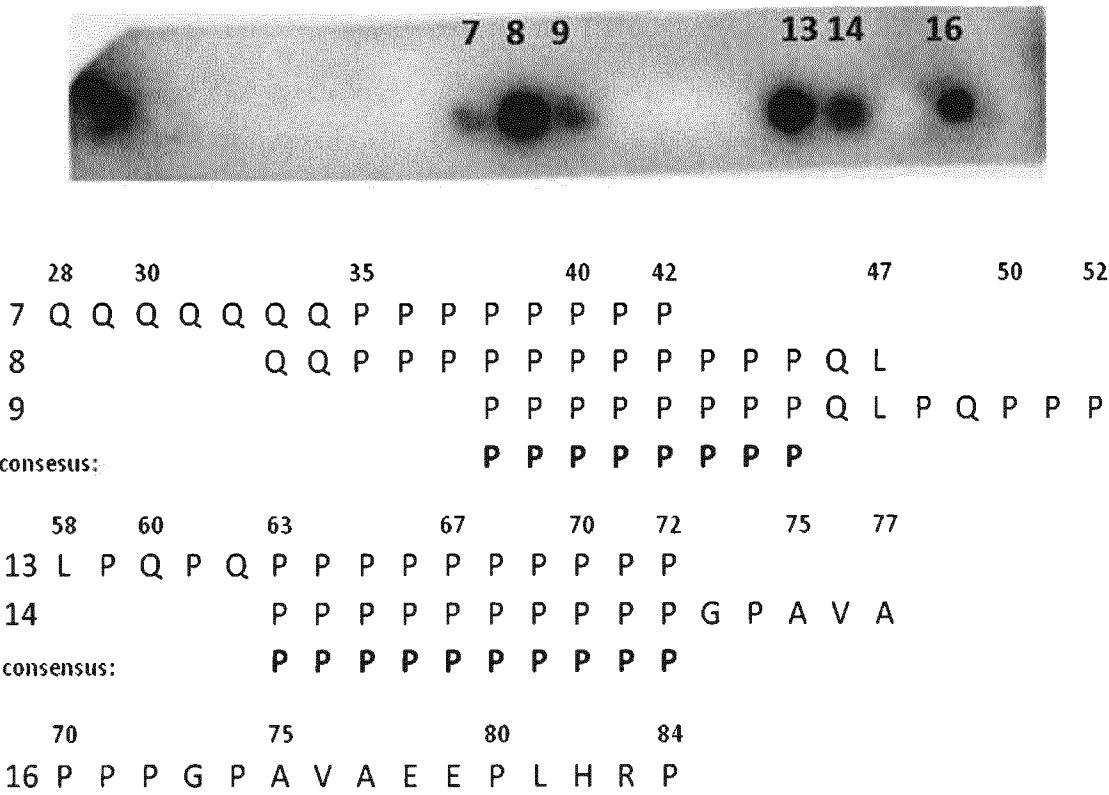
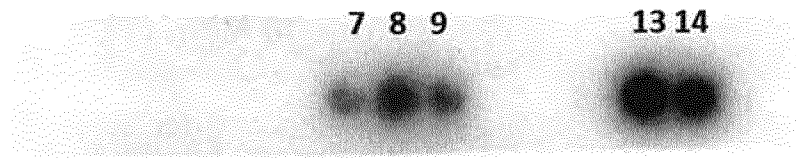


Fig. 23

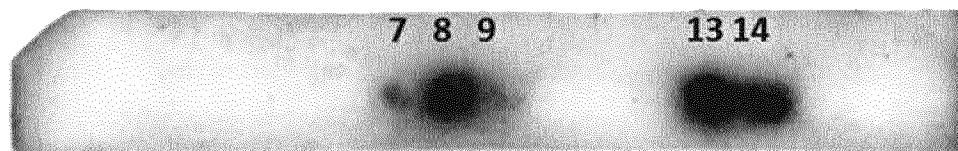
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**(C) NI-302.15F9 1µg/ml (16 Spot membrane)**

	28	30		35		40	42		47		50	52
7	Q	Q	Q	Q	Q	Q	P	P	P	P	P	P
8				Q	Q	P	P	P	P	P	P	P
9							P	P	P	P	P	P
consensus:				P	P	P	P	P	P	P	P	P

	58	60		63		67		70	72		75	77
13	L	P	Q	P	Q	P	P	P	P	P	P	P
14				P	P	P	P	P	P	P	G	P
consensus:				P	P	P	P	P	P	P	P	P

**(D) NI-302.39G12 1µg/ml (16 Spot membrane)**

	28	30		35		40	42		47		50	52
7	Q	Q	Q	Q	Q	Q	P	P	P	P	P	P
8				Q	Q	P	P	P	P	P	P	P
9							P	P	P	P	P	P
consensus:				P	P	P	P	P	P	P	P	P

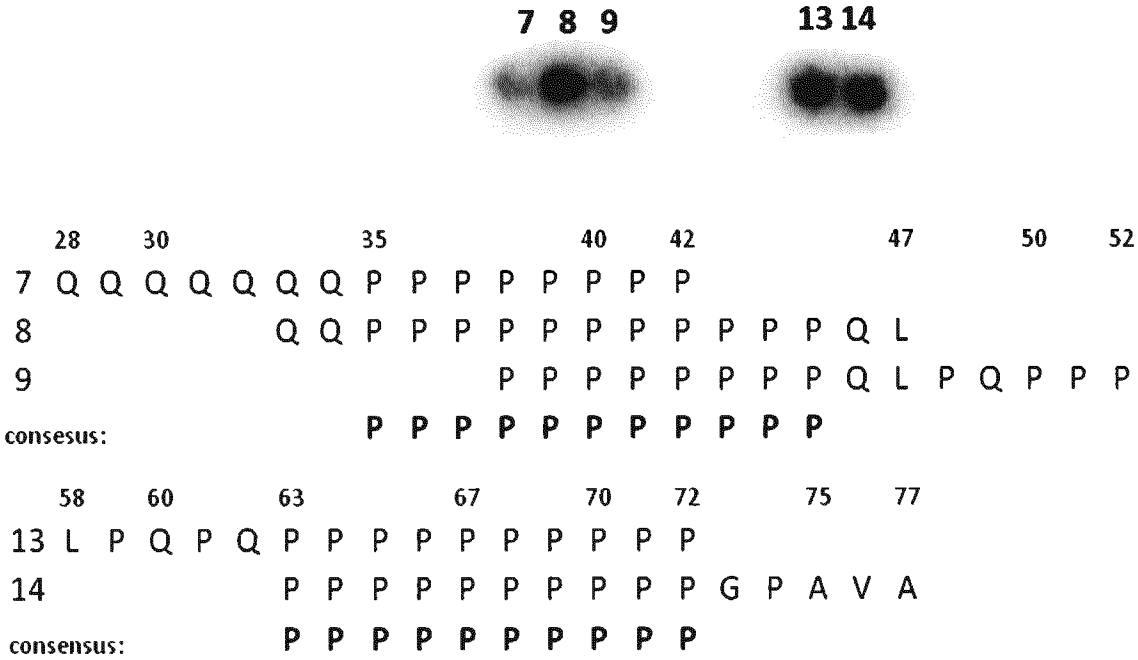
	58	60		63		67		70	72		75	77
13	L	P	Q	P	Q	P	P	P	P	P	P	P
14				P	P	P	P	P	P	P	G	P
consensus:				P	P	P	P	P	P	P	P	P

Fig. 23 (continued)



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(E) NI-302.11A4 1µg/ml (16 Spot membrane)



(F) NI-302.22H9 1µg/ml (16 Spot membrane)

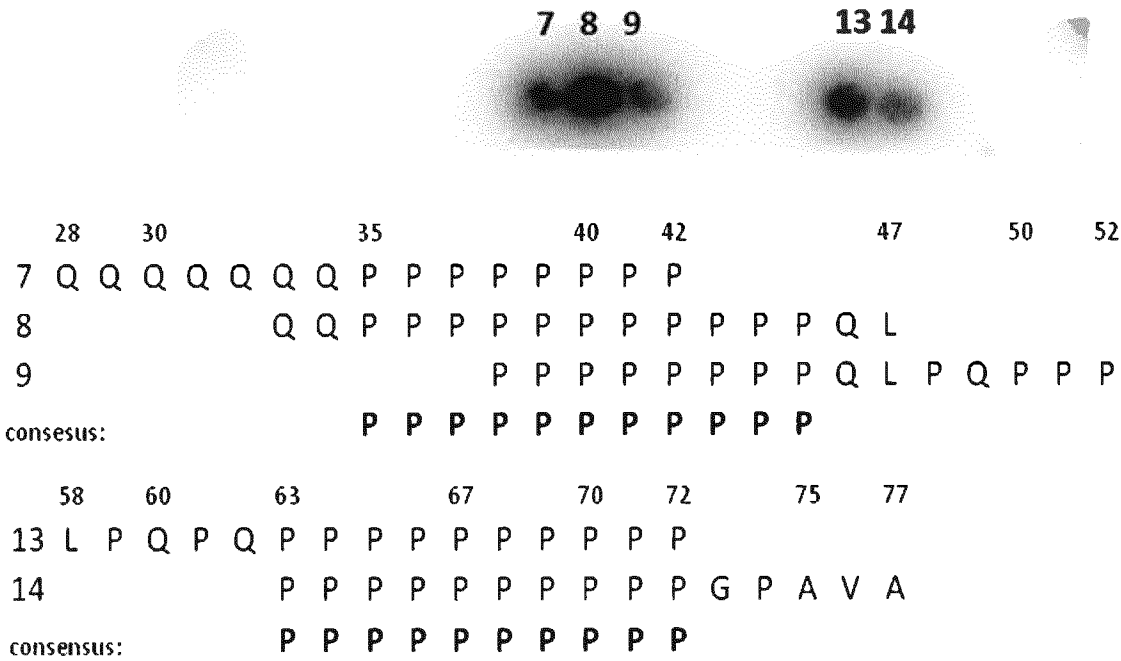
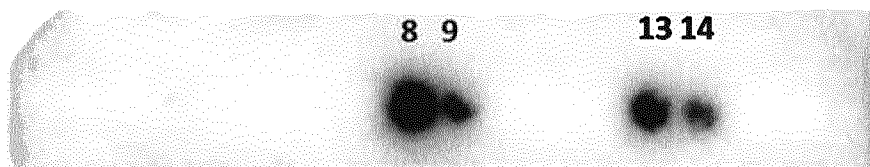


Fig. 23 (continued)

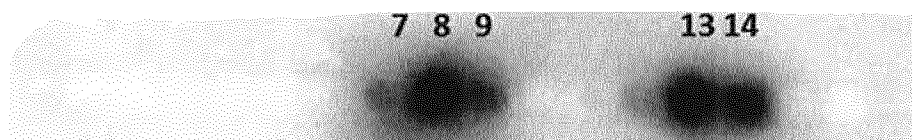
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**(G)** NI-302.44D7 1µg/ml (16 Spot membrane)

	33	35		40	42		47	50	52	
8	Q	Q	P	P	P	P	P	P	Q	L
9				P	P	P	P	P	Q	L
consensus:				P	P	P	P	P	Q	L

	58	60		63		67		70	72	75	77
13	L	P	Q	P	Q	P	P	P	P	P	P
14				P	P	P	P	P	P	P	G
consensus:				P	P	P	P	P	P	P	P

**(H)** NI-302.37C12 1µg/ml (16 Spot membrane)

	28	30		35		40	42		47	50	52
7	Q	Q	Q	Q	Q	P	P	P	P	P	P
8				Q	Q	P	P	P	P	P	Q
9						P	P	P	P	P	Q
consensus:				P	P	P	P	P	P	P	P

	58	60		63		67		70	72	75	77
13	L	P	Q	P	Q	P	P	P	P	P	P
14				P	P	P	P	P	P	P	G
consensus:				P	P	P	P	P	P	P	P

Fig. 23 (continued)

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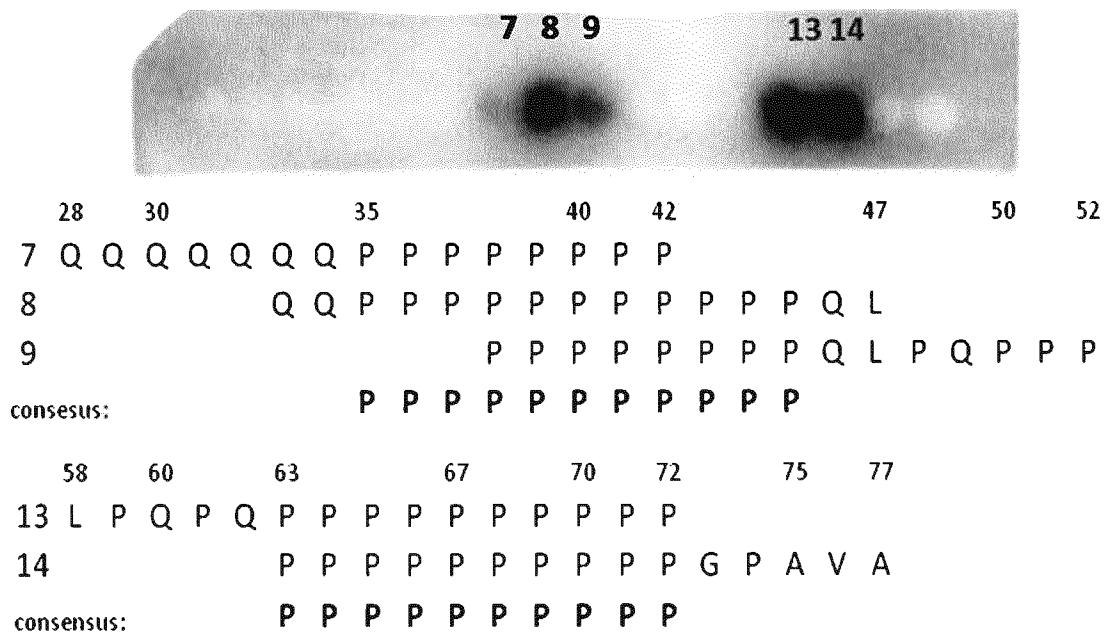
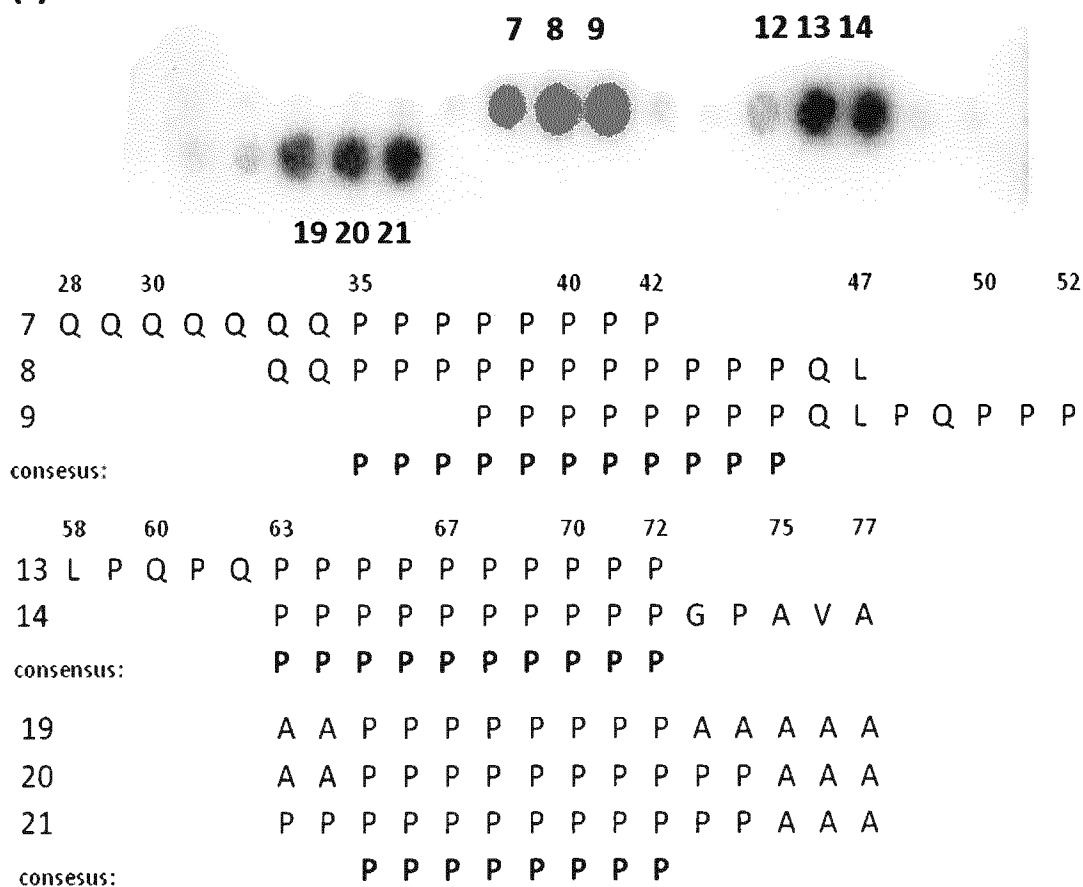
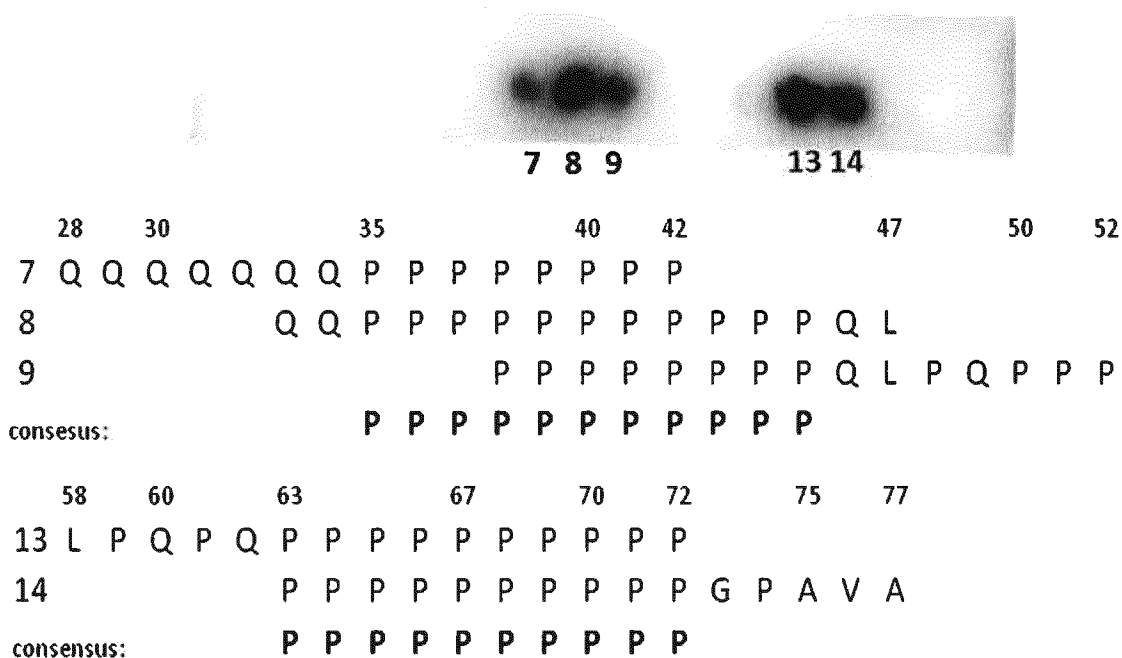
(I) 55D8 1 $\mu$ g/ml (16 Spot membrane)(J) 7A8 1 $\mu$ g/ml (21 Spot membrane)

Fig. 23 (continued)

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(K)

NI-302.78H12 1 $\mu$ g/ml (16 Spot membrane)

(L)

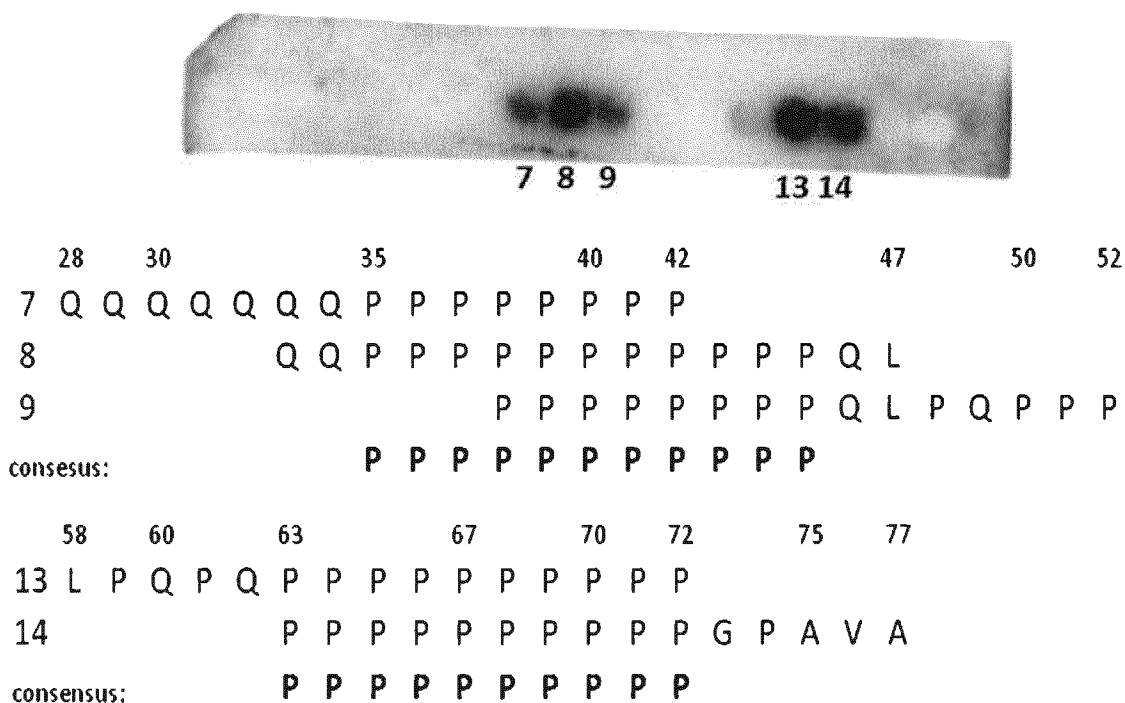
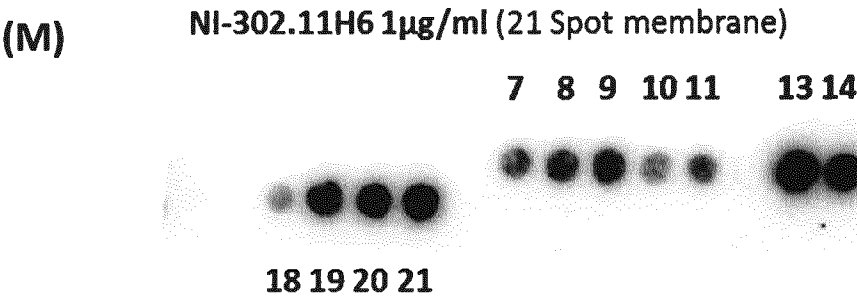
NI-302.71F6 1 $\mu$ g/ml (16 Spot membrane)

Fig. 23 (continued)

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	28	30				35				40	42		47		50	52		55	57		60	62								
7	Q	Q	Q	Q	Q	Q	P	P	P	P	P	P	P	P																
8						Q	Q	P	P	P	P	P	P	P	P	Q	L													
9									P	P	P	P	P	P	P	Q	L	P	Q	P	P	P								
10											P	P	P	Q	L	P	Q	P	P	P	Q	A	Q	P	L					
11																P	Q	P	P	P	Q	A	Q	P	L	L	P	Q	P	Q
consensus:							P	P	P	P	P	P	P	Q	L	P	Q	P	P	P										

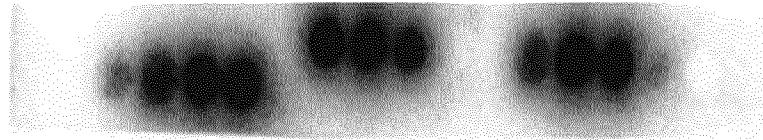
	58	60		63			67		70	72		75	77			
13	L	P	Q	P	Q	P	P	P	P	P	P	P	P			
14				P	P	P	P	P	P	P	P	G	P	A	V	A
consensus:				P	P	P	P	P	P	P	P					

18				A	A	P	P	P	P	P	P	A	A	A	A	A	A
19				A	A	P	P	P	P	P	P	P	A	A	A	A	A
20				A	A	P	P	P	P	P	P	P	P	A	A	A	A
21				P	P	P	P	P	P	P	P	P	P	A	A	A	A
consensus:				P	P	P	P	P	P	P	P						

Fig. 23 (continued)

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(N) NI-302.18A1 1µg/ml (21 Spot membrane)



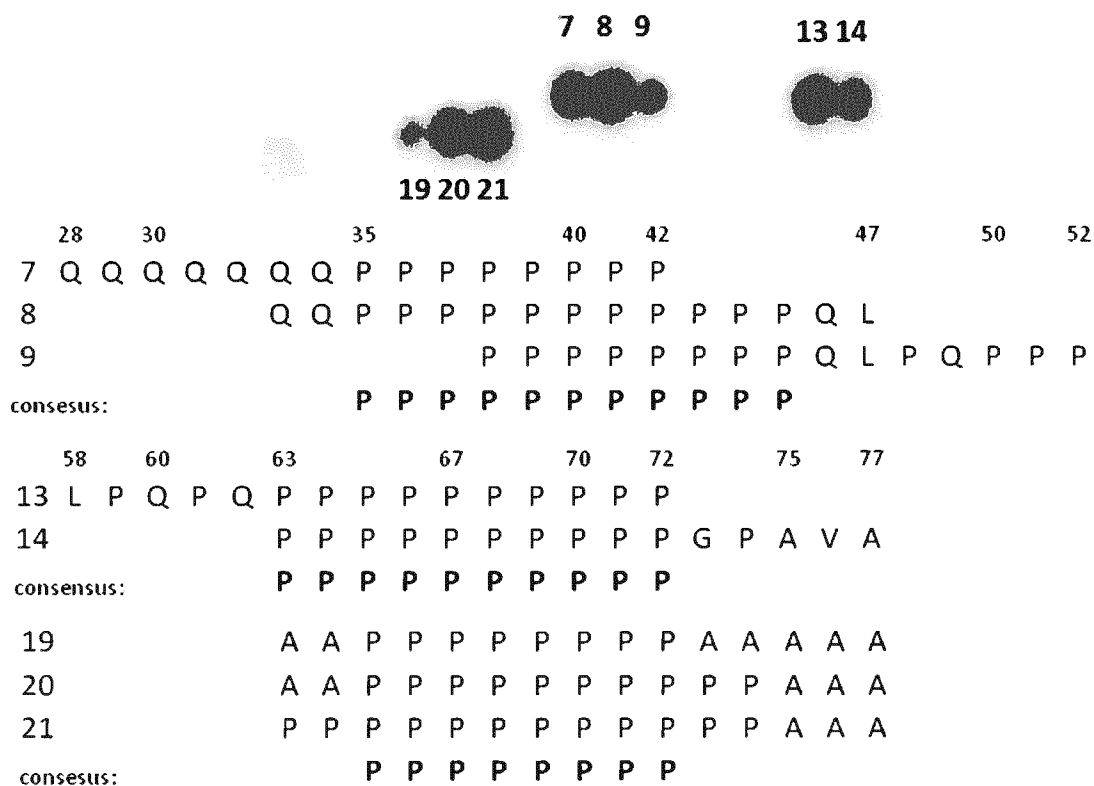
18 19 20 21

	28	30		35		40	42		47	50	52
7	Q	Q	Q	Q	Q	P	P	P	P	P	P
8				Q	Q	P	P	P	P	P	P
9							P	P	P	P	P
consensus:							P	P	P	P	P
	53		58	60	63		67	70	72	75	77
12	Q	A	Q	P	L	L	P	Q	P	Q	P
13			L	P	Q	P	Q	P	P	P	P
14						P	P	P	P	P	P
consensus:						P	P	P	P	P	P
18			A	A	P	P	P	P	P	A	A
19			A	A	P	P	P	P	P	P	A
20			A	A	P	P	P	P	P	P	A
21			P	P	P	P	P	P	P	P	A
consensus:			P	P	P	P	P	P	P	P	P

Fig. 23 (continued)

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(O)

NI-302.3D8 1 $\mu$ g/ml (21 Spot membrane)

(P)

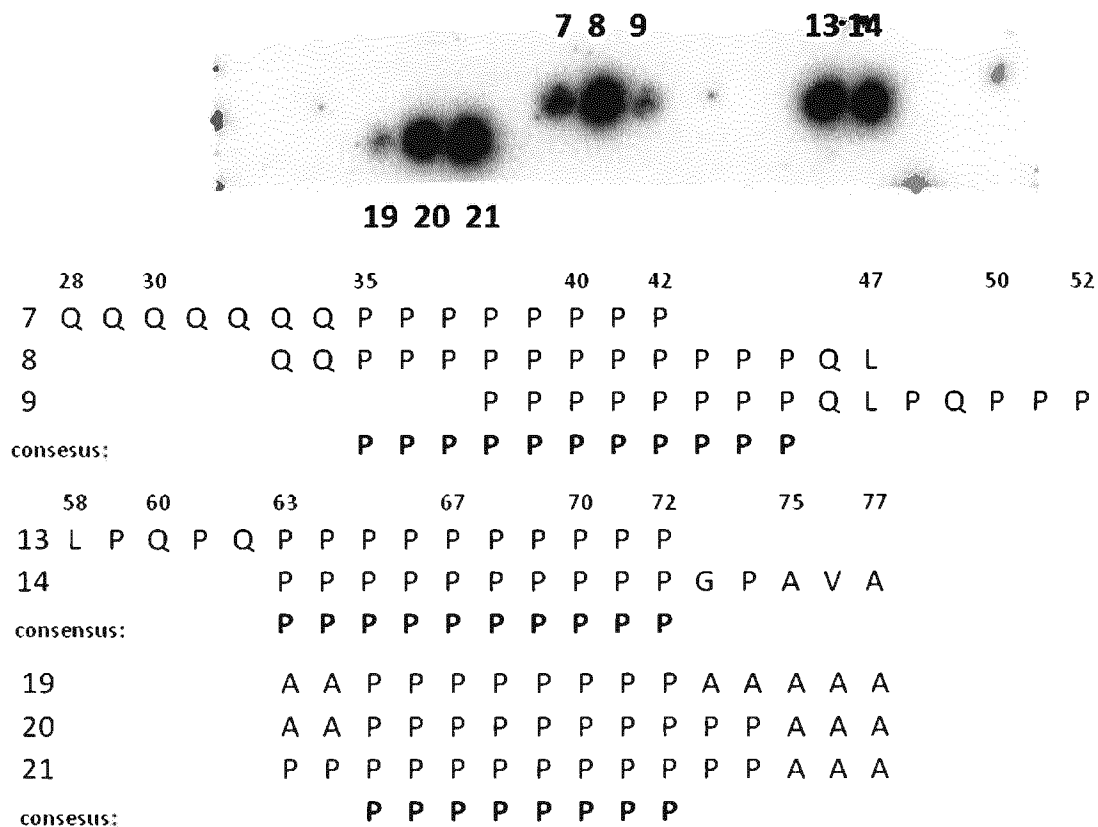
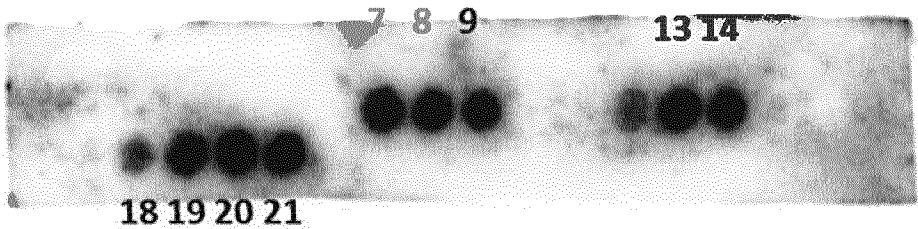
NI-302.46C9 1 $\mu$ g/ml (21 Spot membrane)

Fig. 23 (continued)

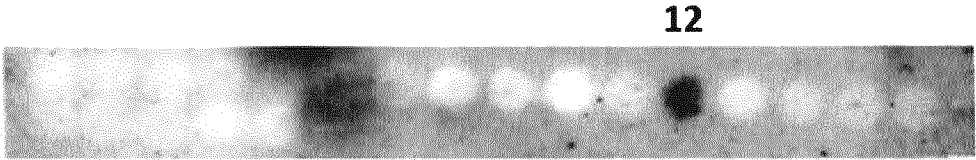
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(Q) NI-302.52D9 1ug/ml (21 Spot membrane)



	28	30		35		40	42		47	50	52
7	Q	Q	Q	Q	Q	Q	P	P	P	P	P
8				Q	Q	P	P	P	P	P	P
9							P	P	P	P	P
consesus:				P	P	P	P	P	P	P	P
	58	60		63		67	70	72		75	77
13	L	P	Q	P	Q	P	P	P	P	P	P
14				P	P	P	P	P	P	G	P
consensus:				P	P	P	P	P	P	P	P
18				A	A	P	P	P	P	A	A
19				A	A	P	P	P	P	P	A
20				A	A	P	P	P	P	P	A
21				P	P	P	P	P	P	P	A
consesus:				P	P	P	P	P	P	P	P

(R) NI-302.2A2 1ug/ml (21 Spot membrane)

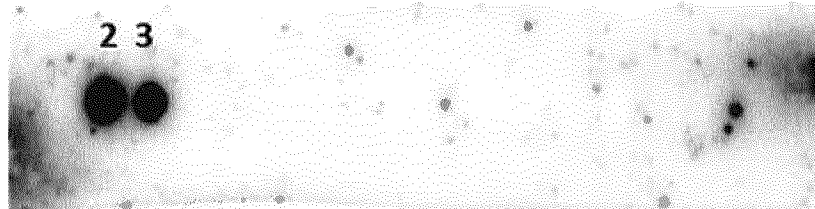


	53		58	60		63		67
12	Q	A	Q	P	L	L	P	Q

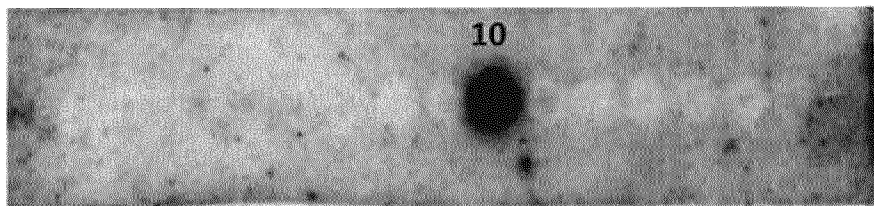
Fig. 23 (continued)



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**(S)** NI-302.15E8 1ug/ml (21 Spot membrane)

	5		10		20														
2	E	K	L	M	K	A	F	E	S	L	K	S	F	Q	Q				
3					K	A	F	E	S	L	K	S	F	Q	Q	Q	Q	Q	Q
consensus:					K	A	F	E	S	L	K	S	F	Q	Q				

**(T)** NI-302.15D3 1ug/ml (21 Spot membrane)

	43		50		57										
10	P	P	P	Q	L	P	Q	P	P	P	Q	A	Q	P	L

Fig. 23 (continued)

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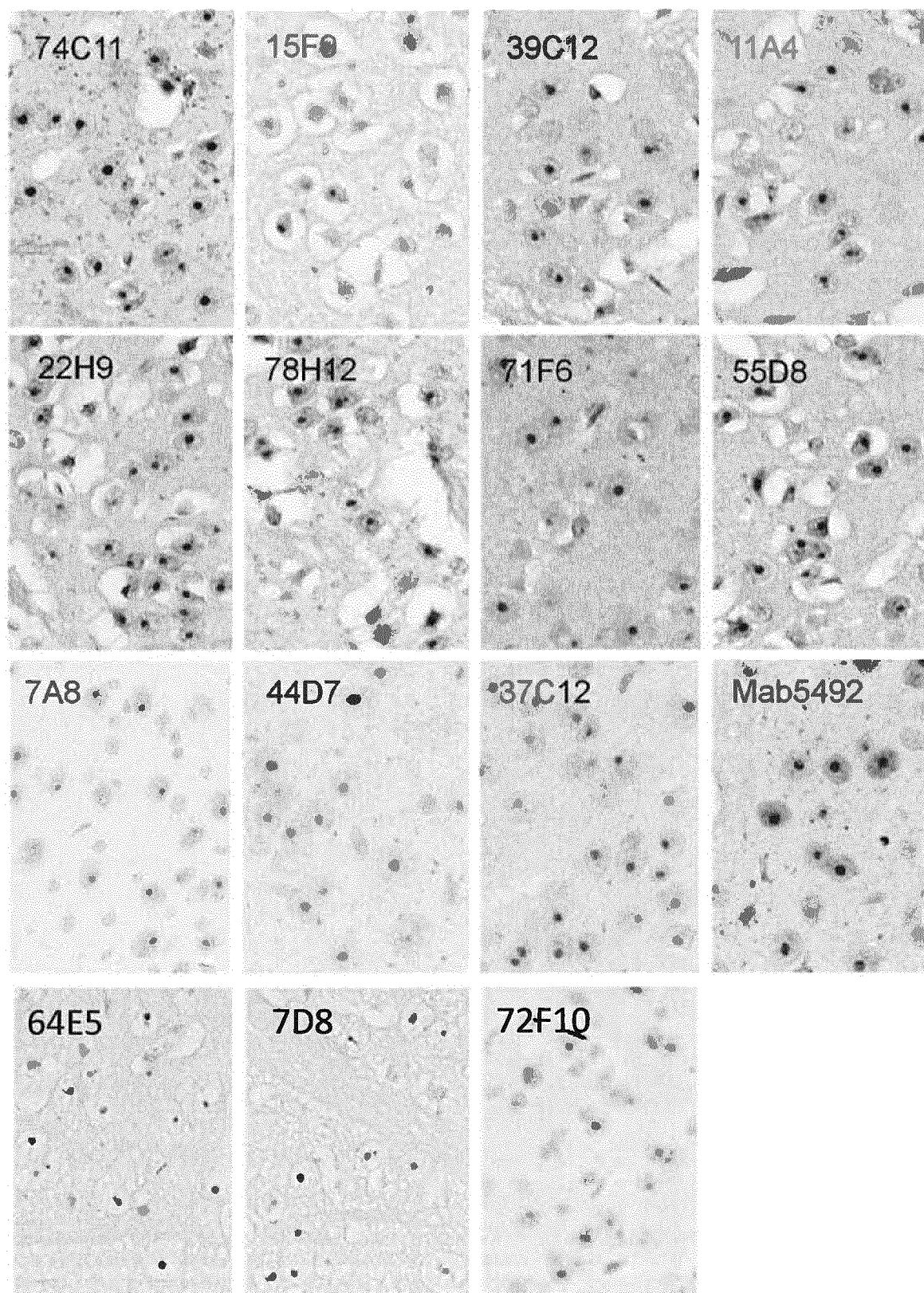


Fig. 24

Strain Name	Transgenic or Knockin	Gene Characteristics	Promoter	Repeat Length	Symptom Onset	Lifespan	Background Strain(s)	References
R6/1	Transgenic fragment	Exon 1 of human <i>HTT</i> gene	1 kb of Human <i>HTT</i>	116	18 weeks	32–40 wks	C57BL/6xCBA or C57BL/6	Mangiarini et al., 1996; Hodges et al., 2008

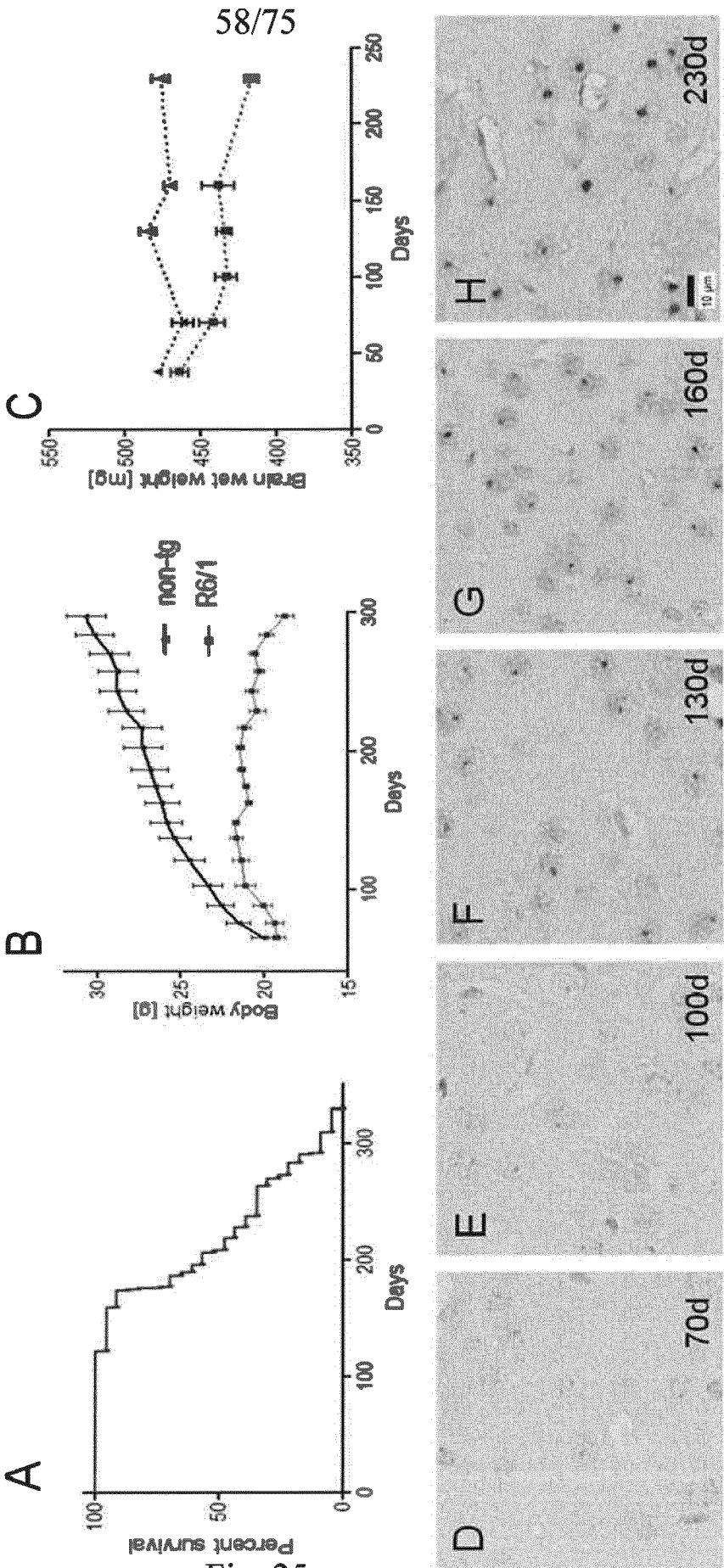
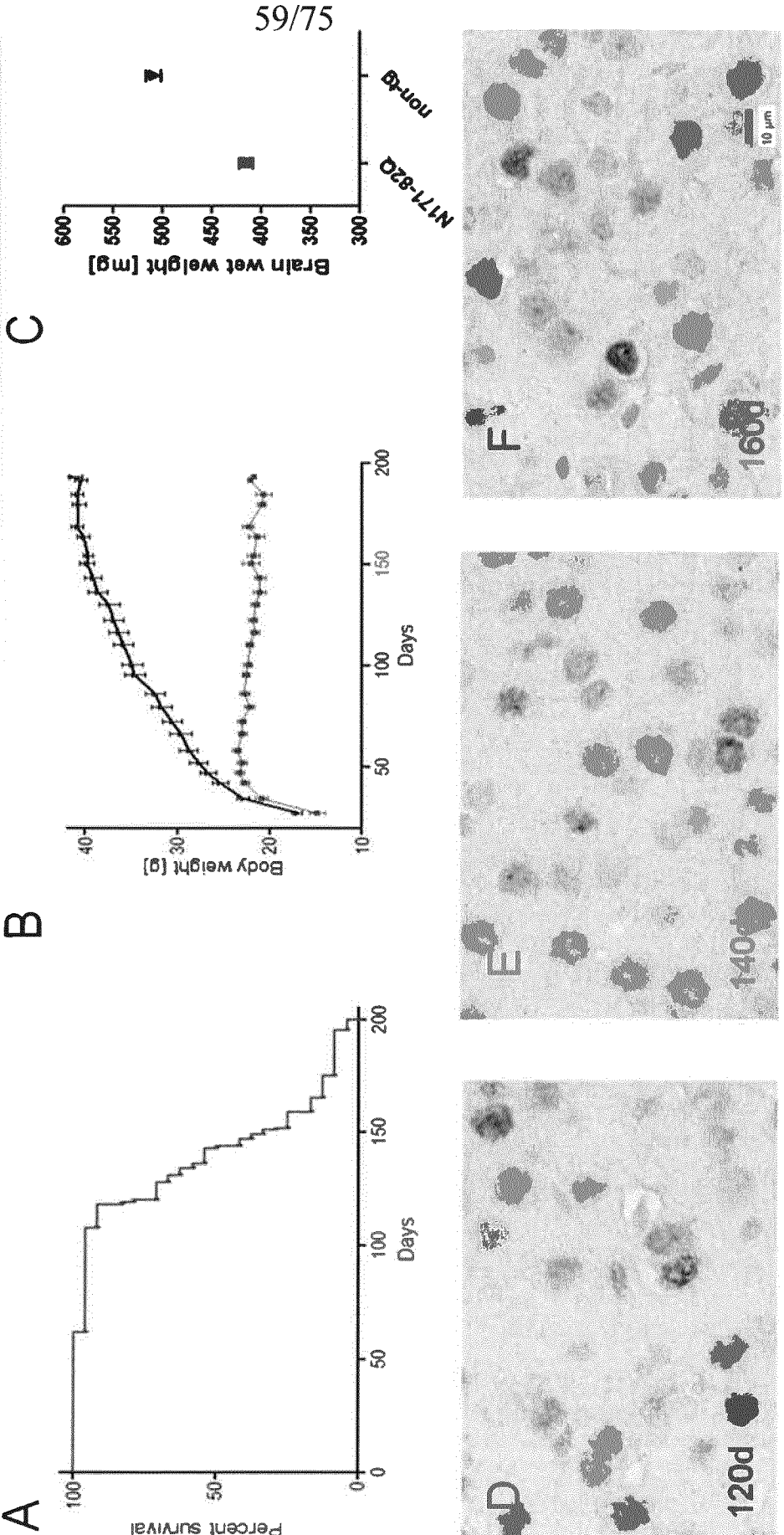


Fig. 25

Strain Name	Transgenic or Knockin	Gene Characteristics	Promoter	Repeat Length	Symptom Onset	Lifespan	Background Strain(s)	References
N171-82Q	Transgenic fragment	First 171 AA of human <i>HTT</i> (exons 1, 2, part of 3)	<i>Pmp</i>	82	3 months	16-22 wks	C57BL/6xC3H/He	Schilling et al., 1999; Schilling et al., 2004





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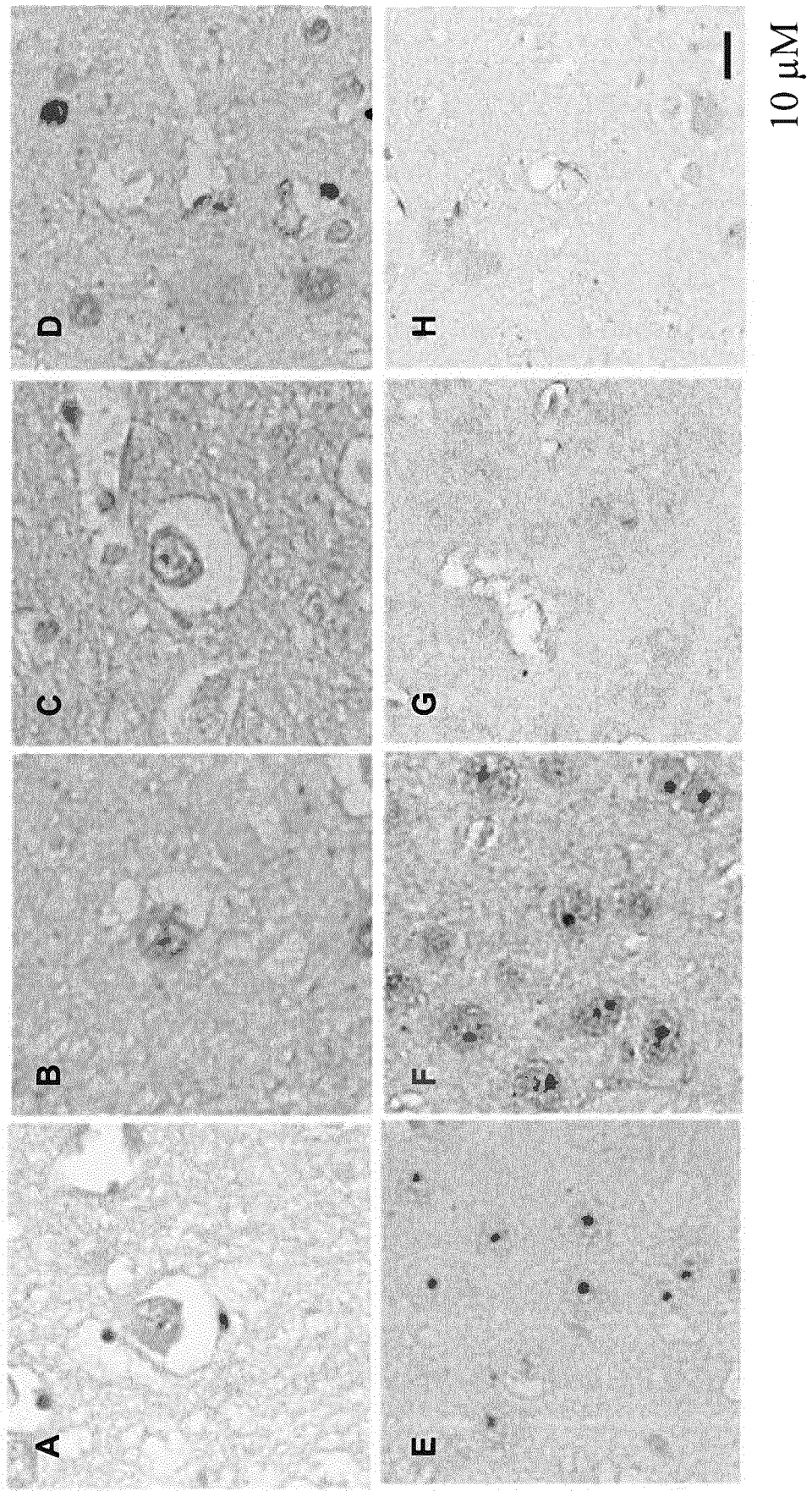


Fig. 27

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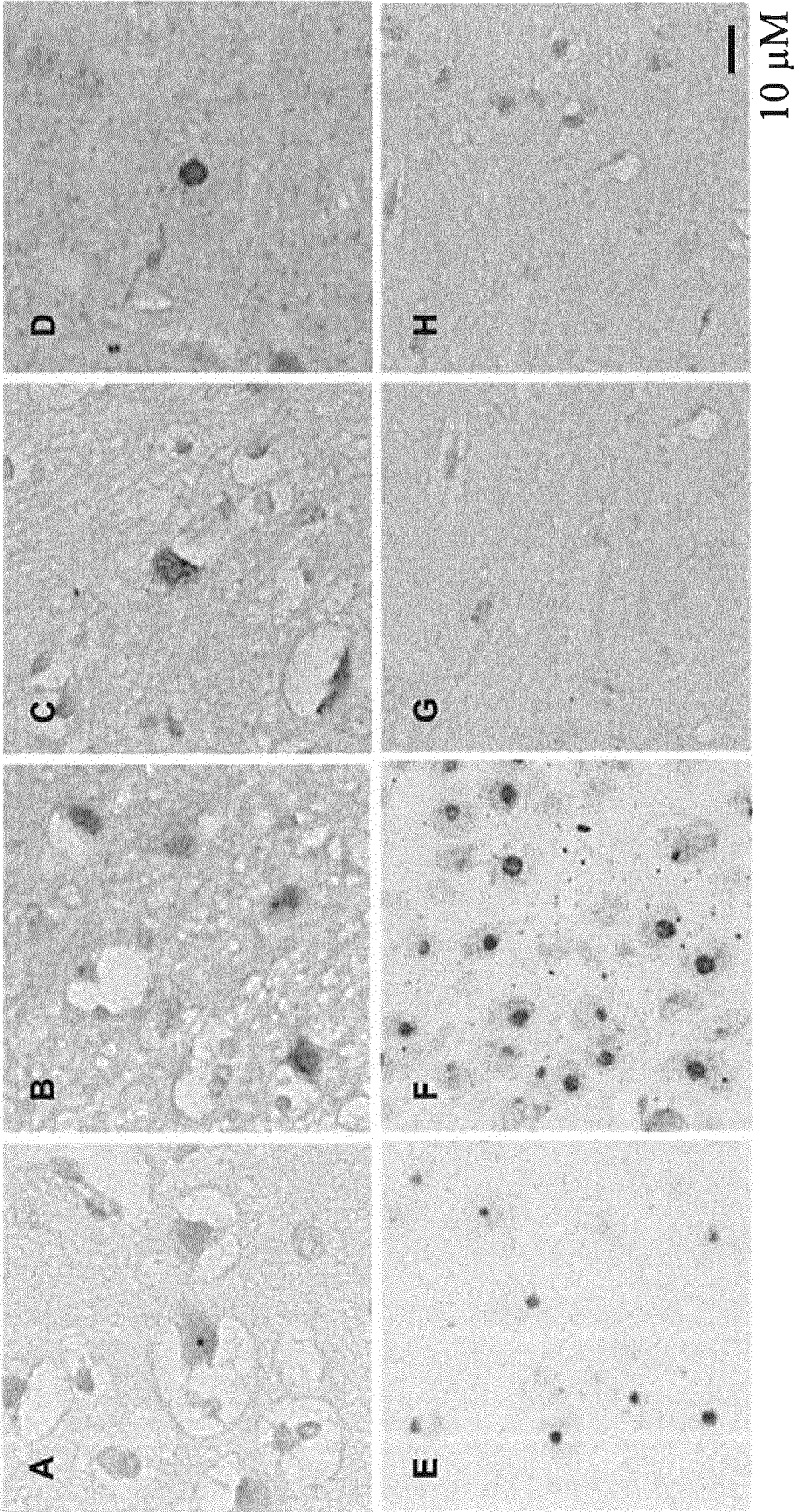


Fig. 28

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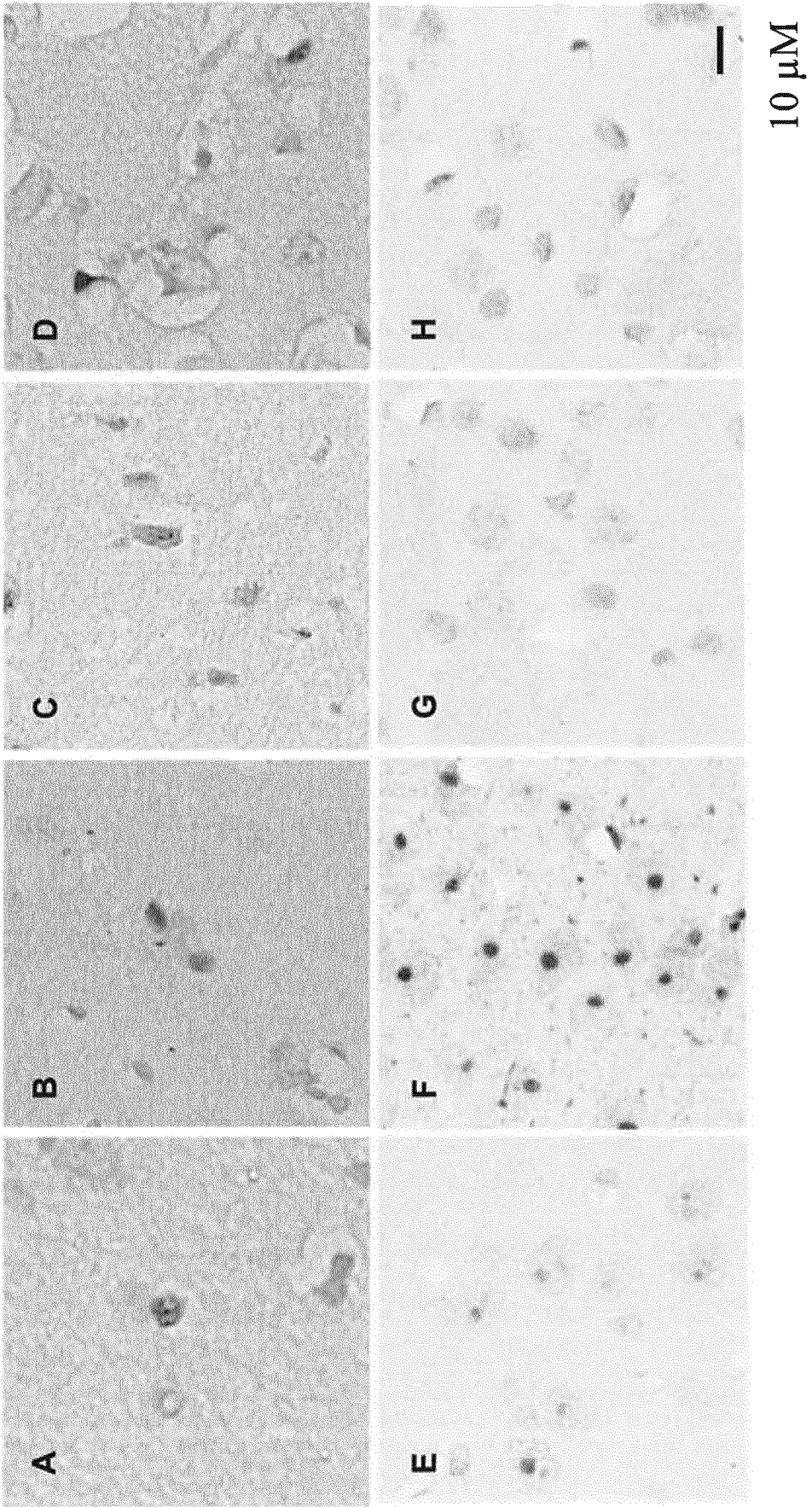


Fig. 29



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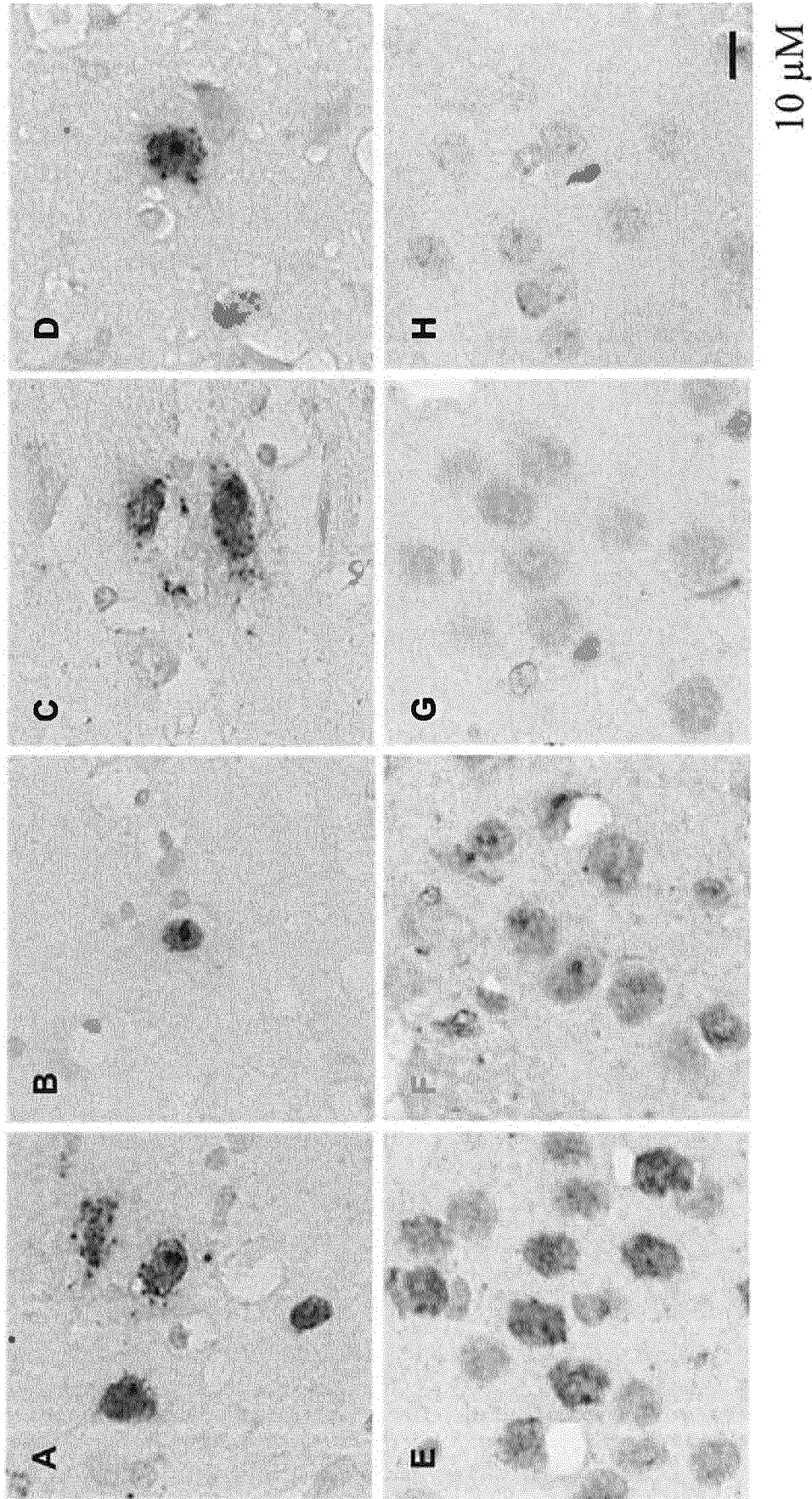


Fig. 30



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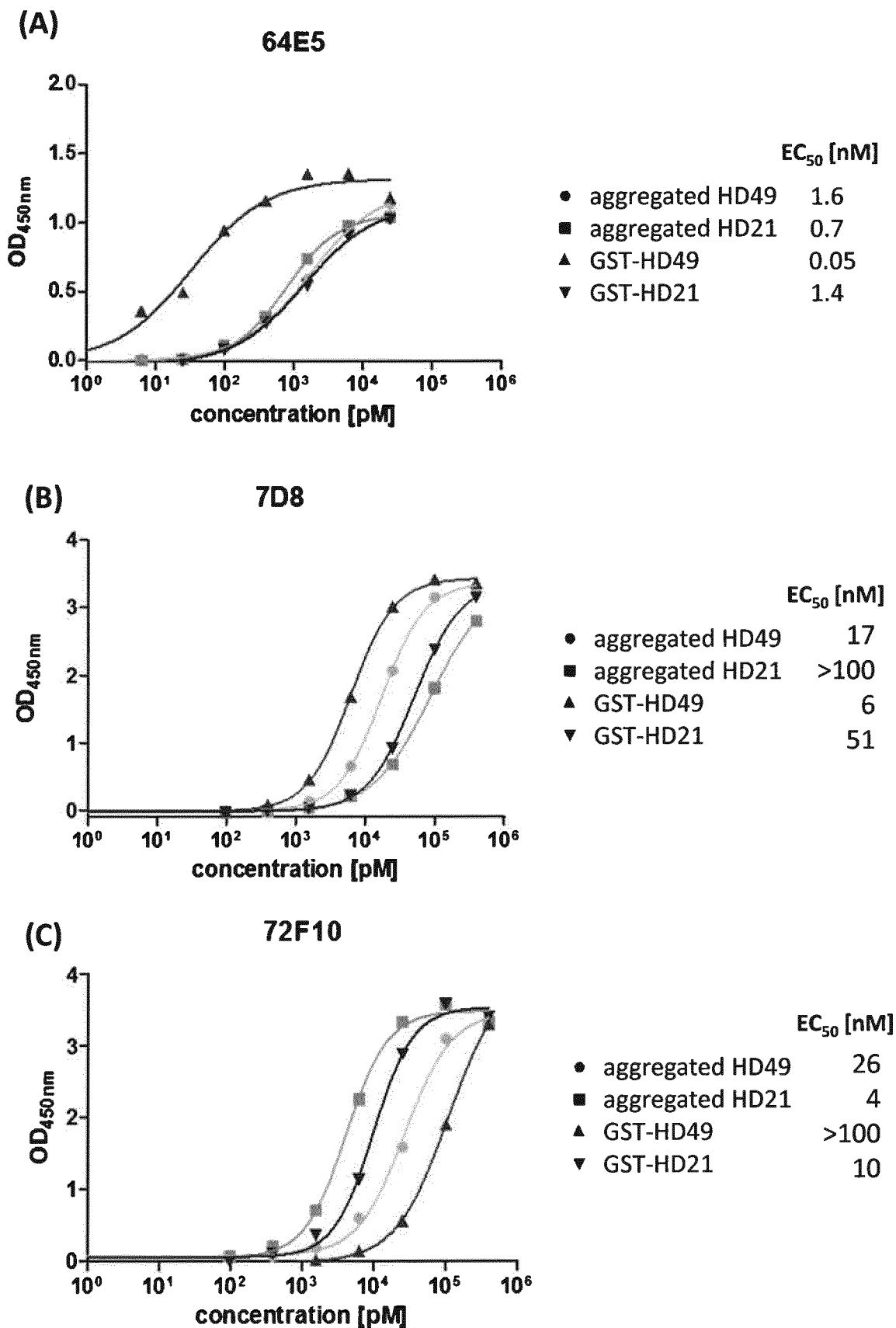
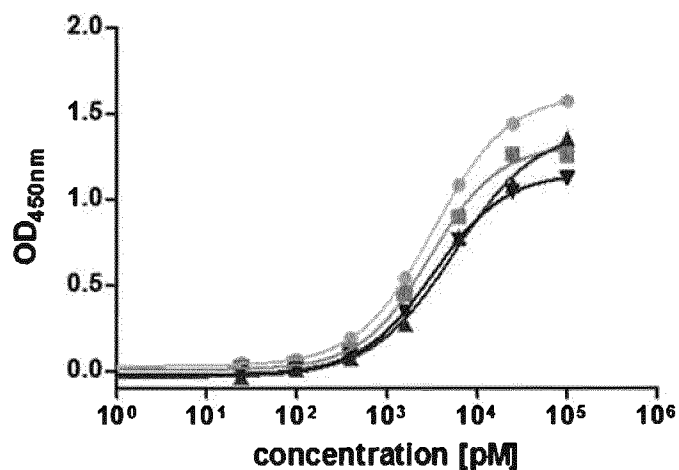


Fig. 31

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(D)

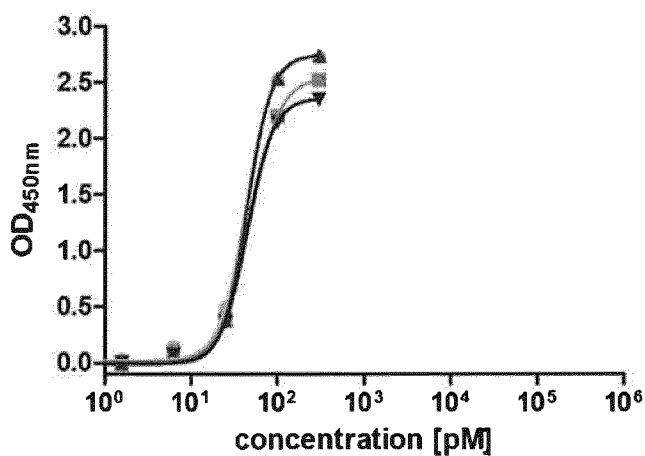
4A6

EC<sub>50</sub> [nM]

● aggregated HD49	3
■ aggregated HD21	3
▲ GST-HD49	6
▼ GST-HD21	3

(E)

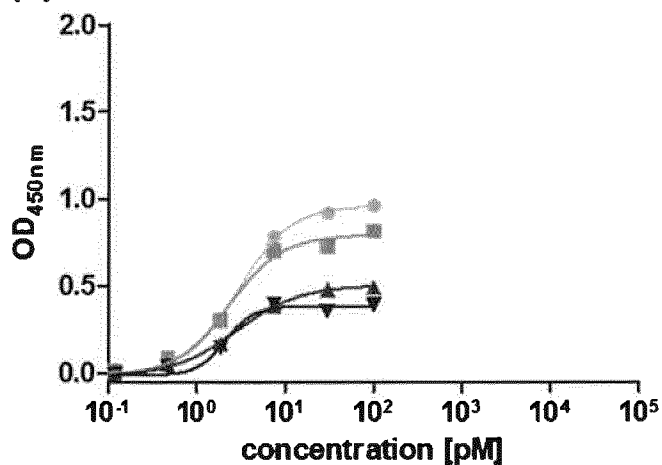
12H2

EC<sub>50</sub> [nM]

● aggregated HD49	0.04
■ aggregated HD21	0.05
▲ GST-HD49	0.04
▼ GST-HD21	0.04

(F)

8M1.

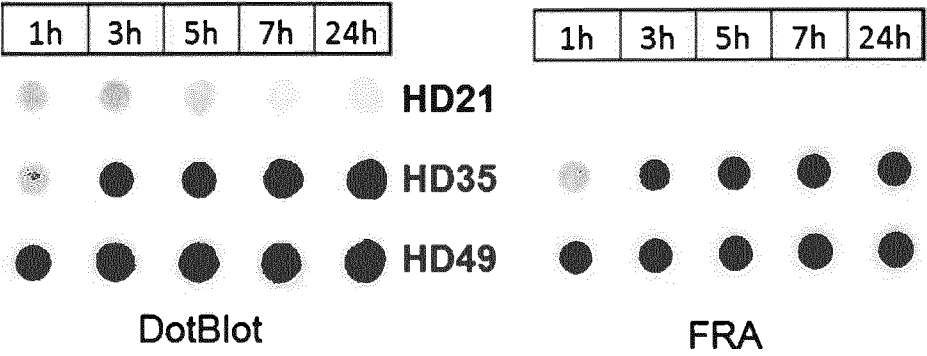
EC<sub>50</sub> [nM]

● aggregated HD49	0.003
■ aggregated HD21	0.002
▲ GST-HD49	0.003
▼ GST-HD21	0.002

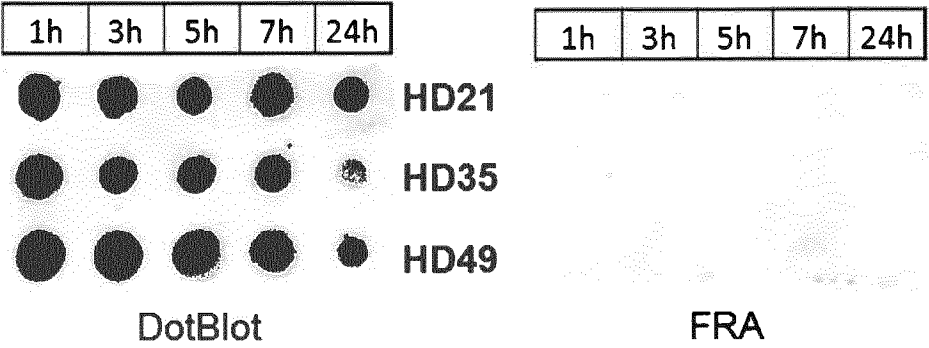
Fig. 31 (continued)

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(A) NI-302.64E5



(B) NI-302.7D8



(C) NI-302.72F10

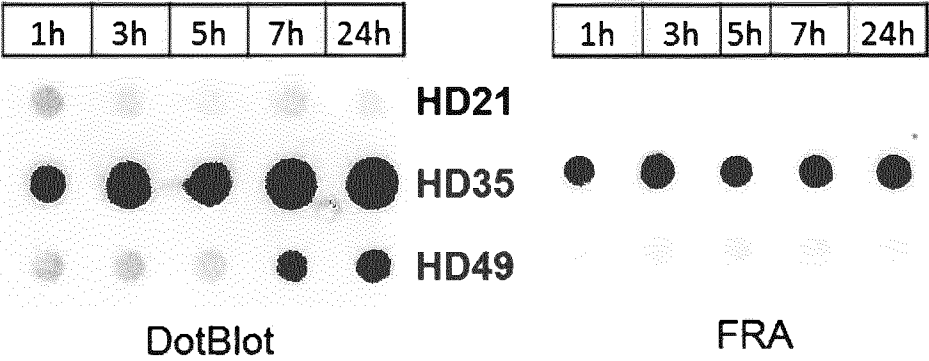


Fig. 32

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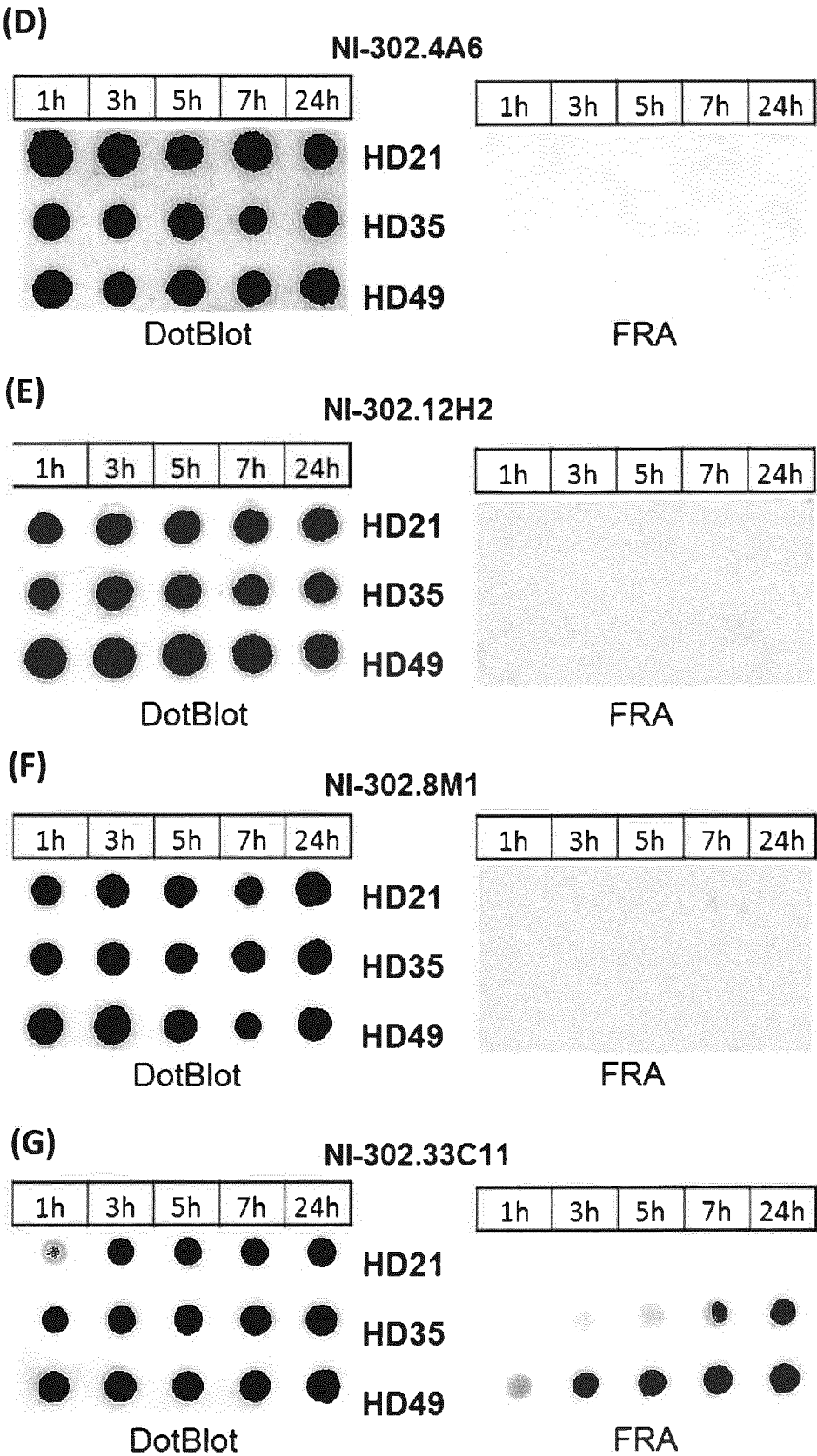


Fig. 32 (continued)

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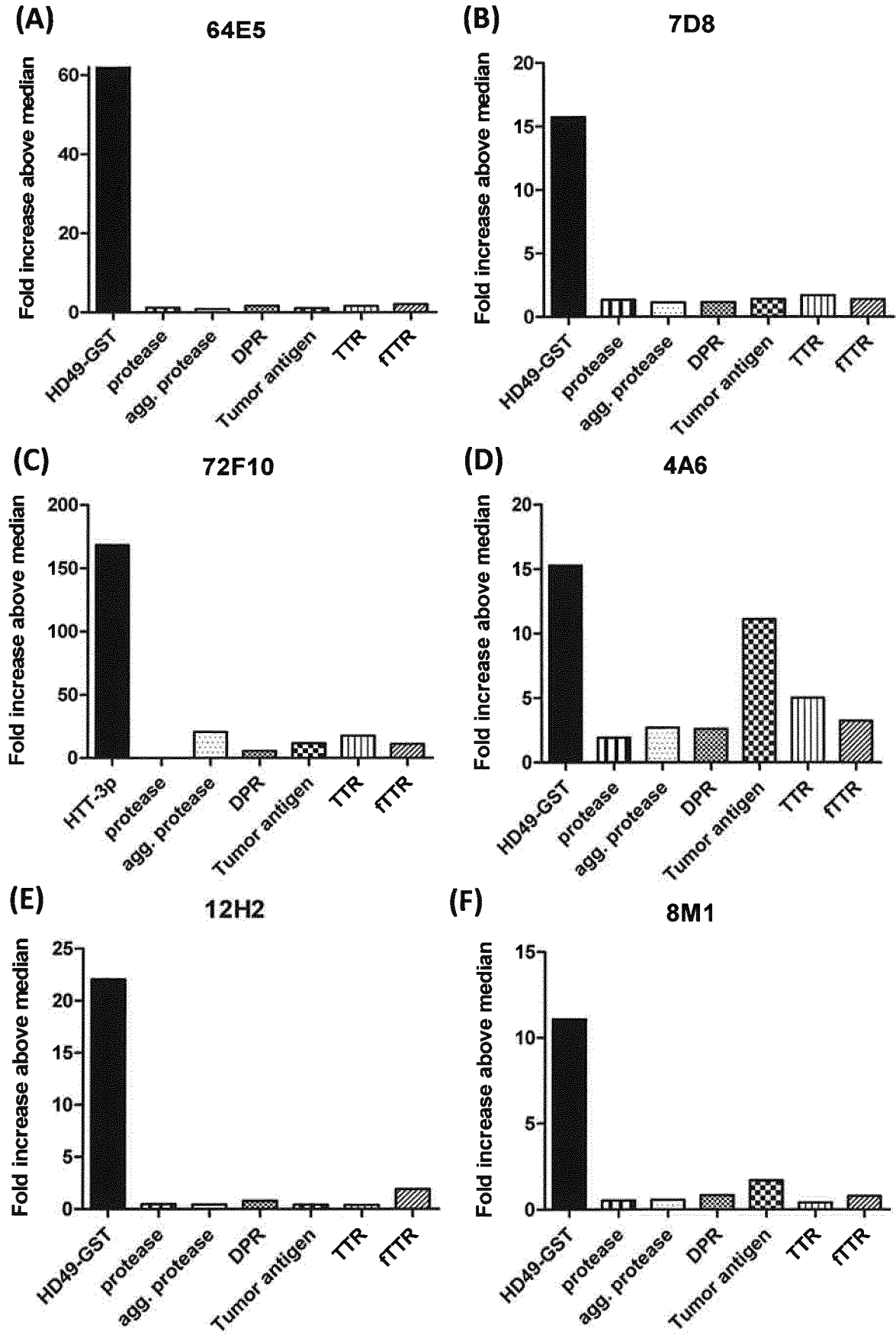
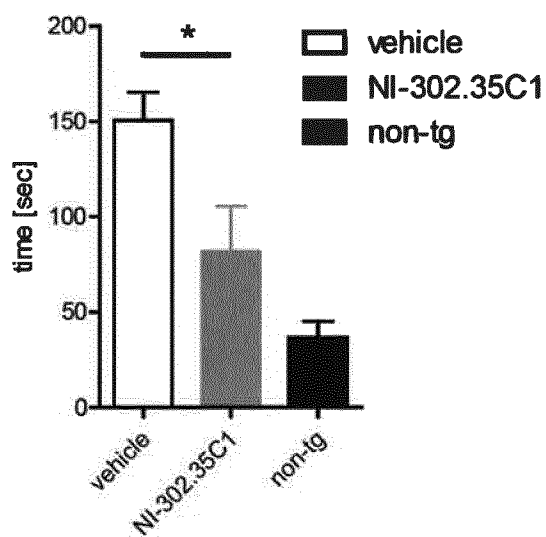


Fig. 33

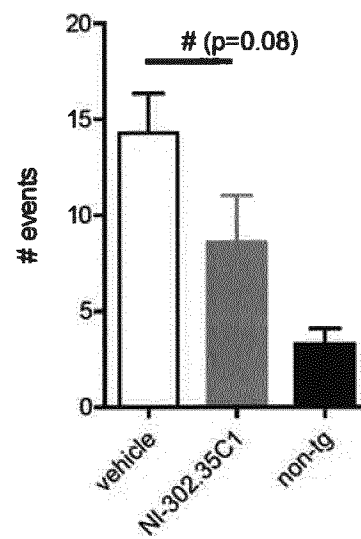
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(A)

Time in open arm

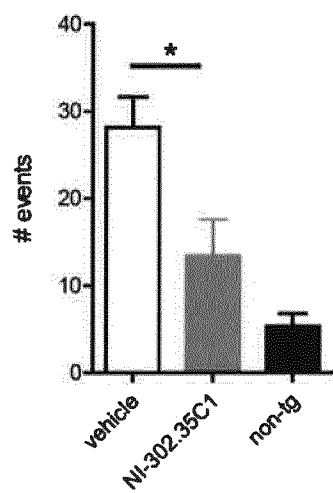


open arm entries



(B)

unprotected head dips



Pole test

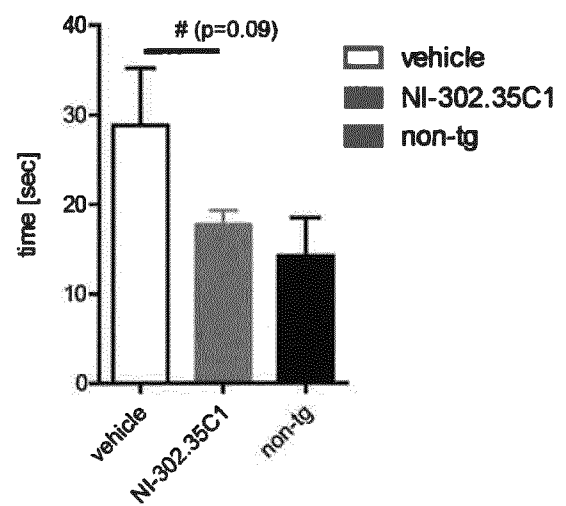


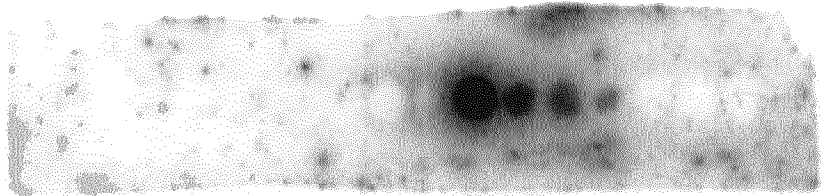
Fig. 34

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(A)

64E5 1ug/ml

10 11 12

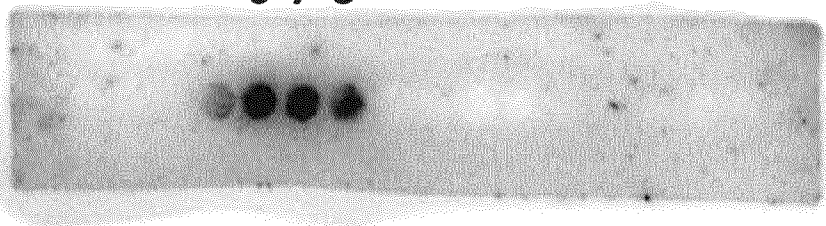


	43		50		57		60		67																
10	P	P	P	Q	L	P	Q	P	P	P	Q	A	Q	P	L										
11						P	Q	P	P	P	Q	A	Q	P	L	L	P	Q	P	Q					
12											Q	A	Q	P	L	L	P	Q	P	Q	P	P	P	P	P
consensus:						P	Q	P	P	P	Q	A	Q	P	L										

(B)

7D8 1ug/ml

6 7 8



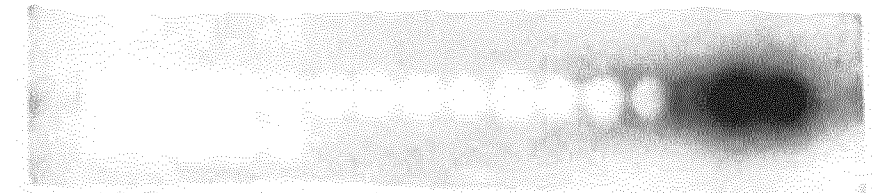
		28	30		35		40	42		47		50	52					
6	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	P	P	P					
7			Q	Q	Q	Q	Q	Q	P	P	P	P	P	P	P			
8						Q	Q	P	P	P	P	P	P	P	P	P	Q	L
consensus:						Q	Q	Q	Q	Q	P	P	P					

Fig. 35

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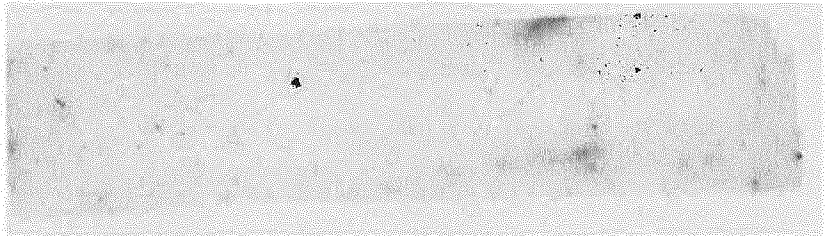
(C) 72F10 1ug/ml

15 16



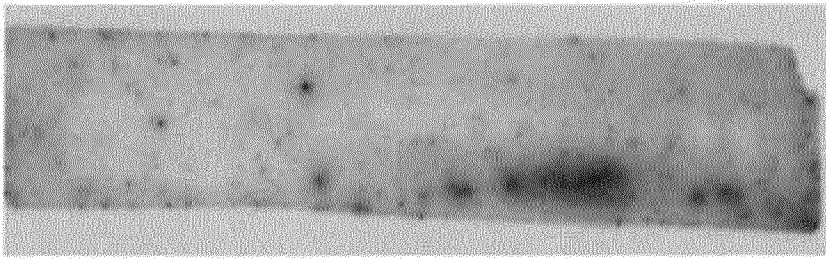
	68	70		75		80		84									
15	P	P	P	P	G	P	A	V	A	E	E	P	L	H			
16			P	P	P	G	P	A	V	A	E	E	P	L	H	R	P
consensus			P	P	P	G	P	A	V	A	E	E	P	L	H		

(D) 4A6 1ug/ml      No binding



(E) 12H2 1ug/ml

No binding



(F) 8M1 1ug/ml

No binding

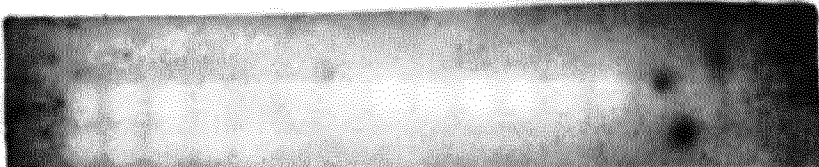


Fig. 35 (continued)



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(A)

NIV-1022 (72F10H)	(1)	1	10	20	30	40	50	60	70	82
NIV-526 (33C11H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-NTYYADSVKGRFTISRDN	SDN			
NIV-559 (35C11H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	D	-EGHNVVRQAPGKGLWVSDISGIGS	--	-YKYYADSVKGRFTISRDN	SKN			
NIV-641 (31F11H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	I	--	-TALSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	AKN		
NIV-873 (52C9H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-TMSWVRQAPGKGLWVSDISGIGS	--	-DTYYADSVKGRFTISRDN	SKN		
NIV-1059 (4A6H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	A	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-561 (44D7H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-1074 (12H2H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-845 (6N9H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-843 (308H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-429 (37C12H+PIMC)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-593 (22H9H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-595 (39G12H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-599 (11A4H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-1057 (7D8H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-795 (63F3H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-1061 (8M1H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-634 (55D8H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-636 (74C11H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-799 (11H6H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-563 (71F6H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-638 (78H12H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-857 (46C9H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-835 (18A1H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-1070 (64E5H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-893 (8F1H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-520 (15F9H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-597 (7A8H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		
NIV-972 (2A2H)	(1)	-EVQLVETGGGGLVQPGGSLRLSCAASGFTFS	S	--	-YAMSWVRQAPGKGLWVSDISGIGS	--	-STYYADSVKGRFTISRDN	SKN		

Fig. 36

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(B)

NIV-1022 (72F10H)	(83)	83	90	100	110	120	130	140	150	164
NIV-526 (33C11H)	(78)	TMELQNSLRAEDTAVYCAKDRK-----RSGWYEQWGQGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-559 (35C11H)	(78)	TMELQNSLRAEDTAVYCAKTHLEYC-SRTTC-----YLHWGQGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-641 (31F11H)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-873 (52C9H)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-1059 (4A6H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-561 (44D7H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-1074 (12H2H)	(79)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-845 (6N9H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-843 (308H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-429 (37C12H-PIMC)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-593 (22H9H)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-595 (39G12H)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-599 (11A4H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-1057 (7D8H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-795 (63F3H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-1061 (8M11H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-634 (55D8H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-636 (74C11H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-799 (11H6H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-563 (71F6H)	(77)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-638 (78H12H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-857 (46C9H)	(79)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-835 (18A11H)	(79)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-1070 (64E5H)	(81)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-893 (8F11H)	(80)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-520 (15F9H)	(79)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-597 (7A8H)	(79)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								
NIV-972 (2A2H)	(78)	TFLOMNSLRAEDTAVYCAKTHLEYC-----DSSGYSAFMGPGTIVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY								

Fig. 36 (continued)

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(c)

	1	10	20	30	40	50	60	70	82
NIV-1058 (7D8L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-564 (71F6L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-894 (8F1L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-639 (78H12L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-635 (55D8L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-637 (74C11L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-562 (44D7L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-800 (11H6L)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-1023 (72F10K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-1071 (64E5K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-796 (63F3K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-973 (2A2K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-430 (37C12K-PI MC)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-836 (18A1K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-874 (52C9K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-642 (31F11K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-594 (22H9K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-521 (15F9K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-598 (7A8K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-1062 (8M1Ka)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-844 (3D8K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-858 (46C9K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-527 (33C11K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-560 (35C1K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-1060 (4A6K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-1075 (12H2K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-846 (6N9K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					
NIV-600 (11A4K)	(1)	-QSALTQ-PASVSGSRGQSITISCTGTSSDVGSEYNLVS----	WYQ-QYEGKAPKLIHHEGSERP	SGVSNRPFSGSKSGNTAS					

Fig. 36 (continued)

75/75

(B)

	(83)	83	90	100	110	120	130	140	150	164
NIV-1058 (7D8L)	(75)	LTISGLQAEDEADYCCSYAGCT	T-FVLEGGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA			
NIV-564 (71F6L)	(75)	LTISGLQAEDEADYCCSYAGST	TWVFGGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA			
NIV-894 (8F1L)	(75)	LTISGLQAEDEADYCCSYAG	--YSTV	EGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-639 (78H12L)	(75)	LTISGLQAEDEADYCCSYAGS	Y-TFEV	EGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-635 (55D8L)	(75)	LAITGLQAEDEADYCHQSDNS	LSGSW	VEFGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-637 (74C11L)	(72)	LTITGLQAEDEADYCHQSDNS	LSGSW	VEFGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-562 (44D7L)	(75)	LTITGAQAEDEADYCHQSDNS	LSGSW	VEFGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-800 (11H6L)	(75)	LTITGAQAEDEADYCHQSDNS	LSGSW	VEFGG	TKLTVLQGP	KAAPSVT	LEPPSSSEELQ	ANKATLVCLISDFYPGAVTVAWKA		
NIV-1023 (72F10K)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-1071 (64E5K)	(80)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-796 (63F3K)	(79)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-973 (2A2K)	(82)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-430 (37C12K-PMC)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-836 (18A1K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-874 (52C9K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-642 (31F11K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-594 (22H9K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-596 (39G12K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-521 (15F9K)	(78)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-598 (7A8K)	(79)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-1062 (8M1Ka)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-844 (308K)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-858 (46C9K)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-527 (33C11K)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-560 (35C1K)	(73)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-1060 (4A6K)	(74)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-1075 (12H2K)	(75)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-846 (6N9K)	(74)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			
NIV-600 (11A4K)	(75)	LTISSELPEDSAVYCHQSKWP	--LTFEGG	TKVEIKRT	WAAPSVE	IFPPSDEQLKSGTASV	VCLINNFYPREAKVQWKV			

Fig. 36 (continued)

eol f-seql  
SEQUENCE LISTING

<110> Neurimmune Holding AG

<120> Human-derived anti-huntingtin (HTT) antibodies and uses thereof

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<150> EP 14179004.8

<151> 2014-07-29

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tcc	ctg	aga	ctc	tcc	tgt	gca	gcg	tct	gga	ttc	agg	ttc	agt	gac	ttt		96
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Arg	Phe	Ser	Asp	Phe		
			20					25					30				
ggc	atg	cac	tgg	gtc	cgc	cag	gct	cca	ggc	aag	gga	ctg	gag	tgg	ctg		144
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Leu		
		35					40					45					
gca	ctt	ata	tgg	tat	gat	gga	ggg	tat	aag	tac	tat	gca	gac	tcc	gtg		192
Ala	Leu	Ile	Trp	Tyr	Asp	Gly	Gly	Tyr	Lys	Tyr	Tyr	Ala	Asp	Ser	Val		
	50					55					60						
aag	ggc	cga	ttc	acc	atc	tcc	aga	gac	aat	tcc	aag	aat	acg	atg	ttt		240
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Met	Phe		
65					70				75					80			
cta	caa	atg	aac	agc	ctg	aga	gcc	gag	gac	acg	gct	ggt	tat	tac	tgt		288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
gcg	acc	cac	cta	gaa	tat	tgc	agt	aga	acc	acc	tgc	tat	ctc	ggc	cac		336
Ala	Thr	His	Leu	Glu	Tyr	Cys	Ser	Arg	Thr	Thr	Cys	Tyr	Leu	Gly	His		



eol f-seql

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tgg ggc cag gga acc ctg gtc acc gtc tcc tcg			369
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser			
115	120		

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	20		25			30	

Gl y Met	Hi s Trp	Val	Arg Gl n	Al a Pro	Gl y Lys	Gl y Leu	Gl u Trp	Leu
	35			40			45	

Al a Leu	I l e Trp	Tyr Asp	Gl y Gl y	Tyr Lys	Tyr Tyr	Al a Asp	Ser Val
50			55		60		

Lys Gl y	Arg Phe	Thr I l e	Ser Arg	Asp Asn	Ser Lys	Asn Thr	Met Phe
65		70		75			80

Leu Gl n	Met Asn	Ser Leu	Arg Al a	Gl u Asp	Thr Al a	Val Tyr	Tyr Cys
	85			90			95

Al a Thr	Hi s Leu	Gl u Tyr	Cys Ser	Arg Thr	Thr Cys	Tyr Leu	Gl y Hi s
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Trp Gl y	Gl n Gl y	Thr Leu	Val Thr	Val Ser	Ser
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gac aca gtc acc ttc act tgc cgg gcc agt cag ggc att agc gat tat 96  
Asp Thr Val Thr Phe Thr Cys Arg Ala Ser Gln Gly Ile Ser Asp Tyr  
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tta gcc tgg ttt cag cag aaa cca ggg att gcc cct aag ctc ctg atc 144  
Leu Ala Trp Phe Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile  
35 40 45

tat gct gcg tcc act ttg caa acc ggg gtc cca tca agg ttc agc ggc 192  
Tyr Ala Ala Ser Thr Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

agt gga tct ggg aca gaa ttc act ctc aca atc cgc agc ctg cag tct 240  
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Arg Ser Leu Gln Ser  
65 70 75 80

gaa gat ttt gga act tat tac tgt cag cag ctt aaa act tac ccg tac 288  
Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Leu Lys Thr Tyr Pro Tyr  
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act ttt ggc cag ggg acc aag gtg gaa atc aaa 321  
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Leu Ala Trp Phe Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile  
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Arg Ser Leu Gln Ser  
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Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Leu Lys Thr Tyr Pro Tyr  
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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
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tca gtg aaa gtt tcc tgc aag gcc tct gga tac acc ttc gag acc cgt	96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Glu Thr Arg	
20 25 30	
tct atg aac tgg gtg cga cag gcc cct gga caa ggg ctt gaa tac atg	144
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Tyr Met	
35 40 45	
gga tgg atc aac acc aac act ggc aac cgc acg tat gtc cag gcc ttc	192
Gly Trp Ile Asn Thr Asn Thr Gly Asn Arg Thr Tyr Val Gln Ala Phe	
50 55 60	
aga gga cga ttt gtc ttc tcc ttg gac acc tct gtc agc acg gca tat	240
Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr	
65 70 75 80	
ctg cag atc agc aac tta aag act gag gac act gcc gtg tat tac tgt	288
Leu Gln Ile Ser Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga ggg gca ggt ggg gga tat tgg ttc gac tcc tgg ggc cag gga	336
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Ser Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Tyr Met  
35 40 45

Gly Trp Ile Asn Thr Asn Thr Gly Asn Arg Thr Tyr Val Gln Ala Phe  
50 55 60

Arg Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr  
65 70 75 80

Leu Gln Ile Ser Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Gly Ala Gly Gly Gly Tyr Trp Phe Asp Ser Trp Gly Gln Gly  
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Glu Arg Ala Thr Ile Asn Cys Lys Ser Asn Gln Ser Leu Phe Tyr Ser  
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tcc aac aat aac aac tac tta gct tgg tac cag cac aaa tcc gga cag 144

eol f-seql

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Pro	Pro	Lys	Leu	Leu	Val	Tyr	Trp	Gly	Ser	Thr	Arg	Glu	Ser	Gly	Val		
		50				55					60						
cct	gac	cgc	ttc	agt	ggc	agc	ggg	tct	ggg	act	gac	ttc	act	ctc	acc		240
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr		
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atc	agt	agc	ctg	cag	gct	gag	gat	gtt	gca	att	tat	tac	tgt	cac	caa		288
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys	His	Gln		
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Tyr	Tyr	His	Asn	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile		
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Lys																	

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			20					25					30				
Ser	Asn	Asn	Asn	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	His	Lys	Ser	Gly	Gln		
		35					40					45					
Pro	Pro	Lys	Leu	Leu	Val	Tyr	Trp	Gly	Ser	Thr	Arg	Glu	Ser	Gly	Val		
		50				55					60						
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr		
					70					75				80			
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys	His	Gln		
				85					90					95			
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gag	gtg	cag	ctg	gtg	gag	tct	ggg	gga	aac	ttg	gta	cag	ccg	ggg	ggg	48
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Asn	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
tcc	ctg	aga	ctc	tcc	tgt	act	gcc	tct	gga	ttc	acc	ttt	agt	ata	acg	96
Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ile	Thr	
			20					25					30			
gcc	ctg	agt	tgg	gtc	cgc	cag	gct	cca	gaa	aag	ggg	ccg	cag	tgg	gtc	144
Ala	Leu	Ser	Trp	Val	Arg	Gln	Ala	Pro	Glu	Lys	Gly	Pro	Gln	Trp	Val	
		35					40					45				
tca	gca	atc	act	gga	aat	gct	tat	ggg	aca	tac	tac	gca	gac	tcc	gtg	192
Ser	Ala	Ile	Thr	Gly	Asn	Ala	Tyr	Gly	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	
	50				55						60					
aag	ggc	cgg	ttc	acc	att	tcc	aga	gac	aac	gcc	aag	aac	aca	ctg	tac	240
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Leu	Tyr	
65					70					75					80	
ttg	caa	atg	aac	ggc	ctg	aga	gcc	gag	gac	acg	gcc	atc	tat	tac	tgt	288
Leu	Gln	Met	Asn	Gly	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
				85					90					95		
gtg	aaa	gga	att	gcc	tcc	gat	agt	agt	ggt	tat	tct	gcc	ttc	tgg	ggc	336
Val	Lys	Gly	Ile	Ala	Ser	Asp	Ser	Ser	Gly	Tyr	Ser	Ala	Phe	Trp	Gly	
			100					105					110			
ccg	ggc	acc	ctg	gtc	acc	gtc	tcc	tcg								363
Pro	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115					120									

<210> 10  
 <211> 121  
 <212> PRT  
 <213> Homo sapiens

<400> 10  
 Glu Val Gln Leu Val Glu Ser Gly Gly Asn Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Ile Thr  
 20 25 30

eof-seq1

Ala Leu Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Pro Gln Trp Val  
35 40 45

Ser Ala Ile Thr Gly Asn Ala Tyr Gly Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr  
65 70 75 80

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

Val Lys Gly Ile Ala Ser Asp Ser Ser Gly Tyr Ser Ala Phe Trp Gly  
100 105 110

Pro Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 11  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(321)  
<223> NI-302.35C1 VK variable light -kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(102)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (148)..(168)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (265)..(291)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 11  
gaa att gtg ctg act cag tct cca gcc acc ctg tct ttg tct cca ggg 48  
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

gaa aga gcc acc ctc tcc tgc agg gcc agt caa agt gtt gac aac cag 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Asn Gln  
20 25 30

ttt gcc tgg tac caa cag aaa cct gcc cag gct ccc agg ctc ctc att 144  
Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

tat gat gca tcc agg agg gcc cct gcc atc cca gac agg ttc agt gcc 192  
Tyr Asp Ala Ser Arg Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser Gly  
50 55 60

eof-seq1

agt ggg tct ggg aca gac ttc act ctc acc att agc agc cta gag cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
65 70 75 80

gaa gat ttc gca att tat tac tgt cag cat cgt tac acc tgg ctc tac 288  
Glu Asp Phe Ala Ile Tyr Tyr Cys Gln His Arg Tyr Thr Trp Leu Tyr  
85 90 95

act ttt ggc cag ggg aca cga ctg gag att aaa 321  
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105

<210> 12  
<211> 107  
<212> PRT  
<213> Homo sapiens  
  
<400> 12

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

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

Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr Asp Ala Ser Arg Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
65 70 75 80

Glu Asp Phe Ala Ile Tyr Tyr Cys Gln His Arg Tyr Thr Trp Leu Tyr  
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105

<210> 13  
<211> 357  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(357)  
<223> NI-302.31F11 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(195)

eof-seq1

<223> complementarity determining region (CDR) VH-CDR2

<220>

<221> V\_region

<222> (292)..(324)

<223> complementarity determining region (CDR) VH-CDR3

<400> 13

gag gtg cag ctg gtg gag tcc gga gga ggc ttg atc cag ccg ggg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly  
1 5 10 15

tcc ctg aga ctc tcc tgt gca gcc tct ggg ttc acc gtc agc agc acc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Thr  
20 25 30

tac atg agt tgg gtc cgc cag gct cca ggg aag ggg ctt gag tgc gtc 144  
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Cys Val  
35 40 45

tca gtt att ttt agt ggc gct gac aca tat tac gca gac tcc gtg aag 192  
Ser Val Ile Phe Ser Gly Ala Asp Thr Tyr Tyr Ala Asp Ser Val Lys  
50 55 60

ggc cga ttc acc gtc tcc aga gac aat tcc aag aac aca ctg ttt ctt 240  
Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu  
65 70 75 80

cag atg aac agc ctg aga gtc gag gac acg gcc aca tat tac tgt gtg 288  
Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Thr Tyr Tyr Cys Val  
85 90 95

aga cat tat tat ggt tca gac ctt cca tct gac ttc tgg ggc cag ggc 336  
Arg His Tyr Tyr Gly Ser Asp Leu Pro Ser Asp Phe Trp Gly Gln Gly  
100 105 110

acc ctg gtc acc gtc tcc tcg 357  
Thr Leu Val Thr Val Ser Ser  
115

<210> 14

<211> 119

<212> PRT

<213> Homo sapiens

<400> 14

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Thr  
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Cys Val  
35 40 45

Ser Val Ile Phe Ser Gly Ala Asp Thr Tyr Tyr Ala Asp Ser Val Lys  
50 55 60

Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu  
65 70 75 80

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

Arg His Tyr Tyr Gly Ser Asp Leu Pro Ser Asp Phe Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210>	15
<211>	336
<212>	DNA
<213>	Homo sapiens

<220>  
<221> CDS  
<222> (1)..(336)  
<223> NI-302.31F11 VK variable light-kappa chain (VK) sequence

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<220>
<221> V_region
<222> (70)..(117)
<223> complementarity determining region (CDR) VK-CDR1
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<220>
<221> V_region
<222> (163)..(183)
<223> complementarity determining region (CDR) VK-CDR2
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<220>
<221> V_region
<222> (280)..(306)
<223> complementarity determining region (CDR) VK-CDR3
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<400> 15  
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc gcc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ala Pro Gly  
1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc cta tac agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Gl n Ser Leu Leu Tyr Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg aag cct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gl n Lys Pro Gly Lys Pro  
35 40 45

cca cag ctc ctg gtc tat ttg ggt tct gat cgg gcc tcc ggg gtc cct 192  
Pro Gl n Leu Leu Val Tyr Leu Gly Ser Asp Arg Al a Ser Gly Val Pro  
50 55 60

gac agg ttc agt ggc agt gga tca ggc aaa gat ttt aca ctg aac atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Asn Ile  
65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt 288  
 Ser Arg Val Gl u Al a Gl u Asp Val Gly Val Tyr Tyr Cys Met Gl n Gly  
 85 90 95

cta caa agt ccg tgg acg ttc ggc caa ggg acc aag ctg gag atc aaa 336  
Leu Gl n Ser Pro Trp Thr Phe Gly Gl n Gly Thr Lys Leu Gl u Ile Lys  
100 105 110

eof-seq1

<210> 16  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 16

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser  
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Lys Pro  
 35 40 45

Pro Gln Leu Leu Val Tyr Leu Gly Ser Asp Arg Ala Ser Gly Val Pro  
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Asn Ile  
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
 85 90 95

Leu Gln Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105 110

<210> 17  
 <211> 354  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(354)  
 <223> NI-302.2A2 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (295)..(321)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 17

gag gtg cag ctg gtg gag tct ggg gga ggc ttg gtc cag cct ggg ggg  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

48

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agt acc tat  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr

96



eol f-seql

20	25	30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtg Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35 40	45	144
gcc aac ata aaa cca gat gga agt gac aaa tac tat gtg gac tct gtg Ala Asn Ile Lys Pro Asp Gly Ser Asp Lys Tyr Tyr Val Asp Ser Val	50 55	60	192
aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tca ctg tat Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr	65 70	75 80	240
ctg caa atg aac agc ctg aga gac gag gac acg gct gtg tat tac tgt Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys	85	90 95	288
gcg aga ggg gac ggc agt ggc tgg aac gtc tac tgg ggc cag gga acc Ala Arg Gly Asp Gly Ser Gly Trp Asn Val Tyr Trp Gly Gln Gly Thr	100 105	110	336
ctg gtc acc gtc tcc tcg Leu Val Thr Val Ser Ser	115		354

<210> 18  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<400> 18

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr 20 25 30
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45
Ala Asn Ile Lys Pro Asp Gly Ser Asp Lys Tyr Tyr Val Asp Ser Val 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr 65 70 75 80
Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Gly Asp Gly Ser Gly Trp Asn Val Tyr Trp Gly Gln Gly Thr 100 105 110
Leu Val Thr Val Ser Ser 115

<210> 19  
 <211> 345

eof-seq1

<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(345)  
<223> NI-302.2A2 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(129)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (175)..(195)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (292)..(315)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 19  
gac atc cag atg acc cag tct cca gac tcc ctg gct gtg tct ctg ggc 48  
Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
1 5 10 15  
  
gag agg gcc acc atc aac tgc aag tcc agc cag agt ctt tta tac acc 96  
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Tyr Thr  
20 25 30  
  
tcc aaa aat aag gac agt aag aac tac tta ggt tgg tac cag cag aaa 144  
Ser Lys Asn Lys Asp Ser Lys Asn Tyr Leu Gly Trp Tyr Gln Gln Lys  
35 40 45  
  
cca gga cag cct cct aag ctg ctc att tac tgg gca tct acc cgg gaa 192  
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu  
50 55 60  
  
tcc ggg gtc cct gac cga ttc agt ggc agc ggg tct ggg aca gat ttc 240  
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe  
65 70 75 80  
  
act ctc acc atc agc agc ctg cag gct gag gat gtg gca gtt tat tac 288  
Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr  
85 90 95  
  
tgt cag cag tat tat act act cct cag ttc ggc gga ggg acc aag gtg 336  
Cys Gln Gln Tyr Tyr Thr Thr Pro Gln Phe Gly Gly Gly Thr Lys Val  
100 105 110  
  
gag atc aaa 345  
Glu Ile Lys  
115

<210> 20  
<211> 115  
<212> PRT  
<213> Homo sapiens

<400> 20  
Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

eof-seq1

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr  
20 25 30  
Ser Lys Asn Lys Asp Ser Lys Asn Tyr Leu Gly Trp Tyr Gln Gln Lys  
35 40 45  
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu  
50 55 60  
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe  
65 70 75 80  
Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr  
85 90 95  
Cys Gln Gln Tyr Tyr Thr Thr Pro Gln Phe Gly Gly Gly Thr Lys Val  
100 105 110  
Glu Ile Lys  
115

<210> 21  
<211> 369  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(369)  
<223> NI-302.6N9 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(336)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 21  
gag gtg cag ctg gtg gag tct ggg gga gac ttg gtg cag cct ggg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly  
1 5 10 15

tcc ctg aga ctc tcc tgt gta gtc tct gga ttc acc ttt agt agt tat 96  
Ser Leu Arg Leu Ser Cys Val Val Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

gcc atg acc tgg gtc cgc cag gct cca ggg aag ggg ctg gcc tgg gtc 144  
Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Ala Trp Val  
35 40 45

eol f-seql

tca	aca	att	agt	gct	act	ggt	ggt	agt	aca	ttc	tac	aca	gac	tcc	gtg	192
Ser	Thr	Ile	Ser	Ala	Thr	Gly	Gly	Ser	Thr	Phe	Tyr	Thr	Asp	Ser	Val	
	50					55					60					
agg	ggc	cgg	ttc	acc	atc	tcc	cga	gac	aat	tcc	aag	aac	aca	ctg	tat	240
Arg	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65					70					75					80	
ctg	caa	atg	aat	agc	ctg	aga	acc	gac	gac	acg	gcc	ata	tat	tat	tgt	288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Thr	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
				85					90					95		
gtg	aaa	gat	cta	ttt	gga	gtg	gac	acc	tcc	tac	tac	ggt	atg	gac	gtc	336
Val	Lys	Asp	Leu	Phe	Gly	Val	Asp	Thr	Ser	Tyr	Tyr	Gly	Met	Asp	Val	
			100					105					110			
tgg	ggc	caa	ggg	acc	acg	gtc	acc	gtc	tcc	tcg						369
Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
		115					120									

<210> 22  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<400> 22

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Asp	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Val	Val	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
			20					25					30			
Ala	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Ala	Trp	Val	
			35				40					45				
Ser	Thr	Ile	Ser	Ala	Thr	Gly	Gly	Ser	Thr	Phe	Tyr	Thr	Asp	Ser	Val	
	50					55					60					
Arg	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65					70				75						80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Thr	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
				85					90					95		
Val	Lys	Asp	Leu	Phe	Gly	Val	Asp	Thr	Ser	Tyr	Tyr	Gly	Met	Asp	Val	
			100					105					110			
Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
		115					120									

<210> 23  
 <211> 324  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS

eof-seql

<222> (1)..(324)  
 <223> NI-302.6N9 VK variable light-kappa chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(105)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (151)..(171)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (268)..(294)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 23  
 gaa att gtg ttg acg cag tct cca ggc acc ctg tct ttg tct cca ggg 48  
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

gaa aga gcc acc ctc tcc tgc agg ccc agt cag agt gtc agc ggc agg 96  
 Glu Arg Ala Thr Leu Ser Cys Arg Pro Ser Gln Ser Val Ser Gly Arg  
 20 25 30

tat gtg gcc tgg tat cag cag aaa cct ggc cag gct ccc agg ctc ctc 144  
 Tyr Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
 35 40 45

ttc tat gct gca tcc aac agg gcc att ggc atc cca gac agg ttc agt 192  
 Phe Tyr Ala Ala Ser Asn Arg Ala Ile Gly Ile Pro Asp Arg Phe Ser  
 50 55 60

ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag 240  
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
 65 70 75 80

cct gaa gat ttt gca gtg tat tac tgt cag cac tat ggt gcc tca tcg 288  
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ala Ser Ser  
 85 90 95

tac act ttt ggc ccg ggg acc aaa gtg gat atc aaa 324  
 Tyr Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
 100 105

<210> 24  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens

<400> 24  
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Pro Ser Gln Ser Val Ser Gly Arg  
 20 25 30

Tyr Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
 35 40 45

Phe Tyr Ala Ala Ser Asn Arg Ala Ile Gly Ile Pro Asp Arg Phe Ser

eof-seql 60

50

55

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ala Ser Ser  
85 90 95

Tyr Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
100 105

<210> 25  
<211> 360  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(360)  
<223> NI-302.74C11 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(186)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(327)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 25  
gag gtg cag ctg gtg cag tct ggg act gag gtg cag aag cct ggg gcc 48  
Glu Val Gln Leu Val Gln Ser Gly Thr Glu Val Gln Lys Pro Gly Ala  
1 5 10 15

tca gta aaa gtc tcc tgc aag gct tct gga tac agt ttc acc ggc tac 96  
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr  
20 25 30

ttt ttg cac tgg gta cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
Phe Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

ggg tgg atc aac cct aac agt ggt gac aca aac tat gca gag aag ttt 192  
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Glu Lys Phe  
50 55 60

cgg ggc aga atc atc atg acc agg gac acg tct gtc agc aca gcc cac 240  
Arg Gly Arg Ile Ile Met Thr Arg Asp Thr Ser Val Ser Thr Ala His  
65 70 75 80

atg gag ttg agc agc ctg aga ttt gac gag acg gcc cta tat tac tgt 288  
Met Glu Leu Ser Ser Leu Arg Phe Asp Asp Thr Ala Leu Tyr Tyr Cys  
85 90 95

acg aga gag gcc cct gac ccg ggc gct gag acg gac gtc tgg ggc caa 336  
Thr Arg Glu Ala Pro Asp Pro Gly Ala Glu Thr Asp Val Trp Gly Gln

eol f-seql

100                      105                      110

ggg acc acg gtc acc gtc tcc tcg                      360  
 Gly Thr Thr Val Thr Val Ser Ser  
           115                      120

<210> 26  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 26

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

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

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

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

Arg Gly Arg Ile Ile Met Thr Arg Asp Thr Ser Val Ser Thr Ala His  
 65                      70                      75                      80

Met Glu Leu Ser Ser Leu Arg Phe Asp Asp Thr Ala Leu Tyr Tyr Cys  
           85                      90                      95

Thr Arg Glu Ala Pro Asp Pro Gly Ala Glu Thr Asp Val Trp Gly Gln  
           100                      105                      110

Gly Thr Thr Val Thr Val Ser Ser  
           115                      120

<210> 27  
 <211> 321  
 <212> DNA  
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<220>  
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 <223> NI-302.74C11 VL variable light chain (VL) sequence

<220>  
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 <223> complementarity determining region (CDR) VL-CDR1

<220>  
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 <222> (145)..(165)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>

eof-seq1

<221> V\_region

<222> (262)..(291)

<223> complementarity determining region (CDR) VL-CDR3

<400> 27

cag tct gtg ctg act cag cca ccc tcg gtg tca gtg tcc cca gga cag 48  
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
1 5 10 15

acg gcc agg atc acc tgc tct gga gat gca gtg cca aag cag tat att 96  
Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Val Pro Lys Gln Tyr Ile  
20 25 30

tat tgg tac cag cag aag cca ggc cag gcc cct att ctg gtg ata tat 144  
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr  
35 40 45

aaa gac act cag agg cct tca ggg atc cct gag cga ttc tct ggc tcc 192  
Lys Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
50 55 60

aac tca ggg aca aca gtc acg ttg acc ata act ggc gtc cag gca gac 240  
Asn Ser Gly Thr Thr Val Thr Leu Thr Ile Thr Gly Val Gln Ala Asp  
65 70 75 80

gac gag ggt gac tat tac tgt caa tca gca gac agt agt gct act tgg 288  
Asp Glu Gly Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ala Thr Trp  
85 90 95

gtg ttc ggc gga ggg acc aaa ttg acc gtc cta 321  
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 28

<211> 107

<212> PRT

<213> Homo sapiens

<400> 28

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Val Pro Lys Gln Tyr Ile  
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr  
35 40 45

Lys Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
50 55 60

Asn Ser Gly Thr Thr Val Thr Leu Thr Ile Thr Gly Val Gln Ala Asp  
65 70 75 80

Asp Glu Gly Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ala Thr Trp  
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105



eol f-seql

<210> 29  
 <211> 360  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(360)  
 <223> NI-302.15F9 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(201)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (298)..(327)  
 <223> complementarity determining region (CDR) VH-CDR3

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gag gtg cag ctg gtg gag tct ggg gga ggc ctg gtc acg ccg ggg ggg		48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Thr Pro Gly Gly		
1 5 10 15		
tcc ctg aga ctc tcg tgt gag gcc tct gga ttt ctc ttc aag aat tct		96
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Leu Phe Lys Asn Ser		
20 25 30		
agc atg aac tgg gtc cgt cag act ccg ggg aag ggg ctg gag tgg gtc		144
Ser Met Asn Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
35 40 45		
tcg tcc att gac act tct gct aca aat tat aag tat tat gca gac tct		192
Ser Ser Ile Asp Thr Ser Ala Thr Asn Tyr Lys Tyr Tyr Ala Asp Ser		
50 55 60		
gtg aag ggc cga ttt acc atc tcc agg gat gac gcc acc aac tct ctc		240
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Thr Asn Ser Leu		
65 70 75 80		
tat ctg caa atg aat agc ctg cga gcc gac gac acg gct act tat tac		288
Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Thr Tyr Tyr		
85 90 95		
tgt gcg cga ggt tat tat acc ccc cgg gac ttt gac tac tgg ggc cag		336
Cys Ala Arg Gly Tyr Tyr Thr Pro Arg Asp Phe Asp Tyr Trp Gly Gln		
100 105 110		
ggc acc ctg gtc acc gtc tcc tcg		360
Gly Thr Leu Val Thr Val Ser Ser		
115 120		

<210> 30  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 30

eol f-seql

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Thr Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Gl u Al a Ser Gly Phe Leu Phe Lys Asn Ser  
 20 25 30  
 Ser Met Asn Trp Val Arg Gl n Thr Pro Gly Lys Gly Leu Gl u Trp Val  
 35 40 45  
 Ser Ser Ile Asp Thr Ser Al a Thr Asn Tyr Lys Tyr Tyr Al a Asp Ser  
 50 55 60  
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Al a Thr Asn Ser Leu  
 65 70 75 80  
 Tyr Leu Gl n Met Asn Ser Leu Arg Al a Asp Asp Thr Al a Thr Tyr Tyr  
 85 90 95  
 Cys Al a Arg Gly Tyr Tyr Thr Pro Arg Asp Phe Asp Tyr Trp Gly Gl n  
 100 105 110  
 Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 31  
 <211> 336  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(336)  
 <223> NI-302.15F9 VK variable light-kappa chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(117)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (163)..(183)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (280)..(306)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 31  
 gat gtt gtg atg act cag tct cca cag acc ctg tcc gtc agc ctt gga 48  
 Asp Val Val Met Thr Gl n Ser Pro Gl n Thr Leu Ser Val Ser Leu Gly  
 1 5 10 15

cag gcg gcc tcc atc tcc tgc agg tcg agt caa agc ctc ttg tat cgt 96  
 Gl n Al a Al a Ser Ile Ser Cys Arg Ser Ser Gl n Ser Leu Leu Tyr Arg  
 20 25 30

gat aac aac aca tac ttg aat tgg ttt cac cag agg cca ggc caa tct 144  
 Page 22

eol f-seql

Asp	Asn	Asn	Thr	Tyr	Leu	Asn	Trp	Phe	His	Gln	Arg	Pro	Gly	Gln	Ser		
		35					40					45					
cca	agg	cgc	ctc	att	tat	agg	gct	tct	gac	cgg	gac	tct	ggg	gtc	cca		192
Pro	Arg	Arg	Leu	Ile	Tyr	Arg	Ala	Ser	Asp	Arg	Asp	Ser	Gly	Val	Pro		
	50					55				60							
gac	aga	ttc	agc	ggc	ggt	ggg	tca	ggc	act	gat	ttc	aca	ttg	aaa	atc		240
Asp	Arg	Phe	Ser	Gly	Gly	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	80	
65				70					75								
agt	gga	gtg	gag	gct	gaa	gat	ggt	ggc	act	tat	tac	tgc	atg	caa	gga		288
Ser	Gly	Val	Glu	Ala	Glu	Asp	Val	Gly	Thr	Tyr	Tyr	Cys	Met	Gln	Gly		
			85					90					95				
aca	cac	tgg	cct	cgg	acg	ttc	ggc	caa	ggg	acc	aag	gtg	gag	atc	aaa		336
Thr	His	Trp	Pro	Arg	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys		
			100				105					110					

<210> 32  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 32

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

Gln	Ala	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	Tyr	Arg
			20					25					30		

Asp	Asn	Asn	Thr	Tyr	Leu	Asn	Trp	Phe	His	Gln	Arg	Pro	Gly	Gln	Ser
		35					40					45			

Pro	Arg	Arg	Leu	Ile	Tyr	Arg	Ala	Ser	Asp	Arg	Asp	Ser	Gly	Val	Pro
	50					55					60				

Asp	Arg	Phe	Ser	Gly	Gly	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70						75				80	

Ser	Gly	Val	Glu	Ala	Glu	Asp	Val	Gly	Thr	Tyr	Tyr	Cys	Met	Gln	Gly
			85					90					95		

Thr	His	Trp	Pro	Arg	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100				105						110		

<210> 33  
 <211> 357  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <223> NI-302.39G12 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region

eof-seql

<222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(195)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (292)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

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 gag gtg cag ctg gtg cag tct ggg gga ggc ttg gtc cac cct tgg ggg 48  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Trp Gly  
 1 5 10 15  
 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc gtc tct aat tac 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Val Ser Asn Tyr  
 20 25 30  
 gcc ata act tgg gtc cgc cgg gct cca ggg aag ggg ctg caa tat att 144  
 Ala Ile Thr Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Gln Tyr Ile  
 35 40 45  
 tca gta att tat cgt gat ggc agg aca tac tac gga gac tcc gtg agg 192  
 Ser Val Ile Tyr Arg Asp Gly Arg Thr Tyr Tyr Gly Asp Ser Val Arg  
 50 55 60  
 ggc cgc ttc acc atc tct agg gac gat tcc aag aac act ctc tat ctt 240  
 Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu  
 65 70 75 80  
 caa atg aac agc ctg aga ttt gag gac acg gct gtg tat tac tgt gcg 288  
 Gln Met Asn Ser Leu Arg Phe Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95  
 aga gcg cac ggc caa tat tac tat ggt gtg gac gtc tgg ggc caa ggg 336  
 Arg Ala His Gly Gln Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly  
 100 105 110  
 acc acg gtc acc gtc tcc tcg 357  
 Thr Thr Val Thr Val Ser Ser  
 115

<210> 34  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 34  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Trp Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Val Ser Asn Tyr  
 20 25 30  
 Ala Ile Thr Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Gln Tyr Ile  
 35 40 45  
 Ser Val Ile Tyr Arg Asp Gly Arg Thr Tyr Tyr Gly Asp Ser Val Arg  
 50 55 60

eof-seql

Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu  
65 70 75 80

Gln Met Asn Ser Leu Arg Phe Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Arg Ala His Gly Gln Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly  
100 105 110

Thr Thr Val Thr Val Ser Ser  
115

<210> 35  
<211> 333  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(333)  
<223> NI-302.39G12 VK variable light-kappa chain (VK) sequence

<220>  
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<222> (70)..(117)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (163)..(183)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (280)..(306)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 35  
gat gtt gtg atg act cag tct cca ctc tcc ctg tcc gtc agc cct gga 48  
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Ser Pro Gly  
1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc cta cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac cgg cag aaa cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Arg Gln Lys Pro Gly Gln Ser  
35 40 45

cca cag ctc ctg atc tat ttg agt tct aat cgg ccc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Ser Ser Asn Arg Pro Ser Gly Val Pro  
50 55 60

gat agg ttc agt gcc agt gga tca ggc aca gag ttc aca ctg caa atc 240  
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Glu Phe Thr Leu Gln Ile  
65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
85 90 95

eol f-seql

333

ctg caa acg ttc act ttc ggc gga ggg acc aaa gtg gat atc aaa  
 Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys  
                   100                                  105                                  110

<210> 36  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<400> 36

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
                   20                                  25                                  30

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

Pro Gln Leu Leu Ile Tyr Leu Ser Ser Asn Arg Pro Ser Gly Val Pro  
                   50                                  55                                  60

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Glu Phe Thr Leu Gln Ile  
 65                                  70                                  75                                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
                   85                                  90                                  95

Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys  
                   100                                  105                                  110

<210> 37  
 <211> 363  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(363)  
 <223> NI-302.11A4 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(195)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (292)..(330)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 37

eol f-seql

gag Glu 1	gtg Val	cag Gln	ctg Leu	gtg Val 5	gag Glu	tct Ser	gga Gly	gga Gly	ggc Gly 10	ttg Leu	atc Ile	cag Gln	ccg Pro	ggg Gly 15	ggg Gly	48
tcc Ser	ctg Leu	aga Arg	ctc Leu 20	tcc Ser	tgt Cys	gca Ala	gcc Ala	tct Ser 25	ggg Gly	ttc Phe	ccc Pro	gtc Val	agt Ser 30	agc Ser	agt Ser	96
tac Tyr	atg Met	agc Ser 35	tgg Trp	gtc Val	cgc Arg	cag Gln	gct Ala 40	cca Pro	gga Gly	gag Glu	ggg Gly	ctg Leu 45	gag Glu	tgg Trp	gtc Val	144
tca Ser	gtt Val 50	ctt Leu	tat Tyr	aga Arg	gac Asp	ggg Gly 55	gac Asp	aca Thr	tac Tyr	tac Tyr	gca Ala 60	gac Asp	tcc Ser	gtg Val	cag Gln	192
ggc Gly 65	cga Arg	ttc Phe	acc Thr	atc Ile	tcc Ser 70	aga Arg	gac Asp	aat Asn	tcc Ser	cag Gln 75	aac Asn	acg Thr	ttc Phe	tat Tyr	ctt Leu 80	240
caa Gln	atg Met	aac Asn	agc Ser	ctg Leu 85	aaa Lys	gcc Ala	gag Glu	gac Asp	acg Thr 90	gcc Ala	gtg Val	tat Tyr	tac Tyr	tgt Cys 95	gcg Ala	288
ggg Gly	gat Asp	aga Arg	agg Arg 100	tgc Ser	tca Ser	cac His	tac Tyr	tat Tyr 105	tac Tyr	ggg Gly	atg Met	gac Asp	gtc Val 110	tgg Trp	ggc Gly	336
cag Gln	ggg Gly	acc Thr 115	acg Thr	gtc Val	acc Thr	gtc Val	tcc Ser 120	tgc Ser								363

<210> 38  
 <211> 121  
 <212> PRT  
 <213> Homo sapiens  
 <400> 38

Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Ile	Gln	Pro	Gly 15	Gly
Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Pro	Val	Ser 30	Ser	Ser
Tyr	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Glu	Gly	Leu 45	Glu	Trp	Val
Ser	Val 50	Leu	Tyr	Arg	Asp	Gly 55	Asp	Thr	Tyr	Tyr	Ala 60	Asp	Ser	Val	Gln
Gly 65	Arg	Phe	Thr	Ile	Ser 70	Arg	Asp	Asn	Ser	Gln 75	Asn	Thr	Phe	Tyr	Leu 80
Gln	Met	Asn	Ser	Leu 85	Lys	Ala	Glu	Asp	Thr 90	Ala	Val	Tyr	Tyr	Cys 95	Ala
Gly	Asp	Arg	Arg 100	Ser	Ser	His	Tyr	Tyr 105	Tyr	Gly	Met	Asp	Val 110	Trp	Gly

eol f-seql

Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 39  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(321)  
<223> NI-302.11A4 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(105)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (151)..(171)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (268)..(291)  
<223> complementarity determining region (CDR) VK-CDR2

<400> 39  
gaa att gtg atg aca cag tct cca ggc acc ctg tct ttg tct cca gga 48  
Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15  
gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt agc agc agc 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ser Gln Ser Val Ser Ser Ser  
20 25 30  
tac ttc gcc tgg tac caa caa aaa cct ggc cag gct ccc agg ctc ctc 144  
Tyr Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
35 40 45  
atc tat ggt acg tcc cgc agg gcc act gcc atc cca gac agg ttc agt 192  
Ile Tyr Gly Thr Ser Arg Arg Ala Thr Ala Ile Pro Asp Arg Phe Ser  
50 55 60  
ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag 240  
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80  
cct gaa gat ttt gca gtg tat tac tgt caa cag tat ggt agc tcg tgg 288  
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Trp  
85 90 95  
acg ttc ggc cca ggg acc aag gtg gag atc aaa 321  
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 40  
<211> 107  
<212> PRT  
<213> Homo sapiens

<400> 40

Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly



eol f-seql

1		5		10		15
Glu	Arg	Ala	Thr	Leu	Ser	Cys
			20			
				Arg	Ala	Ser
				25		
					Gln	Ser
						Val
						30
						Ser
						Ser
Tyr	Phe	Ala	Trp	Tyr	Gln	Gln
		35				
				Lys	Pro	Gly
				40		
					Gln	Ala
						45
					Pro	Arg
						Leu
						Leu
Ile	Tyr	Gly	Thr	Ser	Arg	Arg
	50					
				Arg	Ala	Thr
				55		
					Ala	Ile
						60
					Pro	Asp
						Arg
						Phe
						Ser
Gly	Ser	Gly	Ser	Gly	Thr	Asp
65					70	
						Phe
						Thr
						Leu
						75
						Ile
						Ser
						Arg
						Leu
						80
Pro	Glu	Asp	Phe	Ala	Val	Tyr
				85		
					Tyr	Cys
						90
					Gln	Gln
						Tyr
						Gly
						Ser
						95
						Ser
						Trp
Thr	Phe	Gly	Pro	Gly	Thr	Lys
			100			
						Val
						105
						Glu
						Ile
						Lys

<210> 41  
 <211> 357  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <223> NI-302.22H9 VH variable heavy chain (VH) sequence

<220>  
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 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(195)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (292)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

<400>	41																		
gag	gtg	cag	ctg	gtg	gag	tct	ggg	gga	ggc	ttg	gtc	cac	cct	tgg	ggg				
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	His	Pro	Trp	Gly				
1				5				10						15					

tcc	ctg	aga	gtc	tcc	tgt	gca	gcc	tct	gga	ttc	agc	gtc	tct	aat	tac				
Ser	Leu	Arg	Val	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Ser	Val		Asn	Tyr				
			20					25					30						

gcc	ata	act	tgg	gtc	cgc	cag	gct	cca	ggg	aag	ggg	ctg	gaa	tat	att				
Ala	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Tyr	Ile				
		35					40					45							

tca	gtg	att	tat	cgt	gat	ggc	agg	aca	tac	tac	gga	gac	tcc	gtg	agg				
Ser	Val	Ile	Tyr	Arg	Asp	Gly	Arg	Thr	Tyr	Tyr	Gly	Asp	Ser	Val	Arg				

						eol f-seq1													
50					55				60										
ggc Gly 65	cgc Arg	ttc Phe	acc Thr	atc Ile	tct Ser 70	agg Arg	gac Asp	gat Asp	tcc Ser	aag Lys 75	aac Asn	act Thr	atc Ile	tat Tyr	ctt Leu 80	240			
caa Gln	atg Met	aac Asn	agc Ser	ctg Leu 85	aga Arg	ttt Phe	gag Glu	gac Asp	acg Thr 90	gct Ala	gtg Val	tat Tyr	tac Tyr	tgt Cys 95	gcg Ala	288			
aga Arg	gcg Ala	cac His	ggc Gly 100	caa Gln	tat Tyr	tat Tyr	tat Tyr	ggt Gly 105	gtg Val	gac Asp	gtc Val	tgg Trp	ggc Gly 110	caa Gln	ggg Gly	336			
acc Thr	acg Thr	gtc Val 115	acc Thr	gtc Val	tcc Ser	tcg Ser										357			

<210>	42
<211>	119
<212>	PRT
<213>	Homo sapi ens

<400> 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Trp Gly  
1 5 10 15

Ser Leu Arg Val Ser Cys Ala Ala Ser Gly Phe Ser Val Ser Asn Tyr  
20 25 30

Ala Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Ile  
35 40 45

Ser Val Ile Tyr Arg Asp Gly Arg Thr Tyr Tyr Gly Asp Ser Val Arg  
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ile Tyr Leu  
65 70 75 80

Gln Met Asn Ser Leu Arg Phe Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

Arg Ala His Gly Gln Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly  
100 105 110

Thr Thr Val Thr Val Ser Ser  
115

<210>	43
<211>	333
<212>	DNA
<213>	Homo sapi ens

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<220>
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<222> (1)..(333)
<223> NI-302.22H9 VK variable light-kappa chain (VK) sequence
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eof-seq1

<220>  
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 <222> (70)..(117)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (163)..(183)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (280)..(303)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 43  
 gat gtt gtg atg act cag tct cca ctc tcc ctg tcc gtc agc cct gga 48  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Ser Pro Gly  
 1 5 10 15  
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc cta cat agt 96  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 aat gga tac aac tat ttg gat tgg tac cgg cag aaa cca ggg cag tct 144  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Arg Gln Lys Pro Gly Gln Ser  
 35 40 45  
 cca caa ctc ctg atc tat ttg aat tct aat cgg gcc tcc ggg gtc cct 192  
 Pro Gln Leu Leu Ile Tyr Leu Asn Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60  
 gat agg ttc agt ggc agt gga tca ggc aca gag ttc aca ctg aca atc 240  
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile  
 65 70 75 80  
 agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct 288  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
 85 90 95  
 ctg caa acg ttc act ttc ggc gga ggg acc aag gtg gag atc aaa 333  
 Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 44  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<400> 44  
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Ser Pro Gly  
 1 5 10 15  
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
 20 25 30  
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Arg Gln Lys Pro Gly Gln Ser  
 35 40 45  
 Pro Gln Leu Leu Ile Tyr Leu Asn Ser Asn Arg Ala Ser Gly Val Pro  
 50 55 60

eof-seql

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
85 90 95

Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 45  
<211> 357  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(357)  
<223> NI-302.44D7 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(324)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 45	
gag gtg cag ctg gtg cag tct ggg gga ggc ttg gta cag cct ggg ggg	48
Glu Val Gln Leu Val Gln Ser Gly Gly Glu Leu Val Gln Pro Gly Gly	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	
20 25 30	
gcc atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
tca ggt att ggt tat agt gat act agc aca tat tac gca gac tcc gtg	192
Ser Gly Ile Gly Tyr Ser Asp Thr Ser Thr Tyr Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cgc ttc acc gtc tcc aga gac att tcc aag aac acg ctg tat	240
Lys Gly Arg Phe Thr Val Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aat agc ctg agg gcc gag gac acg gcc gta tat tac tgc	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aaa ggt acc agg gac tat tac ggt atg gac gtc tgg ggc caa ggg	336
Ala Lys Gly Thr Arg Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly	
100 105 110	

aca atg gtc acc gtc tct tcg  
 Thr Met Val Thr Val Ser Ser  
 115

<210> 46  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens  
 <400> 46

Gl u Val Gl n Leu Val Gl n Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Al a Met Ser Trp Val Arg Gl n Al a Pro Gly Lys Gly Leu Gl u Trp Val  
 35 40 45

Ser Gly Ile Gly Tyr Ser Asp Thr Ser Thr Tyr Tyr Al a Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gl n Met Asn Ser Leu Arg Al a Gl u Asp Thr Al a Val Tyr Tyr Cys  
 85 90 95

Al a Lys Gly Thr Arg Asp Tyr Tyr Gly Met Asp Val Trp Gly Gl n Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser  
 115

<210> 47  
 <211> 330  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(330)  
 <223> NI-302.44D7 VL variable light chain (VL) sequence

<220>  
 <221> V\_region  
 <222> (67)..(108)  
 <223> complementarity determining region (CDR) VL-CDR1

<220>  
 <221> V\_region  
 <222> (192)..(198)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (271)..(300)

eof-seql

<223> complementarity determining region (CDR) VL-CDR3

<400> 47

cag act gtg gtg act cag gag cca tcg ttc tca gtg tcc cct gga ggg 48  
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly  
1 5 10 15

aca gtc aca ctc act tgt ggc ttg agt tct ggc tca gtt tct act agt 96  
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser  
20 25 30

tac tac ccc agc tgg tac cag cag acc cca ggc cgg gct cca cgc acg 144  
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Arg Ala Pro Arg Thr  
35 40 45

ctc atc tac agc aca aac act cgc tct tct ggg gtc cct gat cgc ttc 192  
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe  
50 55 60

tct ggc tcc atc ctt ggg aac aag gct gcc ctc acc atc acg ggg gcc 240  
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala  
65 70 75 80

cag gca gat gat gaa tct gat tat tac tgt gtg ctg ttt atg ggt agt 288  
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Phe Met Gly Ser  
85 90 95

ggc att ggg gtg ttc ggc gga ggg acc agg ctg acc gtc cta 330  
Gly Ile Gly Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu  
100 105 110

<210> 48

<211> 110

<212> PRT

<213> Homo sapiens

<400> 48

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly  
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser  
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Arg Ala Pro Arg Thr  
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe  
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala  
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Phe Met Gly Ser  
85 90 95

Gly Ile Gly Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu  
100 105 110

<210> 49

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<211> 357  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <223> NI-302.37C12 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(192)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (292)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 49	
gag gtg cag ctg gtg gag tct ggt gga ggc ttg gtc cag cct ggg ggg	48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
1 5 10 15	
tcc ctg aga ctc tct tgt gtt gcc tct gca ctc acc gtc act aac agc	96
Ser Leu Arg Leu Ser Cys Val Ala Ser Ala Leu Thr Val Thr Asn Ser	
20 25 30	
caa atg acc tgg gtc cgc cgg gct cca ggg agg ggg ttg gag tgg gtc	144
Gln Met Thr Trp Val Arg Arg Ala Pro Gly Arg Gly Leu Glu Trp Val	
35 40 45	
tca gtt att tac acc agt ggt agt gca tac tac gca gac tcc gtg aag	192
Ser Val Ile Tyr Thr Ser Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys	
50 55 60	
ggc aga ttc acc atc tcc aga gac aat tcc aag aac aca gtg ttt ctt	240
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Phe Leu	
65 70 75	
caa atg aac agc ctg aga gtc gaa gac acg gct gtg tat tac tgt gcg	288
Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys Ala	
85 90 95	
aaa ggc cca tca gcc tat tat tac ggt ttg gac ctt tgg ggc caa ggg	336
Lys Gly Pro Ser Ala Tyr Tyr Tyr Gly Leu Asp Leu Trp Gly Gln Gly	
100 105 110	
acc acg gtc acc gtc tcc tcg	357
Thr Thr Val Thr Val Ser Ser	
115	

<210> 50  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 50  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

eof-seq1

Ser Leu Arg Leu Ser Cys Val Ala Ser Ala Leu Thr Val Thr Asn Ser  
20 25 30  
Gln Met Thr Trp Val Arg Arg Ala Pro Gly Arg Gly Leu Glu Trp Val  
35 40 45  
Ser Val Ile Tyr Thr Ser Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys  
50 55 60  
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Phe Leu  
65 70 75 80  
Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95  
Lys Gly Pro Ser Ala Tyr Tyr Tyr Gly Leu Asp Leu Trp Gly Gln Gly  
100 105 110  
Thr Thr Val Thr Val Ser Ser  
115

<210> 51  
<211> 333  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(333)  
<223> NI-302.37C12 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(117)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (163)..(183)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (280)..(303)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 51  
gat att gtg atg act caa tca cca ctc tcc ctg ccc gtc acc cct gga 48  
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag ccg ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
35 40 45



eof-seql

cca	cag	ctc	ctg	atc	tat	ttg	ggg	tct	act	cgg	gcc	tcc	ggg	gtc	cct	192
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Thr	Arg	Ala	Ser	Gly	Val	Pro	
	50					55					60					
gac	agg	ttc	agt	ggc	agt	gga	tca	ggc	aca	gat	ttt	aca	ctg	aag	atc	240
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	
65				70					75						80	
agc	aga	gtg	gag	gct	gag	gat	gtt	ggg	gtt	tat	tac	tgc	atg	caa	ggg	288
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Gly	
			85					90						95		
cta	cag	acg	tac	act	ttt	ggc	cag	ggg	acc	aag	ctg	gag	atc	aaa		333
Leu	Gln	Thr	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys		
			100					105					110			

<210> 52  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<400> 52

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	
1				5					10					15		
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser	
			20					25					30			
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	
		35					40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Thr	Arg	Ala	Ser	Gly	Val	Pro	
	50					55					60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	
65				70						75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Gly	
			85					90						95		
Leu	Gln	Thr	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys		
			100					105					110			

<210> 53  
 <211> 378  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(378)  
 <223> NI-302.55D8 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

eof-seq1

<220>  
 <221> V\_region  
 <222> (148)..(213)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (295)..(345)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 53  
 cag gtg cag ctg gtg cag tct ggg tct gag gtg aag aag cct ggg gcc 48  
 Gln Val Gln Leu Val Gln Ser Gly Ser Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15  
 tca gtg aag gtc tcc tgc aag gct tct gga tac acc ttc acc gac tac 96  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr  
 20 25 30  
 tat ata cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 gga cgg atc aac cct aac aat ggt ggc aca aac tat gca cag aac ttt 192  
 Gly Arg Ile Asn Pro Asn Asn Gly Gly Thr Asn Tyr Ala Gln Asn Phe  
 50 55 60  
 cag ggc tgg gtc acc atg acc agg gac acg tcc atc agc aca gcc tac 240  
 Gln Gly Trp Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr  
 65 70 75 80  
 atg gag ctc agc aga ctg aga tct gac gac acg gcc gtc tat tac tgt 288  
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gtg ggg ggc gag ctg cta cga gaa ggc ggc tat cac tac tac 336  
 Ala Arg Val Gly Gly Glu Leu Leu Arg Glu Gly Gly Tyr His Tyr Tyr  
 100 105 110  
 atg gac gtc tgg ggc aag ggg acc acg gtc acc gtc tcc tcg 378  
 Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser  
 115 120 125

<210> 54  
 <211> 126  
 <212> PRT  
 <213> Homo sapiens

<400> 54  
 Gln Val Gln Leu Val Gln Ser Gly Ser 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 Asp Tyr  
 20 25 30  
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 Gly Arg Ile Asn Pro Asn Asn Gly Gly Thr Asn Tyr Ala Gln Asn Phe  
 50 55 60

eol f-seql

Gln Gly Trp Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr  
65 70 75 80

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

Ala Arg Val Gly Gly Glu Leu Leu Arg Glu Gly Gly Tyr His Tyr Tyr  
100 105 110

Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

<210> 55  
<211> 336  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(336)  
<223> NI-302.55D8 VL variable light chain (VL) sequence

<220>  
<221> V\_region  
<222> (67)..(108)  
<223> complementarity determining region (CDR) VL-CDR1

<220>  
<221> V\_region  
<222> (154)..(174)  
<223> complementarity determining region (CDR) VL-CDR2

<220>  
<221> V\_region  
<222> (271)..(306)  
<223> complementarity determining region (CDR) VL-CDR3

<400> 55	
cag tct gtg ttg acg cag ccg ccc tca gtg tct ggg gcc cca ggg cag	48
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln	
1 5 10 15	
agg gtc acc atc tcc tgc act ggg aac agc tcc aac atc ggg gca ggt	96
Arg Val Thr Ile Ser Cys Thr Gly Asn Ser Ser Asn Ile Gly Ala Gly	
20 25 30	
tat gat gta cac tgg tac cag cag ctt cca gga aca gcc ccc aaa ctc	144
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu	
35 40 45	
ctc atc ttt gat aat acc aat cgg ccc tca ggg gtc cct gac cga ttc	192
Leu Ile Phe Asp Asn Thr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe	
50 55 60	
tct ggc tcc aag tct ggc acc tca gcc tcc ctg gcc atc act ggg ctc	240
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu	
65 70 75 80	
cag gct gag gat gag gct aat tat cac tgc cag tcc tat gac aac agc	288
Gln Ala Glu Asp Glu Ala Asn Tyr His Cys Gln Ser Tyr Asp Asn Ser	
85 90 95	
ctg agt ggt tct tgg gtg ttc ggc gga ggg acc aag ctg acc gtc cta	336

Leu Ser Gly Ser Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105 110

<210> 56  
<211> 112  
<212> PRT  
<213> Homo sapiens

<400> 56

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln  
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Asn Ser Ser Asn Ile Gly Ala Gly  
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu  
35 40 45

Leu Ile Phe Asp Asn Thr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe  
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu  
65 70 75 80

Gln Ala Glu Asp Glu Ala Asn Tyr His Cys Gln Ser Tyr Asp Asn Ser  
85 90 95

Leu Ser Gly Ser Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105 110

<210> 57  
<211> 369  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(369)  
<223> NI-302.7A8 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(336)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 57  
gag gtg cag ctg gtg gag tct ggg gga ggc tcg gtc cag cct ggg ggg  
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly

48

1	eol f-seql										15					
	10															
tcc	ctg	aga	ctc	tcc	tgt	gta	gcc	tct	gga	ttc	ata	ttt	aga	aac	agt	96
Ser	Leu	Arg	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Ile	Phe	Arg	Asn	Ser	
			20					25					30			
tgg	atg	acc	tgg	gtc	cgc	cag	gat	cca	ggg	aag	ggg	ctg	gag	tgg	gtg	144
Trp	Met	Thr	Trp	Val	Arg	Gln	Asp	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
gcc	aac	ata	aag	gaa	gat	gga	agt	cgg	aca	tac	tat	gtg	gac	tct	gtg	192
Ala	Asn	Ile	Lys	Glu	Asp	Gly	Ser	Arg	Thr	Tyr	Tyr	Val	Asp	Ser	Val	
	50					55					60					
aag	ggc	cga	ttc	acc	atc	tcc	aga	gac	aac	gcc	aag	aac	tca	ctg	tat	240
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr	
65					70					75					80	
ctg	cag	atg	aac	agc	ctg	aga	gcc	gag	gac	acg	gct	gta	tat	tac	tgt	288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
gcg	aga	gga	gat	tat	aat	tcg	ggc	atc	tat	tac	ttt	ccc	ggg	gac	tac	336
Ala	Arg	Gly	Asp	Tyr	Asn	Ser	Gly	Ile	Tyr	Tyr	Phe	Pro	Gly	Asp	Tyr	
			100					105					110			
tgg	ggc	cag	ggc	acc	ctg	gtc	acc	gtc	tcc	tcg						369
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
		115					120									

<210> 58  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<400> 58

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Pro	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Ile	Phe	Arg	Asn	Ser
			20					25					30		
Trp	Met	Thr	Trp	Val	Arg	Gln	Asp	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Asn	Ile	Lys	Glu	Asp	Gly	Ser	Arg	Thr	Tyr	Tyr	Val	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Gly	Asp	Tyr	Asn	Ser	Gly	Ile	Tyr	Tyr	Phe	Pro	Gly	Asp	Tyr
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
		115					120								

eof-seq1

<210> 59  
 <211> 336  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(336)  
 <223> NI-302.7A8 VK variable light-kappa chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(117)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (163)..(183)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (280)..(306)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 59		
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc ctt gga		48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly		
1 5 10 15		
cag ccg gcc tcc atc tcc tgt agg tct agt caa agc ctc gta tac agt		96
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser		
20 25 30		
gat gga aac acc tac ttg aat tgg ttt cag cag agg cca ggc cag tct		144
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser		
35 40 45		
cca agg cgc ctc att tat aag gtt tct aac cgg gac tct ggg gtc cca		192
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro		
50 55 60		
gac aga ttc agc ggc agt ggg tca ggc act gat ttc aca ctg aga atc		240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile		
65 70 75 80		
agc agg gtg gag gct gag gat gtt ggc att tat tac tgc atg caa ggt		288
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly		
85 90 95		
aca cac tgg cct ggg acg ttc ggc caa ggg acc aag gtg gag atc aaa		336
Thr His Trp Pro Gly Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
100 105 110		

<210> 60  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 60

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

eof-seq1

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser  
20 25 30  
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser  
35 40 45  
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro  
50 55 60  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile  
65 70 75 80  
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly  
85 90 95  
Thr His Trp Pro Gly Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 61  
<211> 381  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(381)  
<223> NI-302.78H12 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(108)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (151)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(348)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 61  
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48  
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1 5 10 15  
acc ctg tcc ctc acc tgt ctt gtc tct agt tac tcc atc agc aat ggt 96  
Thr Leu Ser Leu Thr Cys Leu Val Ser Ser Tyr Ser Ile Ser Asn Gly  
20 25 30  
tac tac tgg ggc tgg att cgg cag ccc cca ggg aag ggg ctg gag tgg 144  
Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
35 40 45  
att ggg agt atc tat cat aat ggg aac acc tat tac aac ccg tcc ctc 192  
Ile Gly Ser Ile Tyr His Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu  
50 55 60

eol f-seql

aag	agt	cga	gtc	atc	att	tca	gta	gac	acg	tcc	aag	aac	cag	ttc	tcc		240
Lys	Ser	Arg	Val	Ile	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser		
65					70					75					80		
ctg	aag	ttg	agg	tct	gtg	acc	gcc	gca	gac	acg	gcc	gtg	tac	tac	tgt		288
Leu	Lys	Leu	Arg	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
gcg	atg	cca	agt	gcc	acc	tat	tat	tat	ggg	tgc	ggg	act	caa	ttc	cat		336
Ala	Met	Pro	Ser	Ala	Thr	Tyr	Tyr	Tyr	Gly	Ser	Gly	Thr	Gln	Phe	His		
			100					105					110				
gcg	ttt	gat	gtc	tgg	ggc	caa	ggg	acc	acg	gtc	acc	gtc	tcc	tgc			381
Ala	Phe	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
		115					120					125					

<210> 62  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<400> 62

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu		
1				5					10					15			
Thr	Leu	Ser	Leu	Thr	Cys	Leu	Val	Ser	Ser	Tyr	Ser	Ile	Ser	Asn	Gly		
			20					25					30				
Tyr	Tyr	Trp	Gly	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp		
		35					40					45					
Ile	Gly	Ser	Ile	Tyr	His	Asn	Gly	Asn	Thr	Tyr	Tyr	Asn	Pro	Ser	Leu		
	50					55					60						
Lys	Ser	Arg	Val	Ile	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser		
65					70					75					80		
Leu	Lys	Leu	Arg	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
Ala	Met	Pro	Ser	Ala	Thr	Tyr	Tyr	Tyr	Gly	Ser	Gly	Thr	Gln	Phe	His		
			100					105					110				
Ala	Phe	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
		115					120					125					

<210> 63  
 <211> 333  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(333)  
 <223> NI-302.78H12 VL variable light chain (VL) sequence

<220>



eof-seql

<221> V\_region  
 <222> (67)..(108)  
 <223> complementarity determining region (CDR) VL-CDR1

<220>  
 <221> V\_region  
 <222> (154)..(174)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (271)..(303)  
 <223> complementarity determining region (CDR) VL-CDR3

<400> 63  
 cag tct gcc ctg act cag cct cgc tca gtg tcc ggg tct cct gga cag 48  
 Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15  
 tca gtc acc atc tcc tgc act gga acc agc aga gat gtt ggt aat tat 96  
 Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Arg Asp Val Gly Asn Tyr  
 20 25 30  
 aac tat gtc tcc tgg tac caa caa cac cca ggc gaa gtc ccc aaa ctc 144  
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Glu Val Pro Lys Leu  
 35 40 45  
 ata att tat gat gtc agt gag cgg ccc tca ggg gtc cct gat cgc ttc 192  
 Ile Ile Tyr Asp Val Ser Glu Arg Pro Ser Gly Val Pro Asp Arg Phe  
 50 55 60  
 tct ggc tcc aag tct ggc aac acg gcc tcg ctg acc atc tct ggg ctc 240  
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65 70 75 80  
 cag gct gag gat gag gct gac tat tac tgc tgc tca tat gct ggc agt 288  
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser  
 85 90 95  
 tac acc ttc gag gta ttt ggc gga ggg acc aag ctg acc gtc cta 333  
 Tyr Thr Phe Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105 110

<210> 64  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<400> 64  
 Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15  
 Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Arg Asp Val Gly Asn Tyr  
 20 25 30  
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Glu Val Pro Lys Leu  
 35 40 45  
 Ile Ile Tyr Asp Val Ser Glu Arg Pro Ser Gly Val Pro Asp Arg Phe  
 50 55 60  
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

eol f-seql																
65				70				75				80				
Gln	Ala	Glu	Asp	Glu <sub>85</sub>	Ala	Asp	Tyr	Tyr	Cys <sub>90</sub>	Cys	Ser	Tyr	Ala	Gly <sub>95</sub>	Ser	
Tyr	Thr	Phe	Glu	Val <sub>100</sub>	Phe	Gly	Gly	Gly <sub>105</sub>	Thr	Lys	Leu	Thr	Val <sub>110</sub>	Leu		
<210> 65																
<211> 360																
<212> DNA																
<213> Homo sapiens																
<220>																
<221> CDS																
<222> (1)..(360)																
<223> NI-302.71F6 VH variable heavy chain (VH) sequence																
<220>																
<221> V_region																
<222> (91)..(105)																
<223> complementarity determining region (CDR) VH-CDR1																
<220>																
<221> V_region																
<222> (148)..(195)																
<223> complementarity determining region (CDR) VH-CDR2																
<220>																
<221> V_region																
<222> (292)..(327)																
<223> complementarity determining region (CDR) VH-CDR3																
<400> 65																
cag	gtg	cag	cta	cag	cag	tgg	ggc	gca	gga	cta	ttg	aag	cct	tcg	gag	48
Gln	Val	Gln	Leu	Gln <sub>5</sub>	Gln	Trp	Gly	Ala <sub>10</sub>	Gly	Leu	Leu	Lys	Pro	Ser <sub>15</sub>	Glu	
1																
acc	ctg	tcc	ctc	acg	tgc	gct	gtc	tat	ggg	ggg	tcc	ctc	agt	ggg	tac	96
Thr	Leu	Ser	Leu	Thr <sub>20</sub>	Cys	Ala	Val	Tyr <sub>25</sub>	Gly	Gly	Ser	Leu	Ser <sub>30</sub>	Gly	Tyr	
tac	tgg	agc	tgg	atc	cgc	cag	ccc	cca	ggg	aag	ggg	ctg	gag	tgg	ata	144
Tyr	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro <sub>40</sub>	Gly	Lys	Gly	Leu <sub>45</sub>	Glu	Trp	Ile	
ggg	gaa	gtc	aat	cat	agt	gga	ggc	acc	aac	ctc	aat	tcg	tcc	ctc	aag	192
Gly	Glu	Val	Asn	His	Ser	Gly <sub>55</sub>	Gly	Thr	Asn	Leu	Asn <sub>60</sub>	Ser	Ser	Leu	Lys	
agt	cga	gtc	atc	att	tca	gta	gac	aag	tcc	aag	aag	cag	ttc	tcc	ctg	240
Ser	Arg	Val	Ile	Ile	Ser <sub>70</sub>	Val	Asp	Lys	Ser	Lys <sub>75</sub>	Lys	Gln	Phe	Ser	Leu	
aaa	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gct	atg	tac	ttc	tgt	gcg	288
Lys	Leu	Ser	Ser	Val <sub>85</sub>	Thr	Ala	Ala	Asp	Thr <sub>90</sub>	Ala	Met	Tyr	Phe	Cys <sub>95</sub>	Ala	
aga	gga	tac	agc	tat	gac	cca	aaa	tac	tac	ttt	gac	tcc	tgg	agc	cag	336
Arg	Gly	Tyr	Ser	Tyr <sub>100</sub>	Asp	Pro	Lys	Tyr <sub>105</sub>	Tyr	Phe	Asp	Ser	Trp <sub>110</sub>	Ser	Gln	
ggc	acc	ctg	gtc	acc	gtc	tcc	tcg									360
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser									

eof-seql

115

120

<210> 66  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 66

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

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Leu Ser Gly Tyr  
 20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
 35 40 45

Gly Glu Val Asn His Ser Gly Gly Thr Asn Leu Asn Ser Ser Leu Lys  
 50 55 60

Ser Arg Val Ile Ile Ser Val Asp Lys Ser Lys Lys Gln Phe Ser Leu  
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Met Tyr Phe Cys Ala  
 85 90 95

Arg Gly Tyr Ser Tyr Asp Pro Lys Tyr Tyr Phe Asp Ser Trp Ser Gln  
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 67  
 <211> 330  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(330)  
 <223> NI-302.71F6 VL variable light chain (VL) sequence

<220>  
 <221> V\_region  
 <222> (67)..(108)  
 <223> complementarity determining region (CDR) VL-CDR1

<220>  
 <221> V\_region  
 <222> (154)..(174)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (271)..(300)  
 <223> complementarity determining region (CDR) VL-CDR3

eol f-seql

<400> 67  
 cag tct gcc ctg act cag cct gcc tcc gtg tct ggg tct cct gga cag 48  
 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15

gcg atc acc atc tcc tgc act gga acc agt agt gat att ggg agt tat 96  
 Ala Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Ser Tyr  
 20 25 30

gat ttt gtc tcc tgg tac cag cag gac cca ggc aaa gcc ccc aaa gtc 144  
 Asp Phe Val Ser Trp Tyr Gln Gln Asp Pro Gly Lys Ala Pro Lys Val  
 35 40 45

att att tat ggg gtc aat aag cgg ccc tca ggg gtt tct aat cgc ttc 192  
 Ile Ile Tyr Gly Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50 55 60

tct ggc tcc aag tct ggc aac acg gcc tcc ctg aca atc tct gga ctc 240  
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65 70 75 80

cag gct gac gac gag gct gat tat tac tgc tgc tca tat gct ggt agt 288  
 Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser  
 85 90 95

acc act tgg gtg ttc ggc gga ggg acc aaa ctg acc gtc cta 330  
 Thr Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105 110

<210> 68  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<400> 68  
 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15

Ala Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Ser Tyr  
 20 25 30

Asp Phe Val Ser Trp Tyr Gln Gln Asp Pro Gly Lys Ala Pro Lys Val  
 35 40 45

Ile Ile Tyr Gly Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65 70 75 80

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser  
 85 90 95

Thr Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105 110

<210> 69  
 <211> 363  
 <212> DNA

eol f-seql

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(363)

<223> NI-302.11H6 VH variable heavy chain (VH) sequence

<220>

<221> V\_region

<222> (91)..(105)

<223> complementarity determining region (CDR) VH-CDR1

<220>

<221> V\_region

<222> (148)..(198)

<223> complementarity determining region (CDR) VH-CDR2

<220>

<221> V\_region

<222> (295)..(330)

<223> complementarity determining region (CDR) VH-CDR3

<400> 69

gag	gtg	cag	ctg	gtg	cag	tct	gga	gct	gtg	atg	aag	aag	cct	gga	gac		48
Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Val	Met	Lys	Lys	Pro	Gly	Asp		
1				5					10					15			

tca	gtg	agg	gtc	tcc	tgc	agg	gct	tct	act	tac	agc	ttt	tcc	acc	tat		96
Ser	Val	Arg	Val	Ser	Cys	Arg	Ala	Ser	Thr	Tyr	Ser	Phe	Ser	Thr	Tyr		
			20					25					30				

agt	ttc	acc	tgg	gtg	cga	cag	gtc	cct	gga	caa	ggc	ctt	gag	tgg	atg		144
Ser	Phe	Thr	Trp	Val	Arg	Gln	Val	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
		35					40					45					

gga	tgg	atc	agc	gct	tat	aat	ggc	cac	aca	aac	tat	gta	gac	agc	ttc		192
Gly	Trp	Ile	Ser	Ala	Tyr	Asn	Gly	His	Thr	Asn	Tyr	Val	Asp	Ser	Phe		
	50					55					60						

cag	ggc	aga	ctc	acg	tgg	acc	aca	gac	aca	tcc	gcg	agt	aca	gcg	tac		240
Gln	Gly	Arg	Leu	Thr	Leu	Thr	Thr	Asp	Thr	Ser	Ala	Ser	Thr	Ala	Tyr		
65					70					75					80		

atg	gaa	ctg	agg	agc	ctc	aga	tct	gac	gac	acg	gcc	atc	tat	tat	tgt		288
Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys		
				85				90						95			

gcg	gct	gta	gac	acc	act	tac	tac	tat	tac	ggc	atg	gac	gtc	tgg	ggc		336
Ala	Ala	Val	Asp	Thr	Thr	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp	Val	Trp	Gly		
			100					105					110				

caa	ggc	acc	ctg	gtc	acc	gtc	tcc	tcg									363
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser									
		115					120										

<210> 70

<211> 121

<212> PRT

<213> Homo sapiens

<400> 70

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

eof-seq1

Ser Val Arg Val Ser Cys Arg Ala Ser Thr Tyr Ser Phe Ser Thr Tyr  
20 25 30

Ser Phe Thr Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly His Thr Asn Tyr Val Asp Ser Phe  
50 55 60

Gln Gly Arg Leu Thr Leu Thr Thr Asp Thr Ser Ala Ser Thr Ala Tyr  
65 70 75 80

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

Ala Ala Val Asp Thr Thr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly  
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 71  
<211> 330  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(330)  
<223> NI-302.11H6 VL variable light chain (VL) sequence

<220>  
<221> V\_region  
<222> (67)..(108)  
<223> complementarity determining region (CDR) VL-CDR1

<220>  
<221> V\_region  
<222> (154)..(174)  
<223> complementarity determining region (CDR) VL-CDR2

<220>  
<221> V\_region  
<222> (271)..(300)  
<223> complementarity determining region (CDR) VL-CDR3

<400> 71  
cag act gtg gtg act cag gag cca acg ttc tca gtg tcc cct gga ggg 48  
Gln Thr Val Val Thr Gln Glu Pro Thr Phe Ser Val Ser Pro Gly Gly  
1 5 10 15

aca gtc aca ctc act tgt gcc ttg agg ttt ggc tca gtc tct agt agc 96  
Thr Val Thr Leu Thr Cys Ala Leu Arg Phe Gly Ser Val Ser Ser Ser  
20 25 30

tac tat ccc agc tgg ttc cag cag acc cca ggc cag gct cca cgc acg 144  
Tyr Tyr Pro Ser Trp Phe Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr  
35 40 45

ctc atc tac agc aca aac acc cgc tct tcg ggg gtc cct gct cga ttc 192

eol f-seql

Leu	Ile	Tyr	Ser	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Ala	Arg	Phe		
50						55					60						
tct	ggc	tcc	att	ctt	ggg	aac	aaa	gct	gcc	ctc	acc	atc	gcg	ggg	gcc		240
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Ala	Gly	Ala		
65					70					75					80		
cag	gca	aat	gat	gag	gct	gac	tat	tac	tgt	gtg	ctg	tat	atg	ggg	agt		288
Gln	Ala	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Val	Leu	Tyr	Met	Gly	Ser		
				85					90					95			
gga	atc	ggg	gtg	ttc	ggc	gga	ggg	acc	aag	ttg	acc	gtc	cta				330
Gly	Ile	Gly	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
			100					105					110				

<210> 72  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens  
 <400> 72

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Thr	Phe	Ser	Val	Ser	Pro	Gly	Gly		
1				5					10					15			
Thr	Val	Thr	Leu	Thr	Cys	Ala	Leu	Arg	Phe	Gly	Ser	Val	Ser	Ser	Ser		
			20					25					30				
Tyr	Tyr	Pro	Ser	Trp	Phe	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr		
		35					40					45					
Leu	Ile	Tyr	Ser	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Ala	Arg	Phe		
						55					60						
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Ala	Gly	Ala		
65					70					75					80		
Gln	Ala	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Val	Leu	Tyr	Met	Gly	Ser		
				85					90					95			
Gly	Ile	Gly	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
			100					105					110				

<210> 73  
 <211> 357  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <223> NI-302.3D8 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (88)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>

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<221> V\_region  
 <222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (295)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 73  
 gag gtg cag ctg gtg cag tct ggg gga ggc ttg gta cag cct ggg ggg 48  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 tcc ctg aga ctc tct tgt gaa gcc tcc gga ttc atc ttt aaa acc tat 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Ile Phe Lys Thr Tyr  
 20 25 30  
 gcc atg agc tgg gtc cgc cag ctt ccc ggg agg ggg ctg gaa tgg gtc 144  
 Ala Met Ser Trp Val Arg Gln Leu Pro Gly Arg Gly Leu Glu Trp Val  
 35 40 45  
 tca gct ata agt gcc act ggt gga agc acc ttc tac gca gag tcc gtg 192  
 Ser Ala Ile Ser Ala Thr Gly Gly Ser Thr Phe Tyr Ala Glu Ser Val  
 50 55 60  
 aag ggc cgg ctc acc att tcc aga gac act gcc aag aat aca gtg tat 240  
 Lys Gly Arg Leu Thr Ile Ser Arg Asp Thr Ala Lys Asn Thr Val Tyr  
 65 70 75 80  
 ctg caa atg aac aac ctg aga gcc gaa gac acg gcc atg tat tac tgt 288  
 Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys  
 85 90 95  
 gcg aaa ggg tcg act gcg gta tat ctc ttt gac tcc tgg ggc cag gga 336  
 Ala Lys Gly Ser Thr Ala Val Tyr Leu Phe Asp Ser Trp Gly Gln Gly  
 100 105 110  
 acc ctg gtc acc gtc tcc tcg 357  
 Thr Leu Val Thr Val Ser Ser  
 115

<210> 74  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 74  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Ile Phe Lys Thr Tyr  
 20 25 30  
 Ala Met Ser Trp Val Arg Gln Leu Pro Gly Arg Gly Leu Glu Trp Val  
 35 40 45  
 Ser Ala Ile Ser Ala Thr Gly Gly Ser Thr Phe Tyr Ala Glu Ser Val  
 50 55 60  
 Lys Gly Arg Leu Thr Ile Ser Arg Asp Thr Ala Lys Asn Thr Val Tyr  
 65 70 75 80



eof-seq1

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

Ala Lys Gly Ser Thr Ala Val Tyr Leu Phe Asp Ser Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210> 75  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(321)  
<223> NI-302.3D8 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(102)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (148)..(168)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (265)..(291)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 75  
gac atc cag atg acc cag tct ccg tcc tca ctg tct gca tct gta ggc 48  
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1 5 10 15

gac aga gtc acc ctc act tgt cgg gcg agt cag gac atc aga aat ttc 96  
Asp Arg Val Thr Leu Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Phe  
20 25 30

ttg gcc tgg att cag cag aag cca ggg aaa ccc cct aag tcc ctg atc 144  
Leu Ala Trp Ile Gln Gln Lys Pro Gly Lys Pro Pro Lys Ser Leu Ile  
35 40 45

tat gct gcg tcc act ttg caa agt ggg gtc cca tca cga ttc agc ggc 192  
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

agt gga tcc ggg aca gat ttc act ctc acc atc agc agc ctg cac cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu His Pro  
65 70 75 80

gaa gat ttt gct act tat tac tgc cag cag ttt tat aat tac cct ccg 288  
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Tyr Asn Tyr Pro Pro  
85 90 95

acg ttc ggc caa ggg acc aag gtg gag atc aaa 321  
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105

eof-seql

<210> 76  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 76

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

Asp Arg Val Thr Leu Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Phe  
 20 25 30

Leu Ala Trp Ile Gln Gln Lys Pro Gly Lys Pro Pro Lys Ser Leu Ile  
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu His Pro  
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Tyr Asn Tyr Pro Pro  
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 77  
 <211> 360  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(360)  
 <223> NI-302.18A1 VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (154)..(201)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (298)..(327)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 77

cag ctg cag ctg cag gag tcg ggc cca gga cta gtg aag cct tcg gag  
 Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15

48

eol f-seql

gcc	ctg	tcc	ctc	acc	tgc	act	gtc	tct	ggg	ggc	tcc	atc	act	act	gat	96
Ala	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Thr	Thr	Asp	
			20					25					30			
tat	tac	tat	tgg	ggc	tgg	atc	cgc	cag	tcc	cca	ggc	aag	gga	cta	gag	144
Tyr	Tyr	Tyr	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Lys	Gly	Leu	Glu	
		35					40					45				
tgg	gtt	ggg	aca	ata	tac	ttt	ggg	ggg	gcc	acc	tac	tac	aat	ccg	tcc	192
Trp	Val	Gly	Thr	Ile	Tyr	Phe	Gly	Gly	Ala	Thr	Tyr	Tyr	Asn	Pro	Ser	
	50					55					60					
ctc	agg	aac	cgg	gtc	tgc	ata	tct	gtg	gac	acg	tcc	aac	act	cgc	ctc	240
Leu	Arg	Asn	Arg	Val	Ser	Ile	Ser	Val	Asp	Thr	Ser	Asn	Thr	Arg	Leu	
65					70					75					80	
tcc	ctg	aga	ctt	atc	tct	ctg	agc	gcc	gct	gac	acg	gcc	gtc	tat	tat	288
Ser	Leu	Arg	Leu	Ile	Ser	Leu	Ser	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	
				85					90					95		
tgt	gcg	aga	gtg	ggc	tac	ttg	gat	agg	agt	ggg	ctt	ctt	gtg	ggc	cag	336
Cys	Ala	Arg	Val	Gly	Tyr	Leu	Asp	Arg	Ser	Gly	Leu	Leu	Val	Gly	Gln	
			100					105					110			
ggc	acc	ctg	gtc	acc	gtc	tcc	tgc									360
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser									
		115					120									

<210> 78  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 78

Gln	Leu	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	
1				5					10					15		
Ala	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Thr	Thr	Asp	
			20					25					30			
Tyr	Tyr	Tyr	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Lys	Gly	Leu	Glu	
		35					40					45				
Trp	Val	Gly	Thr	Ile	Tyr	Phe	Gly	Gly	Ala	Thr	Tyr	Tyr	Asn	Pro	Ser	
	50					55					60					
Leu	Arg	Asn	Arg	Val	Ser	Ile	Ser	Val	Asp	Thr	Ser	Asn	Thr	Arg	Leu	
65					70				75						80	
Ser	Leu	Arg	Leu	Ile	Ser	Leu	Ser	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	
				85					90					95		
Cys	Ala	Arg	Val	Gly	Tyr	Leu	Asp	Arg	Ser	Gly	Leu	Leu	Val	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser									
		115					120									

eof-seq1

<210> 79  
 <211> 336  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(336)  
 <223> NI-302.18A1 VK variable light-kappa chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(117)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (163)..(183)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (280)..(306)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 79	
gaa att gtg ctg acg cag tct cca ctc tcc gtg ccc gtc acc ccc gga	48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Val Pro Val Thr Pro Gly	
1 5 10 15	
 gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat aat	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Asn	
20 25 30	
 aat gga tac aac tat ttg gat tgg tac ctg aag aag cct ggg cag tct	144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser	
35 40 45	
 cca caa ctc ctg atc tat ttg ggc tct act cgg gcc tcc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro	
50 55 60	
 gac agg ttc agt gcc agt gga tca ggc aca gac ttt aca ctg gaa atc	240
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile	
65 70 75 80	
 agc aga gtg gag gct gaa gat gtt ggc gtt tac tac tgc atg caa gct	288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala	
85 90 95	
 ctg cag act cct ccg act ttc ggc aga ggg acc aag gtg gag atc aaa	336
Leu Gln Thr Pro Pro Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys	
100 105 110	

<210> 80  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 80

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Asn

eof-seq1

20

25

30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gl n Ser  
35 40 45

Pro Gl n Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Gl u Ile  
65 70 75 80

Ser Arg Val Gl u Ala Gl u Asp Val Gly Val Tyr Tyr Cys Met Gl n Ala  
85 90 95

Leu Gl n Thr Pro Pro Thr Phe Gly Arg Gly Thr Lys Val Gl u Ile Lys  
100 105 110

<210> 81  
<211> 366  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(366)  
<223> NI-302.8F1 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(204)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (301)..(333)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 81  
gag gtg cag ctg gtg gag tct ggg gga ggc ttg gtg aag ccg ggg ggg 48  
Glu Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Lys Pro Gl y Gl y  
1 5 10 15

tcc ctt aca atc tcc tgt gca gcc tct ggt ttc acc ttc agt aat gcc 96  
Ser Leu Thr Ile Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala  
20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggt aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gl n Ala Pro Gly Lys Gl y Leu Gl u Trp Val  
35 40 45

ggc cat att aga acg caa gct gaa gga ggg aca tca gac tat gct gca 192  
Gly His Ile Arg Thr Gl n Ala Gl u Gly Gl y Thr Ser Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa ggc aga ttc acc atc tca aga gat gac tca aaa aac acg 240  
Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr

65											eol f-seql											80								
															75															
ctg	tat	ctg	caa	atg	aac	agc	ctg	aaa	acc	gag	gac	aca	gcc	gta	tat	288														
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr															
															85															
tat	tgt	atc	ccc	ccc	ccc	tac	tac	tac	tat	tac	ggg	ctg	gac	gtc	tgg	336														
Tyr	Cys	Ile	Pro	Pro	Pro	Tyr	Tyr	Tyr	Tyr	Tyr	Gly	Leu	Asp	Val	Trp															
															100															
ggc	caa	ggg	acc	acg	gtc	acc	gtc	tcc	tgc							366														
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser																					
															115															
															120															

<210> 82  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 82

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

Ser	Leu	Thr	Ile	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Ala
			20					25					30		

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

Gly	His	Ile	Arg	Thr	Gln	Ala	Glu	Gly	Gly	Thr	Ser	Asp	Tyr	Ala	Ala
	50					55					60				

Pro	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
65					70					75				80	

Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
				85					90					95	

Tyr	Cys	Ile	Pro	Pro	Pro	Tyr	Tyr	Tyr	Tyr	Gly	Leu	Asp	Val	Trp
			100				105					110		

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

<210> 83  
 <211> 327  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(327)  
 <223> NI-302.8F1 VL variable light chain (VL) sequence

<220>  
 <221> V\_region  
 <222> (67)..(108)

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<223> complementarity determining region (CDR) VL-CDR1

<220>

<221> V\_region

<222> (154)..(174)

<223> complementarity determining region (CDR) VL-CDR2

<220>

<221> V\_region

<222> (271)..(297)

<223> complementarity determining region (CDR) VL-CDR3

<400> 83

cag tct gcc ctg act cag cct gcc tcc gtg tct ggg tct cct gga cag 48  
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
1 5 10 15

tcg atc acc atc tcc tgc act gga gcc agc agt gat gtt ggg act tat 96  
Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Thr Tyr  
20 25 30

gac ctt gtc tcc tgg tac caa caa cat cca ggc aaa gcc ccc aaa ctc 144  
Asp Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu  
35 40 45

att att tat gag gtc aat aag cgg ccc tca ggg gtt tct tat cgc ttc 192  
Ile Ile Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Ser Tyr Arg Phe  
50 55 60

tct gcc tcc aag tct gcc aac acg gcc tcc ctg aca ata tct ggg ctc 240  
Ser Ala Ser Lys Ser Ala Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
65 70 75 80

cag gct gag gac gag gct gaa tat tac tgc tgc tca tat gca ggt tat 288  
Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Cys Ser Tyr Ala Gly Tyr  
85 90 95

agc acg gta ttc ggc gga ggg acc aag ctg acc gtc cta 327  
Ser Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 84

<211> 109

<212> PRT

<213> Homo sapiens

<400> 84

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Thr Tyr  
20 25 30

Asp Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu  
35 40 45

Ile Ile Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Ser Tyr Arg Phe  
50 55 60

Ser Ala Ser Lys Ser Ala Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
65 70 75 80

eol f-seql

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Cys Ser Tyr Ala Gly Tyr  
85 90 95

Ser Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 85  
<211> 357  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(357)  
<223> NI-302.52C9 VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(195)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (292)..(324)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 85  
gag gtg cag ctg gtg cag tct ggg gga ggc ttg gtc caa cct ggg ggg 48  
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
1 5 10 15  
tcc ctg aga ctc tcc tgt gca ggc tct gga ttc acc gtc agt gac acc 96  
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Val Ser Asp Thr  
20 25 30  
tac atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45  
tca ggt att cat gcc ggt ggt gaa aca tat tac gca gac tcc gtg aag 192  
Ser Gly Ile His Ala Gly Gly Glu Thr Tyr Tyr Ala Asp Ser Val Lys  
50 55 60  
ggc cga ttc acc atc tcc aga gac aac tcc aag aac acg ctg tat ctt 240  
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu  
65 70 75  
caa atg aat agg ctg aca cct gag gac acg gct gtc ttt tat tgt gcg 288  
Gln Met Asn Arg Leu Thr Pro Glu Asp Thr Ala Val Phe Tyr Cys Ala  
85 90 95  
aga cac tac tac ggt aat gac gac gac act gat tat tgg ggc cag gga 336  
Arg His Tyr Tyr Gly Asn Asp Asp Asp Thr Asp Tyr Trp Gly Gln Gly  
100 105 110  
acc ctg gtc acc gtc tcc tcg 357  
Thr Leu Val Thr Val Ser Ser  
115



eof-seq1

<210> 86  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 86

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Val Ser Asp Thr  
 20 25 30  
 Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ser Gly Ile His Ala Gly Gly Glu Thr Tyr Tyr Ala Asp Ser Val Lys  
 50 55 60  
 Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu  
 65 70 75 80  
 Gln Met Asn Arg Leu Thr Pro Glu Asp Thr Ala Val Phe Tyr Cys Ala  
 85 90 95  
 Arg His Tyr Tyr Gly Asn Asp Asp Asp Thr Asp Tyr Trp Gly Gln Gly  
 100 105 110  
 Thr Leu Val Thr Val Ser Ser  
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gag Glu	ccg Pro	gcc Ala	tcc Ser 20	atc Ile	tcc Ser	tgc Cys	agg Arg	tct Ser 25	agt Ser	cag Gln	agc Ser	ctc Leu	ctg Leu 30	cat His	agt Ser		96
aat Asn	gga Gly	tac Tyr 35	aac Asn	tat Tyr	ttg Leu	gat Asp	tgg Trp 40	tac Tyr	gtg Val	cag Gln	aag Lys	cca Pro 45	ggg Gly	cag Gln	tct Ser		144
cca Pro	cag Gln 50	ctc Leu	ctc Leu	atc Ile	tat Tyr	ttg Leu 55	ggg Gly	tct Ser	act Thr	cgg Arg	gcc Ala 60	tcc Ser	ggg Gly	gtc Val	cct Pro		192
gac Asp 65	aga Arg	ttc Phe	agt Ser	ggc Gly	agt Ser 70	gga Gly	tca Ser	ggc Gly	aca Thr	gat Asp 75	ttt Phe	aca Thr	ctg Leu	aaa Lys	atc Ile 80		240
agc Ser	aga Arg	gtg Val	gag Glu	gct Ala 85	gag Glu	gat Asp	gtt Val	ggg Gly	gtt Val 90	tat Tyr	tac Tyr	tgc Cys	tta Leu	caa Gln 95	gct Ala		288
caa Gln	caa Gln	att Ile	ccg Pro 100	tgg Trp	acg Thr	ttc Phe	ggc Gly	caa Gln 105	ggg Gly	acc Thr	aag Lys	gtg Val	gag Glu 110	atc Ile	aaa Lys		336

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Asn	Gly	Tyr 35	Asn	Tyr	Leu	Asp	Trp 40	Tyr	Val	Gln	Lys	Pro 45	Gly	Gln	Ser		
Pro	Gln 50	Leu	Leu	Ile	Tyr	Leu 55	Gly	Ser	Thr	Arg	Ala 60	Ser	Gly	Val	Pro		
Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80		
Ser	Arg	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	Cys	Leu	Gln 95	Ala		
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 acc ctg tcc ctc acc tgc act gtt tct ggt gcc tcc gtc agc agt ggt 96  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ala Ser Val Ser Ser Gly  
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 gcc tac tac tgg agt tgg atc cgg cag ccc gcc ggg aag cga ctg gag 144  
 Ala Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu  
 35 40 45  
 tgg att ggg cgt gtc tat ccc act tgg agc acc aac tac aac ccc tcc 192  
 Trp Ile Gly Arg Val Tyr Pro Thr Trp Ser Thr Asn Tyr Asn Pro Ser  
 50 55 60  
 ctc gag agt cga gtc acc ata tcg tta gac acg tcc aac aac cag ttc 240  
 Leu Glu Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Asn Asn Gln Phe  
 65 70 75 80  
 tcc ctg aag ctg acc tct ttg act gcc gca gac acg gcc gtt tat tac 288  
 Ser Leu Lys Leu Thr Ser Leu Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95  
 tgt gcg aga gag gct cct ggt gac tac gat gct gcg ccc cta gcc tac 336  
 Cys Ala Arg Glu Ala Pro Gly Asp Tyr Asp Ala Ala Pro Leu Ala Tyr  
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 tgg ggc cag ggc acc ctg gtc acc gtc tcc tcg 369  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
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eof-seq1

Ala Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu  
35 40 45  
Trp Ile Gly Arg Val Tyr Pro Thr Trp Ser Thr Asn Tyr Asn Pro Ser  
50 55 60  
Leu Glu Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Asn Asn Gln Phe  
65 70 75 80  
Ser Leu Lys Leu Thr Ser Leu Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
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Cys Ala Arg Glu Ala Pro Gly Asp Tyr Asp Ala Ala Pro Leu Ala Tyr  
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<220>  
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<223> complementarity determining region (CDR) VK-CDR2

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gac aga gtc acc atc act tgc cgg gca agt cag tac att agc cac tat 96  
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Tyr Ile Ser His Tyr  
20 25 30

tta aat tgg tat cgg cag aaa cca ggg aaa gcc cct cag ctc gta atc 144  
Leu Asn Trp Tyr Arg Gln Lys Pro Gly Lys Ala Pro Gln Leu Val Ile  
35 40 45

tat gct gca tcc agt ttg caa agt gag gtc cca tca agg ttc agt ggg 192  
Tyr Ala Ala Ser Ser Leu Gln Ser Glu Val Pro Ser Arg Phe Ser Gly  
50 55 60

eof-seql

agt gga tct ggg cca gag ttc act ctc acc atc agc agt ctg caa cct 240  
Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gl n Pro  
65 70 75 80

gaa gat ttt gca act tat tac tgt caa cag agt tac act acc cct cga 288  
Glu Asp Phe Ala Thr Tyr Tyr Cys Gl n Gl n Ser Tyr Thr Thr Pro Arg  
85 90 95

act ttt ggc cag ggg acc aag ctg gag atc aaa 321  
Thr Phe Gly Gl n Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 92  
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<212> PRT  
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gl n Tyr Ile Ser His Tyr  
20 25 30

Leu Asn Trp Tyr Arg Gl n Lys Pro Gly Lys Ala Pro Gl n Leu Val Ile  
35 40 45

Tyr Ala Ala Ser Ser Leu Gl n Ser Glu Val Pro Ser Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gl n Pro  
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gl n Gl n Ser Tyr Thr Thr Pro Arg  
85 90 95

Thr Phe Gly Gl n Gly Thr Lys Leu Glu Ile Lys  
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<210> 93  
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exon 1 N-terminal amino acids 1-19

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Met Ala Thr Leu Glu Lys Leu Met Lys Ala Phe Glu Ser Leu Lys Ser  
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Phe Gl n Gl n

eof-seq1

<210> 94  
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 <213> Artificial Sequence

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<400> 94

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Gln Pro Gln Pro Pro  
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<210> 95  
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 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> BSA-coupled synthetic peptides (Schafer-N, Denmark) of the HTT exon 1 polyP repeat

<400> 95

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
 1 5 10

<210> 96  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> BSA-coupled synthetic peptides (Schafer-N, Denmark) of the HTT exon 1 C-terminal amino acids

<400> 96

Pro Pro Gly Pro Ala Val Ala Glu Glu Pro Leu His Arg Pro  
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<210> 97  
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eof-seql

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<222> (295)..(336)

<223> complementarity determining region (CDR) VH-CDR3

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Asn  
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tcc ctg aga ctc tcc tgt gca gcg tct gga ttc agg ttc agt gac ttt 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Arg Phe Ser Asp Phe  
20 25 30

ggc atg cac tgg gtc cgc cag gct cca ggc aag gga ctg gag tgg ctg 144  
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu  
35 40 45

gca ctt ata tgg tat gat gga ggg tat aag tac tat gca gac tcc gtg 192  
Ala Leu Ile Trp Tyr Asp Gly Gly Tyr Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

aag ggc cga ttc acc atc tcc aga gac aat tcc aag aat acg atg ttt 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Met Phe  
65 70 75 80

cta caa atg aac agc ctg aga gcc gag gac acg gct gtt tat tac tgt 288  
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gcg acc cac cta gaa tat tgc agt aga acc acc tgc tat ctc ggc cac 336  
Ala Thr His Leu Glu Tyr Cys Ser Arg Thr Thr Cys Tyr Leu Gly His  
100 105 110

tgg ggc cag gga acc ctg gtc acc gtc tcc tgc 369  
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 98

<211> 123

<212> PRT

<213> Homo sapiens

<400> 98

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Asn  
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Arg Phe Ser Asp Phe  
20 25 30

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

Ala Leu Ile Trp Tyr Asp Gly Gly Tyr Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Met Phe  
65 70 75 80

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

Ala Thr His Leu Glu Tyr Cys Ser Arg Thr Thr Cys Tyr Leu Gly His  
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

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1 5 10 15

gac aca gtc acc ttc act tgc cgg gcc agt cag ggc att agc gat tat 96  
Asp Thr Val Thr Phe Thr Cys Arg Ala Ser Gln Gly Ile Ser Asp Tyr  
20 25 30

tta gcc tgg ttt cag cag aaa cca ggg att gcc cct aag ctc ctg atc 144  
Leu Ala Trp Phe Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile  
35 40 45

tat gct gcg tcc act ttg caa acc ggg gtc cca tca agg ttc agc ggc 192  
Tyr Ala Ala Ser Thr Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

agt gga tct ggg aca gaa ttc act ctc aca atc cgc agc ctg cag tct 240  
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Arg Ser Leu Gln Ser  
65 70 75 80

gaa gat ttt gga act tat tac tgt cag cag ctt aaa act tac ccg tac 288  
Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Leu Lys Thr Tyr Pro Tyr  
85 90 95

act ttt ggc cag ggg acc aag ctg gag atc aaa 321  
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
100 105



eof-seq1

<210> 100  
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 <212> PRT  
 <213> Homo sapiens

<400> 100

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 1 5 10 15

Asp Thr Val Thr Phe Thr Cys Arg Ala Ser Gln Gly Ile Ser Asp Tyr  
 20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile  
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Arg Ser Leu Gln Ser  
 65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Leu Lys Thr Tyr Pro Tyr  
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105

<210> 101  
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 <212> DNA  
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<220>  
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<220>  
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 <223> complementarity determining region (CDR) VK-CDR2

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 1 5 10 15

48

gag agg gcc acc atc aac tgc aag tcc aat cag agt ctt ttc tac agt  
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Asn Gln Ser Leu Phe Tyr Ser

96

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Ser	Asn	Asn	Asn	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	His	Lys	Ser	Gly	Gln								
		35					40					45											
cct	cct	aag	ctg	ctc	gtt	tac	tgg	gga	tct	acc	cgg	gaa	tcc	ggg	gtc	192							
Pro	Pro	Lys	Leu	Leu	Val	Tyr	Trp	Gly	Ser	Thr	Arg	Glu	Ser	Gly	Val								
	50					55					60												
cct	gac	cgc	ttc	agt	ggc	agc	ggg	tct	ggg	act	gac	ttc	act	ctc	acc	240							
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr								
65					70					75				80									
atc	agt	agc	ctg	cag	gct	gag	gat	gtt	gca	att	tat	tac	tgt	cac	caa	288							
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys	His	Gln								
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tat	tat	cat	aat	ccg	tac	act	ttt	ggc	cag	ggg	acc	aag	ctg	gag	atc	336							
Tyr	Tyr	His	Asn	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile								
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aaa																339							
Lys																							

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 20 25 30

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

Pro Pro Lys Leu Leu Val Tyr Trp Gly Ser Thr Arg Glu Ser Gly Val  
 50 55 60

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

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys His Gln  
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Tyr Tyr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile  
 100 105 110

Lys

<210> 103  
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<212> DNA  
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<223> complementarity determining region (CDR) VK-CDR1
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eof-seq1

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20 25 30  
Ser Asn Asn Asn Asn Tyr Leu Ala Trp Tyr Gln His Lys Ser Gly Gln  
35 40 45  
Pro Pro Lys Leu Leu Val Tyr Trp Gly Ser Thr Arg Glu Ser Gly Val  
50 55 60  
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
65 70 75 80  
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys His Gln  
85 90 95  
Tyr Tyr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile  
100 105 110

Lys

<210> 105  
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<220>  
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<223> complementarity determining region (CDR) VK-CDR2

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gag agg gcc acc atc aac tgc aag tcc aat cag ggc ctt ttc tac agt 96  
Glu Arg Ala Thr Ile Asn Cys Lys Ser Asn Gln Gly Leu Phe Tyr Ser  
20 25 30

tcc aac aat aac aac tac tta gct tgg tac cag cac aaa tcc gga cag 144  
Ser Asn Asn Asn Tyr Leu Ala Trp Tyr Gln His Lys Ser Gly Gln  
35 40 45

eol f-seql

cct	cct	aag	ctg	ctc	ggt	tac	tgg	gga	tct	acc	cgg	gaa	tcc	ggg	gtc	192
Pro	Pro	Lys	Leu	Leu	Val	Tyr	Trp	Gly	Ser	Thr	Arg	Glu	Ser	Gly	Val	
	50					55					60					
cct	gac	cgc	ttc	agt	ggc	agc	ggg	tct	ggg	act	gac	ttc	act	ctc	acc	240
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	
65					70					75					80	
atc	agt	agc	ctg	cag	gct	gag	gat	ggt	gca	att	tat	tac	tgt	cac	caa	288
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys	His	Gln	
				85					90					95		
tat	tat	cat	aat	ccg	tac	act	ttt	ggc	cag	ggg	acc	aag	ctg	gag	atc	336
Tyr	Tyr	His	Asn	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	
			100					105					110			
aaa																339
Lys																

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<400> 106

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
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Glu Arg Ala Thr Ile Asn Cys Lys Ser Asn Gln Gly Leu Phe Tyr Ser  
 20 25 30

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

Pro Pro Lys Leu Leu Val Tyr Trp Gly Ser Thr Arg Glu Ser Gly Val  
 50 55 60

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

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys His Gln  
 85 90 95

Tyr Tyr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile  
 100 105 110

Lys

<210> 107  
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 <212> DNA  
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<220>  
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<222> (1)..(339)  
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<220>  
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<220>  
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<220>  
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 <223> complementarity determining region (CDR) VK-CDR3

<400> 107  
 gat att gtg atg act caa tca cca gac tcc ctg gct gtg tct ctg ggc 48  
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
 1 5 10 15  
 gag agg gcc acc atc aac tgc aag tcc caa cag agt ctt ttc tac agt 96  
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Gln Gln Ser Leu Phe Tyr Ser  
 20 25 30  
 tcc aac aat aac aac tac tta gct tgg tac cag cac aaa tcc gga cag 144  
 Ser Asn Asn Asn Asn Tyr Leu Ala Trp Tyr Gln His Lys Ser Gly Gln  
 35 40 45  
 cct cct aag ctg ctc gtt tac tgg gga tct acc cgg gaa tcc ggg gtc 192  
 Pro Pro Lys Leu Leu Val Tyr Trp Gly Ser Thr Arg Glu Ser Gly Val  
 50 55 60  
 cct gac cgc ttc agt ggc agc ggg tct ggg act gac ttc act ctc acc 240  
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 65 70 75 80  
 atc agt agc ctg cag gct gag gat gtt gca att tat tac tgt cac caa 288  
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys His Gln  
 85 90 95  
 tat tat cat aat ccg tac act ttt ggc cag ggg acc aag ctg gag atc 336  
 Tyr Tyr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile  
 100 105 110  
 aaa 339  
 Lys

<210> 108  
 <211> 113  
 <212> PRT  
 <213> Homo sapiens

<400> 108  
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
 1 5 10 15  
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Gln Gln Ser Leu Phe Tyr Ser  
 20 25 30  
 Ser Asn Asn Asn Asn Tyr Leu Ala Trp Tyr Gln His Lys Ser Gly Gln

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40

45

Pro Pro Lys Leu Leu Val Tyr Trp Gly Ser Thr Arg Glu Ser Gly Val  
50 55 60  
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
65 70 75 80  
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys His Gln  
85 90 95  
Tyr Tyr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile  
100 105 110

Lys

<210> 109  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(321)  
<223> NI-302.35C1-PIMC VK variable kappa-light chain (VK) sequence

<220>  
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<222> (70)..(102)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (148)..(168)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (265)..(291)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 109  
gaa att gtg ctg act cag tct cca gcc acc ctg tct ttg tct cca ggg 48  
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

gaa aga gcc acc ctc tcc tgc agg gcc agt caa agt gtt gac aac cag 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Asn Gln  
20 25 30

ttt gcc tgg tac caa cag aaa cct ggc cag gct ccc agg ctc ctc att 144  
Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

tat gat gca tcc agg agg gcc cct ggc atc cca gac agg ttc agt ggc 192  
Tyr Asp Ala Ser Arg Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser Gly  
50 55 60

agt ggg tct ggg aca gac ttc act ctc acc att agc agc cta gag cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65		70		eol f-seql										80		
									75							
gaa	gat	ttc	gca	att	tat	tac	tgt	cag	cat	cgt	tac	acc	tgg	ctc	tac	288
Glu	Asp	Phe	Ala	Ile	Tyr	Tyr	Cys	Gln	His	Arg	Tyr	Thr	Trp	Leu	Tyr	
				85					90					95		

act	ttt	ggc	cag	ggg	acc	aag	ctg	gag	atc	aaa	321
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
			100					105			

<210> 110  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens  
 <400> 110

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

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

Phe	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
		35					40					45			

Tyr	Asp	Ala	Ser	Arg	Arg	Ala	Pro	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro
65					70					75				80	

Glu	Asp	Phe	Ala	Ile	Tyr	Tyr	Cys	Gln	His	Arg	Tyr	Thr	Trp	Leu	Tyr
				85					90					95	

Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100					105		

<210> 111  
 <211> 336  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(336)  
 <223> NI-302.31F11-PIMC VK variable kappa-light chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(117)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (163)..(183)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>



eol f-seql

<221> V\_region

<222> (280)..(306)

<223> complementarity determining region (CDR) VK-CDR3

<400> 111

gat att gtg atg act caa tca cca ctc tcc ctg ccc gtc gcc cct gga 48  
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ala Pro Gly  
1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc cta tac agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg aag cct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Lys Pro  
35 40 45

cca cag ctc ctg gtc tat ttg ggt tct gat cgg gcc tcc ggg gtc cct 192  
Pro Gln Leu Leu Val Tyr Leu Gly Ser Asp Arg Ala Ser Gly Val Pro  
50 55 60

gac agg ttc agt ggc agt gga tca ggc aaa gat ttt aca ctg aac atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Asn Ile  
65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
85 90 95

cta caa agt ccg tgg acg ttc ggc caa ggg acc aag gtg gaa atc aaa 336  
Leu Gln Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 112

<211> 112

<212> PRT

<213> Homo sapiens

<400> 112

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser  
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Lys Pro  
35 40 45

Pro Gln Leu Leu Val Tyr Leu Gly Ser Asp Arg Ala Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Asn Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly  
85 90 95

Leu Gln Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105 110

eof-seq1

<210> 113  
 <211> 345  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(345)  
 <223> NI-302.2A2-PI MC VK variable kappa-light chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(129)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (175)..(195)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (292)..(315)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 113	
gat att gtg atg act caa tca cca gac tcc ctg gct gtg tct ctg ggc	48
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly	
1 5 10 15	
gag agg gcc acc atc aac tgc aag tcc agc cag agt ctt tta tac acc	96
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr	
20 25 30	
tcc aaa aat aag gac agt aag aac tac tta ggt tgg tac cag cag aaa	144
Ser Lys Asn Lys Asp Ser Lys Asn Tyr Leu Gly Trp Tyr Gln Gln Lys	
35 40 45	
cca gga cag cct cct aag ctg ctc att tac tgg gca tct acc cgg gaa	192
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu	
50 55 60	
tcc ggg gtc cct gac cga ttc agt ggc agc ggg tct ggg aca gat ttc	240
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe	
65 70 75 80	
act ctc acc atc agc agc ctg cag gct gag gat gtg gca gtt tat tac	288
Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr	
85 90 95	
tgt cag cag tat tat act act cct cag ttc ggc gga ggg acc aag gtg	336
Cys Gln Gln Tyr Tyr Thr Thr Pro Gln Phe Gly Gly Gly Thr Lys Val	
100 105 110	
gaa atc aaa	345
Glu Ile Lys	
115	

<210> 114  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<400> 114

eol f-seql

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr  
20 25 30

Ser Lys Asn Lys Asp Ser Lys Asn Tyr Leu Gly Trp Tyr Gln Gln Lys  
35 40 45

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

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

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

Cys Gln Gln Tyr Tyr Thr Thr Pro Gln Phe Gly Gly Gly Thr Lys Val  
100 105 110

Glu Ile Lys  
115

<210> 115  
<211> 360  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(360)  
<223> NI-302.74C11-PIMC VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(186)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(327)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 115  
cag gtg cag ctg gtg caa tct ggg act gag gtg cag aag cct ggg gcc 48  
Gln Val Gln Leu Val Gln Ser Gly Thr Glu Val Gln Lys Pro Gly Ala  
1 5 10 15

tca gta aaa gtc tcc tgc aag gct tct gga tac agt ttc acc ggc tac 96  
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr  
20 25 30

ttt ttg cac tgg gta cga cag gcc cct gga caa ggg ctt gag tgg atg 144

eol f-seql

Phe	Leu	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
		35					40					45				
ggg	tgg	atc	aac	cct	aac	agt	ggt	gac	aca	aac	tat	gca	gag	aag	ttt	192
Gly	Trp	Ile	Asn	Pro	Asn	Ser	Gly	Asp	Thr	Asn	Tyr	Ala	Glu	Lys	Phe	
	50					55					60					
cgg	ggc	aga	atc	atc	atg	acc	agg	gac	acg	tct	gtc	agc	aca	gcc	cac	240
Arg	Gly	Arg	Ile	Ile	Met	Thr	Arg	Asp	Thr	Ser	Val	Ser	Thr	Ala	His	
65					70					75					80	
atg	gag	ttg	agc	agc	ctg	aga	ttt	gac	gac	acg	gcc	cta	tat	tac	tgt	288
Met	Glu	Leu	Ser	Ser	Leu	Arg	Phe	Asp	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys	
			85						90					95		
acg	aga	gag	gcc	cct	gac	ccg	ggc	gct	gag	acg	gac	gtc	tgg	ggc	caa	336
Thr	Arg	Glu	Ala	Pro	Asp	Pro	Gly	Ala	Glu	Thr	Asp	Val	Trp	Gly	Gln	
			100					105					110			
gga	acc	acg	gtc	acc	gtc	tcc	tcg									360
Gly	Thr	Thr	Val	Thr	Val	Ser	Ser									
		115					120									

<210> 116  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 116

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Thr	Glu	Val	Gln	Lys	Pro	Gly	Ala	
1				5					10					15		
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	
			20					25					30			
Phe	Leu	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
		35					40					45				
Gly	Trp	Ile	Asn	Pro	Asn	Ser	Gly	Asp	Thr	Asn	Tyr	Ala	Glu	Lys	Phe	
	50					55					60					
Arg	Gly	Arg	Ile	Ile	Met	Thr	Arg	Asp	Thr	Ser	Val	Ser	Thr	Ala	His	
65					70					75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Phe	Asp	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys	
			85						90					95		
Thr	Arg	Glu	Ala	Pro	Asp	Pro	Gly	Ala	Glu	Thr	Asp	Val	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Thr	Val	Thr	Val	Ser	Ser									
		115					120									

<210> 117  
 <211> 321  
 <212> DNA  
 <213> Homo sapiens

eof-seq1

<220>  
 <221> CDS  
 <222> (1)..(321)  
 <223> NI-302.74C11-PIMC VL variable light chain (VL) sequence

<220>  
 <221> V\_region  
 <222> (67)..(99)  
 <223> complementarity determining region (CDR) VL-CDR1

<220>  
 <221> V\_region  
 <222> (145)..(165)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (262)..(291)  
 <223> complementarity determining region (CDR) VL-CDR3

<400> 117  
 tcc tat gag ctg act cag cca ccc tcg gtg tca gtg tcc cca gga cag 48  
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
 1 5 10 15  
 acg gcc agg atc acc tgc tct gga gat gca gtg cca aag cag tat att 96  
 Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Val Pro Lys Gln Tyr Ile  
 20 25 30  
 tat tgg tac cag cag aag cca ggc cag gcc cct att ctg gtg ata tat 144  
 Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr  
 35 40 45  
 aaa gac act cag agg cct tca ggg atc cct gag cga ttc tct ggc tcc 192  
 Lys Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
 50 55 60  
 aac tca ggg aca aca gtc acg ttg acc ata act ggc gtc cag gca gac 240  
 Asn Ser Gly Thr Thr Val Thr Leu Thr Ile Thr Gly Val Gln Ala Asp  
 65 70 75 80  
 gac gag ggt gac tat tac tgt caa tca gca gac agt agt gct act tgg 288  
 Asp Glu Gly Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ala Thr Trp  
 85 90 95  
 gtg ttc ggc gga ggg acc aaa ttg acc gtc cta 321  
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 100 105

<210> 118  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 118  
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
 1 5 10 15  
 Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Val Pro Lys Gln Tyr Ile  
 20 25 30  
 Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr  
 35 40 45

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Lys Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
50 55 60

Asn Ser Gly Thr Thr Val Thr Leu Thr Ile Thr Gly Val Gln Ala Asp  
65 70 75 80

Asp Glu Gly Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ala Thr Trp  
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105

<210> 119  
<211> 357  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(357)  
<223> NI-302.39G12-PIMC VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(195)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (292)..(324)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 119  
gag gtg cag ctg gtg gag tct ggg gga ggc ttg gtc cac cct tgg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Trp Gly  
1 5 10 15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc gtc tct aat tac 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Val Ser Asn Tyr  
20 25 30

gcc ata act tgg gtc cgc cgg gct cca ggg aag ggg ctg caa tat att 144  
Ala Ile Thr Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Gln Tyr Ile  
35 40 45

tca gta att tat cgt gat ggc agg aca tac tac gga gac tcc gtg agg 192  
Ser Val Ile Tyr Arg Asp Gly Arg Thr Tyr Tyr Gly Asp Ser Val Arg  
50 55 60

ggc cgc ttc acc atc tct agg gac gat tcc aag aac act ctc tat ctt 240  
Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu  
65 70 75 80

caa atg aac agc ctg aga ttt gag gac acg gct gtg tat tac tgt gcg 288  
Gln Met Asn Ser Leu Arg Phe Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

eol f-seql

aga gcg cac ggc caa tat tac tat ggt gtg gac gtc tgg ggc caa gga 336  
Arg Ala His Gly Gln Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly  
100 105 110

acc acg gtc acc gtc tcc tcg 357  
Thr Thr Val Thr Val Ser Ser  
115

<210> 120  
<211> 119  
<212> PRT  
<213> Homo sapiens

<400> 120

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Trp Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Val Ser Asn Tyr  
20 25 30

Ala Ile Thr Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Gln Tyr Ile  
35 40 45

Ser Val Ile Tyr Arg Asp Gly Arg Thr Tyr Tyr Gly Asp Ser Val Arg  
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu  
65 70 75 80

Gln Met Asn Ser Leu Arg Phe Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Arg Ala His Gly Gln Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly  
100 105 110

Thr Thr Val Thr Val Ser Ser  
115

<210> 121  
<211> 333  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(333)  
<223> NI-302.39G12-PIMC VK variable kappa-light chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(117)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (163)..(183)

eof-seql

<223> complementarity determining region (CDR) VK-CDR2

<220>

<221> V\_region

<222> (280)..(303)

<223> complementarity determining region (CDR) VK-CDR3

<400> 121

gac atc gtg atg acc cag tct cca ctc tcc ctg tcc gtc agc cct gga 48  
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Ser Pro Gly  
1 5 10 15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc cta cat agt 96  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

aat gga tac aac tat ttg gat tgg tac cgg cag aaa cca ggg cag tct 144  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Arg Gln Lys Pro Gly Gln Ser  
35 40 45

cca cag ctc ctg atc tat ttg agt tct aat cgg ccc tcc ggg gtc cct 192  
Pro Gln Leu Leu Ile Tyr Leu Ser Ser Asn Arg Pro Ser Gly Val Pro  
50 55 60

gat agg ttc agt gcc agt gga tca ggc aca gag ttc aca ctg caa atc 240  
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Glu Phe Thr Leu Gln Ile  
65 70 75 80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
85 90 95

ctg caa acg ttc act ttc ggc gga ggg acc aag gtg gaa atc aaa 333  
Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 122

<211> 111

<212> PRT

<213> Homo sapiens

<400> 122

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser  
20 25 30

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

Pro Gln Leu Leu Ile Tyr Leu Ser Ser Asn Arg Pro Ser Gly Val Pro  
50 55 60

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Glu Phe Thr Leu Gln Ile  
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser  
85 90 95



Leu Gln Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210>	123
<211>	321
<212>	DNA
<213>	Homo sapi ens

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<220>
<221> CDS
<222> (1)..(321)
<223> NI-302.11A4-PIMC VK variable kappa-light chain (VK) sequence
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<220>
<221> V_region
<222> (70)..(105)
<223> complementarity determining region (CDR) VK-CDR1
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<220>
<221> V_region
<222> (151)..(171)
<223> complementarity determining region (CDR) VK-CDR2
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<220>
<221> V_region
<222> (268)..(291)
<223> complementarity determining region (CDR) VK-CDR3
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<400> 123  
gaa att gtg ctg act cag tct cca ggc acc ctg tct ttg tct cca gga 48  
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt agc agc agc 96  
 Gl u Arg Al a Thr Leu Ser Cys Arg Al a Ser Gl n Ser Val Ser Ser Ser  
 20 25 30

tac ttc gcc tgg tac caa caa aaa cct ggc cag gct ccc agg ctc ctc 144  
 Tyr Phe Ala Trp Tyr Gl n Gl n Lys Pro Gl y Gl n Ala Pro Arg Leu Leu  
 35 40 45

atc tat ggt acg tcc cgc agg gcc act gcc atc cca gac agg ttc agt 192  
Ile Tyr Gly Thr Ser Arg Arg Ala Thr Ala Ile Pro Asp Arg Phe Ser  
50 55 60

ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag 240  
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

cct gaa gat ttt gca gtg tat tac tgt caa cag tat ggt agc tcg tgg 288  
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Trp  
85 90 95

acg ttc ggc cca ggg acc aag gtg gaa atc aaa 321  
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys  
100 105

<210>	124
<211>	107
<212>	PRT
<213>	Homo sapi ens

<400> 124

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
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1		5		10		15									
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser
			20					25					30		
Tyr	Phe	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
		35					40					45			
Ile	Tyr	Gly	Thr	Ser	Arg	Arg	Ala	Thr	Ala	Ile	Pro	Asp	Arg	Phe	Ser
	50					55					60				
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Arg	Leu	Glu
65					70					75					80
Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Gly	Ser	Ser	Trp
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Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Glu	Ile	Lys					
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<220>  
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 <223> complementarity determining region (CDR) VK-CDR1

<220>  
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 <223> complementarity determining region (CDR) VK-CDR2

<220>  
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 <222> (280)..(303)  
 <223> complementarity determining region (CDR) VK-CDR3

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

gag	ccg	gcc	tcc	atc	tcc	tgc	agg	tct	agt	cag	agc	ctc	cta	cat	agt		96
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu		His	Ser		
			20					25					30				

aat	gga	tac	aac	tat	ttg	gat	tgg	tac	cgg	cag	aaa	cca	ggg	cag	tct		144
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Arg	Gln	Lys	Pro	Gly	Gln	Ser		
		35					40					45					

cca	caa	ctc	ctg	atc	tat	ttg	aat	tct	aat	cgg	gcc	tcc	ggg	gtc	cct		192
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Asn	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro		

eol f-seql 60

50 55 60  
gat agg ttc agt ggc agt gga tca ggc aca gag ttc aca ctg aca atc 240  
Asp Arg Phe Ser Gly Ser Gly Ser Thr Glu Phe Thr Leu Thr Ile  
65 70 75 80  
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct 288  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Ser  
85 90 95  
ctg caa acg ttc act ttc ggc gga ggg acc aag gtg gaa atc aaa 333  
Leu Glu Thr Phe Thr Phe Gly Gly Glu Thr Lys Val Glu Ile Lys  
100 105 110

<210> 126  
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<213> Homo sapiens  
<400> 126

Asp Ile Val Met Thr Glu Ser Pro Leu Ser Leu Ser Val Ser Pro Gly  
1 5 10 15  
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Leu Leu His Ser  
20 25 30  
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Arg Glu Lys Pro Gly Glu Ser  
35 40 45  
Pro Glu Leu Leu Ile Tyr Leu Asn Ser Asn Arg Ala Ser Gly Val Pro  
50 55 60  
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile  
65 70 75 80  
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Ser  
85 90 95  
Leu Glu Thr Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105 110

<210> 127  
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<220>  
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<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region

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<222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
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 <222> (295)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

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 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg ggg 48  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 gcc atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 tca ggt att ggt tat agt gat act agc aca tat tac gca gac tcc gtg 192  
 Ser Gly Ile Gly Tyr Ser Asp Thr Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cgc ttc acc gtc tcc aga gac att tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Val Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 ctg caa atg aat agc ctg agg gcc gag gac acg gcc gta tat tac tgc 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aaa ggt acc agg gac tat tac ggt atg gac gtc tgg ggc caa gga 336  
 Ala Lys Gly Thr Arg Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly  
 100 105 110  
 acc acg gtc acc gtc tcc tcg 357  
 Thr Thr Val Thr Val Ser Ser  
 115

<210> 128  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 128  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ser Gly Ile Gly Tyr Ser Asp Thr Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Val Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

eof-seq1

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

Ala Lys Gly Thr Arg Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly  
100 105 110

Thr Thr Val Thr Val Ser Ser  
115

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<212> DNA  
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<222> (1)..(381)  
<223> NI-302.78H12-PIMC VH variable heavy chain (VH) sequence

<220>  
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<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (151)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(348)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 129	
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag	48
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu	
1 5 10 15	
acc ctg tcc ctc acc tgt ctt gtc tct agt tac tcc atc agc aat ggt	96
Thr Leu Ser Leu Thr Cys Leu Val Ser Ser Tyr Ser Ile Ser Asn Gly	
20 25 30	
tac tac tgg ggc tgg att cgg cag ccc cca ggg aag ggg ctg gag tgg	144
Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp	
35 40 45	
att ggg agt atc tat cat aat ggg aac acc tat tac aac ccg tcc ctc	192
Ile Gly Ser Ile Tyr His Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu	
50 55 60	
aag agt cga gtc atc att tca gta gac acg tcc aag aac cag ttc tcc	240
Lys Ser Arg Val Ile Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser	
65 70 75 80	
ctg aag ttg agg tct gtg acc gcc gca gac acg gcc gtg tac tac tgt	288
Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg atg cca agt gcc acc tat tat tat ggt tcg ggg act caa ttc cat	336
Ala Met Pro Ser Ala Thr Tyr Tyr Tyr Gly Ser Gly Thr Gln Phe His	
100 105 110	

gcg ttt gat gtc tgg ggc caa ggg aca atg gtc acc gtc tct tcg  
 Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser  
 115 120 125

<210> 130  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens  
 <400> 130

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

Thr Leu Ser Leu Thr Cys Leu Val Ser Ser Tyr Ser Ile Ser Asn Gly  
 20 25 30

Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Ser Ile Tyr His Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu  
 50 55 60

Lys Ser Arg Val Ile Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Met Pro Ser Ala Thr Tyr Tyr Tyr Gly Ser Gly Thr Gln Phe His  
 100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser  
 115 120 125

<210> 131  
 <211> 384  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)..(384)  
 <223> NI-302.15E8 VH variable heavy chain (VH) sequence

<220>  
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 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(201)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
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 <222> (298)..(351)

eof-seql

<223> complementarity determining region (CDR) VH-CDR3

<400> 131

gag gtg cag ctg gtg gag tct ggg gga ggc ttg ata cag ccg ggg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly  
1 5 10 15

tcc ctg aga ctc tcc tgt gca gtc tct gga ttc acc gtc agt agt tat 96  
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Val Ser Ser Tyr  
20 25 30

agc atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

tca tac act agt agt agc aga agt aat acc aaa aag tac gca gac tct 192  
Ser Tyr Thr Ser Ser Ser Arg Ser Asn Thr Lys Lys Tyr Ala Asp Ser  
50 55 60

gtg aag ggc cga ttc acc atc tct aga gac aat gcc agg aac tca ctc 240  
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ser Leu  
65 70 75 80

tat ctg caa atg aac agc ctg aga gac gag gac acg gct gtg tat tac 288  
Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr  
85 90 95

tgt gcg aga gca ggg gac ttc ggg gag tta ctc act ggt gag ggg tat 336  
Cys Ala Arg Ala Gly Asp Phe Gly Glu Leu Leu Thr Gly Glu Gly Tyr  
100 105 110

tac ggt atg gac gtc tgg ggc caa ggg acc acg gtc acc gtc tcc tcg 384  
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

<210> 132

<211> 128

<212> PRT

<213> Homo sapiens

<400> 132

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Val Ser Ser Tyr  
20 25 30

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

Ser Tyr Thr Ser Ser Ser Arg Ser Asn Thr Lys Lys Tyr Ala Asp Ser  
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ser Leu  
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr  
85 90 95

Cys Ala Arg Ala Gly Asp Phe Gly Glu Leu Leu Thr Gly Glu Gly Tyr

100

105

110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
           115                                  120                                  125

<210> 133  
 <211> 318  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)..(318)  
 <223> NI-302.15E8 VL variable light chain (VL) sequence

<220>  
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<220>  
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 <222> (145)..(165)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (262)..(288)  
 <223> complementarity determining region (CDR) VL-CDR3

<400> 133  
 tcc tat gag ctg act cag cca ccc tca gtg tcc gtg tcc cca gga cag 48  
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
 1                  5                                  10                                  15

aca gcc acc atc acc tgc tgc gga gat gaa ttg ggg gat aaa tat gtt 96  
 Thr Ala Thr Ile Thr Cys Ser Gly Asp Glu Leu Gly Asp Lys Tyr Val  
                   20                                  25                                  30

ggt tgg tat caa cag aag cca ggc cag tcc cct ctg ctg gtc atc tat 144  
 Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr  
                   35                                  40                                  45

caa gat gcg aag cgg ccc tca ggg atc cct gag cga ttc tct ggc tcc 192  
 Gln Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
                   50                                  55                                  60

aac tct ggg aac aca gcc act ctg acc atc agc ggg acc cag gct atg 240  
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met  
 65                                  70                                  75                                  80

gat gag gct gac tac tac tgt cag gcg tgg gac agc ggc acg atg gtt 288  
 Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Met Val  
                   85                                  90                                  95

ttc ggc gga ggg acc agg ctg acc gtc cta 318  
 Phe Gly Gly Gly Thr Arg Leu Thr Val Leu  
                   100                                  105

<210> 134  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens



eof-seq1

<400> 134

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
1 5 10 15  
Thr Ala Thr Ile Thr Cys Ser Gly Asp Glu Leu Gly Asp Lys Tyr Val  
20 25 30  
Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr  
35 40 45  
Gln Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
50 55 60  
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met  
65 70 75 80  
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Met Val  
85 90 95  
Phe Gly Gly Gly Thr Arg Leu Thr Val Leu  
100 105

<210> 135  
<211> 372  
<212> DNA  
<213> Homo sapiens

<220>  
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<223> NI-302.15D3 variable heavy chain (VH) sequence

<220>  
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<223> complementarity determining region (CDR) VH-CDR1

<220>  
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<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
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<222> (295)..(339)  
<223> complementarity determining region (CDR) VH-CDR3

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gag gtg cag ctg gtg gag tct ggg gga gac tta gtt cag cct ggg ggg 48  
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly  
1 5 10 15  
tcc cta aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tac 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30  
tgg atg cac tgg gtc cgc caa gct cca ggg aag ggt ctg gtg tgg gtc 144  
Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val  
35 40 45

eol f-seql

tca cgt att agt aat gat ggc agt agc aaa acc tac gcg gac tcc gtg 192  
Ser Arg Ile Ser Asn Asp Gly Ser Ser Lys Thr Tyr Ala Asp Ser Val  
50 55 60

aag ggc cga ttc acc atc tcc aga gac aac gcc aaa aac acg ctg tat 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr  
65 70 75 80

ctg caa atg aac agt ctg aga gcc gag gac acg gct gtg tat tac tgt 288  
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gca ata ctt ggc gga tat tgt agt agt acc agt tgt cgt ccc ttt gac 336  
Ala Ile Leu Gly Gly Tyr Cys Ser Ser Thr Ser Cys Arg Pro Phe Asp  
100 105 110

aac tgg ggc cag gga acc ctg gtc acc gtc tcc tcg 372  
Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 136  
<211> 124  
<212> PRT  
<213> Homo sapiens  
<400> 136

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Asp Leu Val Gl n Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

Trp Met His Trp Val Arg Gl n Ala Pro Gly Lys Gly Leu Val Trp Val  
35 40 45

Ser Arg Ile Ser Asn Asp Gly Ser Ser Lys Thr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gl n Met Asn Ser Leu Arg Ala Gl u Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Ile Leu Gly Gly Tyr Cys Ser Ser Thr Ser Cys Arg Pro Phe Asp  
100 105 110

Asn Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 137  
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<220>

eof-seql

<221> CDS  
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<220>  
 <221> V\_region  
 <222> (154)..(174)  
 <223> complementarity determining region (CDR) VL-CDR2

<220>  
 <221> V\_region  
 <222> (271)..(300)  
 <223> complementarity determining region (CDR) VL-CDR3

<400> 137  
 cag tct gcc ctg act cag cct gcc tcc gtg tct ggg tct cct gga cag 48  
 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15  
 tcg atc acc atc tcc tgc act gga acc agc agt gac gtt ggt gtt tat 96  
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Val Tyr  
 20 25 30  
 aac tat gtc tcc tgg tac caa caa cac cca ggc aaa gcc ccc aaa ctc 144  
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu  
 35 40 45  
 atg att ttt gat gtc agt aat cgg ccc tca ggg att tct aat cgc ttc 192  
 Met Ile Phe Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Asn Arg Phe  
 50 55 60  
 tct ggc tcc aag tct ggc aac acg gcc tcc ctg acc atc tct ggg ctc 240  
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65 70 75 80  
 cag gct gag gac gag gct gat tat tac tgc agc tca tat aca agc agc 288  
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 85 90 95  
 gac act tgg gtg ttc ggc gga ggg acc aag ctg acc atc cta 330  
 Asp Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Ile Leu  
 100 105 110

<210> 138  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<400> 138  
 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln  
 1 5 10 15  
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Val Tyr  
 20 25 30  
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu  
 35 40 45

Met Ile Phe Asp Val Ser Asn Arg Pro Ser Gly Ile Ser Asn Arg Phe  
50 55 60 eol f-seql

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
85 90 95

Asp Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Ile Leu  
100 105 110

<210> 139  
<211> 8  
<212> PRT  
<213> Arti fici al Sequence

<220>  
<223> Epi tope of NI -302. 33C11 anti body

<400> 139

Pro Pro Pro Pro Pro Pro Pro Pro  
1 5

<210> 140  
<211> 10  
<212> PRT  
<213> Arti fici al Sequence

<220>  
<223> Epi tope of NI -302. 63F3 anti body

<400> 140

Pro Gln Pro Pro Pro Gln Ala Gln Pro Leu  
1 5 10

<210> 141  
<211> 10  
<212> PRT  
<213> Arti fici al Sequence

<220>  
<223> Epi tope of NI -302. 31F11 anti body

<400> 141

Pro Pro Pro Gln Leu Pro Gln Pro Pro Pro  
1 5 10

<210> 142  
<211> 15  
<212> PRT  
<213> Arti fici al Sequence

<220>  
<223> Epi tope of NI -302. 2A2 anti body

<400> 142

eol f-seql

Gln	Ala	Gln	Pro	Leu	Leu	Pro	Gln	Pro	Gln	Pro	Pro	Pro	Pro	Pro
1				5					10					15

<210> 143  
 <211> 15  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI 302. 15D3 anti body

<400> 143

Pro	Pro	Pro	Gln	Leu	Pro	Gln	Pro	Pro	Pro	Gln	Ala	Gln	Pro	Leu
1				5					10					15

<210> 144  
 <211> 11  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI 302. 15E8 anti body

<400> 144

Lys	Ala	Phe	Glu	Ser	Leu	Lys	Ser	Phe	Gln	Gln
1				5					10	

<210> 145  
 <211> 14  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 35C1 anti body

<400> 145

Pro	Pro	Gly	Pro	Ala	Val	Ala	Glu	Glu	Pro	Leu	His	Arg	Pro
1				5					10				

<210> 146  
 <211> 11  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 74C11 anti body

<400> 146

Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro
1				5					10	

<210> 147  
 <211> 11  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 15F9 anti body

&lt;400&gt; 147

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

&lt;210&gt; 148

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Arti fi ci al Sequence

&lt;220&gt;

&lt;223&gt; Epi tope of NI -302. 39G12 anti body

&lt;400&gt; 148

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

&lt;210&gt; 149

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Arti fi ci al Sequence

&lt;220&gt;

&lt;223&gt; Epi tope of NI -302. 11A4 anti body

&lt;400&gt; 149

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

&lt;210&gt; 150

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Arti fi ci al Sequence

&lt;220&gt;

&lt;223&gt; Epi tope of NI -302. 22H9 anti body

&lt;400&gt; 150

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

&lt;210&gt; 151

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Arti fi ci al Sequence

&lt;220&gt;

&lt;223&gt; Epi tope of NI -302. 44D7 anti body

&lt;400&gt; 151

Pro Pro Pro Pro Pro Pro Pro Pro  
1 5

&lt;210&gt; 152

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Arti fi ci al Sequence

&lt;220&gt;

<223> Epi tope of NI -302. 37C12 anti body

<400> 152

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

<210> 153

<211> 11

<212> PRT

<213> Arti fi ci al Sequence

<220>

<223> Epi tope of NI -302. 55D8 anti body

<400> 153

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

<210> 154

<211> 8

<212> PRT

<213> Arti fi ci al Sequence

<220>

<223> Epi tope of NI -302. 7A8 anti body

<400> 154

Pro Pro Pro Pro Pro Pro Pro Pro  
1 5

<210> 155

<211> 11

<212> PRT

<213> Arti fi ci al Sequence

<220>

<223> Epi tope of NI -302. 78H12 anti body

<400> 155

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

<210> 156

<211> 11

<212> PRT

<213> Arti fi ci al Sequence

<220>

<223> Epi tope of NI -302. 71F6 anti body

<400> 156

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

<210> 157

<211> 6

<212> PRT

<213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 11H6 anti body  
 <400> 157

Pro Pro Pro Pro Pro Pro  
 1 5

<210> 158  
 <211> 8  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 3D8 anti body  
 <400> 158

Pro Pro Pro Pro Pro Pro Pro Pro  
 1 5

<210> 159  
 <211> 6  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 18A1anti body  
 <400> 159

Pro Pro Pro Pro Pro Pro  
 1 5

<210> 160  
 <211> 6  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 52C9 anti body  
 <400> 160

Pro Pro Pro Pro Pro Pro  
 1 5

<210> 161  
 <211> 8  
 <212> PRT  
 <213> Arti fi ci al Sequence

<220>  
 <223> Epi tope of NI -302. 46C9 anti body  
 <400> 161

Pro Pro Pro Pro Pro Pro Pro Pro  
 1 5

<210> 162  
 <211> 15



eof-seql

<212> PRT  
<213> Artificial Sequence

<220>  
<223> Alternative epitope of NI-302.63F3 antibody

<400> 162

Pro Pro Pro Gln Leu Pro Gln Pro Pro Pro Gln Ala Gln Pro Leu  
1 5 10 15

<210> 163  
<211> 11  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Alternative epitope of NI-302.33C11 antibody

<400> 163

Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro  
1 5 10

<210> 164  
<211> 366  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(366)  
<223> NI-302.64E5-VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(204)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (301)..(355)  
<223> complementarity determining region (CDR) VH-CDR2

<400> 164  
gag gtg cag ctg gtg gag act ggg gga ggc ttg gta aag cct ggg ggg 48  
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

tcc ctt aga ctc tcc tgt gca gcc tct gga ttc act ttc gac cag gcc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Gln Ala  
20 25 30

tgg atg agc tgg gtc cgc cag gtt cca ggg aag ggg ctg gag tgg gtt 144  
Trp Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgg att aaa acg aaa act gag ggt gaa gca aca gac tac gca gcg 192  
Gly Arg Ile Lys Thr Lys Thr Glu Gly Glu Ala Thr Asp Tyr Ala Ala  
50 55 60

eol f-seql

ccc gtg aga ggc aga ttc acc atc tca aga gat gat tca gaa gac acg 240  
Pro Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asp Thr  
65 70 75 80

gtg ttt ctg caa atg aac agc ctg aaa acc gag gac aca gcc ctg tat 288  
Val Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

tac tgt acg tca acg gga gtc tta gca gca gct gtc gat gtc tac tgg 336  
Tyr Cys Thr Ser Thr Gly Val Leu Ala Ala Ala Val Asp Val Tyr Trp  
100 105 110

ggc cag gga acc ctg gtc acc gtc tcc tgc 366  
Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 165  
<211> 122  
<212> PRT  
<213> Homo sapiens

<400> 165

Gl u Val Gl n Leu Val Gl u Thr Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Gl n Ala  
20 25 30

Trp Met Ser Trp Val Arg Gl n Val Pro Gly Lys Gly Leu Gl u Trp Val  
35 40 45

Gly Arg Ile Lys Thr Lys Thr Gl u Gly Gl u Ala Thr Asp Tyr Ala Ala  
50 55 60

Pro Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Gl u Asp Thr  
65 70 75 80

Val Phe Leu Gl n Met Asn Ser Leu Lys Thr Gl u Asp Thr Ala Leu Tyr  
85 90 95

Tyr Cys Thr Ser Thr Gly Val Leu Ala Ala Ala Val Asp Val Tyr Trp  
100 105 110

Gly Gl n Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 166  
<211> 366  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(366)  
<223> NI-302.64E5-PIMC VH variable heavy chain (VH) sequence

eof-seql

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(204)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (301)..(355)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 166  
 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta aag cct ggg ggg 48  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15  
 tcc ctt aga ctc tcc tgt gca gcc tct gga ttc act ttc gac cag gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Gln Ala  
 20 25 30  
 tgg atg agc tgg gtc cgc cag gtt cca ggg aag ggg ctg gag tgg gtt 144  
 Trp Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgg att aaa acg aaa act gag ggt gaa gca aca gac tac gca gcg 192  
 Gly Arg Ile Lys Thr Lys Thr Glu Gly Glu Ala Thr Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aga ggc aga ttc acc atc tca aga gat gat tca gaa gac acg 240  
 Pro Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asp Thr  
 65 70 75 80  
 gtg ttt ctg caa atg aac agc ctg aaa acc gag gac aca gcc ctg tat 288  
 Val Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tca acg gga gtc tta gca gca gct gtc gat gtc tac tgg 336  
 Tyr Cys Thr Ser Thr Gly Val Leu Ala Ala Ala Val Asp Val Tyr Trp  
 100 105 110  
 ggc cag ggc acc ctg gtc acc gtc tcc tcg 366  
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 167  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 167  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Gln Ala  
 20 25 30  
 Trp Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

eol f-seql

Gly Arg Ile Lys Thr Lys Thr Glu Gly Glu Ala Thr Asp Tyr Ala Ala  
50 55 60

Pro Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asp Thr  
65 70 75 80

Val Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

Tyr Cys Thr Ser Thr Gly Val Leu Ala Ala Ala Val Asp Val Tyr Trp  
100 105 110

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

<210> 168  
<211> 339  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(339)  
<223> NI-302.64E5 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(120)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (166)..(186)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (283)..(309)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 168  
gac atc cag ttg acc cag tct cca gac tcc ctg gct gtg tct ctg ggc 48  
Asp Ile Gln Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

gag agg gcc acc atg acc tgc aag tcc agc cag agt ctt ttc tac agt 96  
Glu Arg Ala Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Tyr Ser  
20 25 30

tac aac aat gag aac tac tta gcc tgg tat cag cag aga cca gga cag 144  
Tyr Asn Asn Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln  
35 40 45

cct cct aag ttg ctc att tac tgg gca tct acc cgg gaa tcc ggg gtc 192  
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val  
50 55 60

cct gac cga ttc agt ggc agc ggg tct ggg aca gat ttc act ctc acc 240  
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
65 70 75 80

atc agc agc ctg cag gct gaa gat gtg gca gtt tat tac tgt cag caa 288

Ile Ser Ser Leu Gln Ala Glu Asp Val eol f-seql Ala Val Tyr Tyr Cys Gln Gln  
 85 90  
 tat tat agt act cct cag acg ttc ggc caa ggg acc aaa gtg gat atc 336  
 Tyr Tyr Ser Thr Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Asp Ile  
 100 105 110  
 aaa 339  
 Lys

<210> 169  
 <211> 113  
 <212> PRT  
 <213> Homo sapiens

<400> 169

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

Glu Arg Ala Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Tyr Ser  
 20 25 30

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

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

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

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

Tyr Tyr Ser Thr Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Asp Ile  
 100 105 110

Lys

<210> 170  
 <211> 339  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(339)  
 <223> NI-302.64E5-PIMC VK variable kappa-light chain (VK) sequence

<220>  
 <221> V\_region  
 <222> (70)..(120)  
 <223> complementarity determining region (CDR) VK-CDR1

<220>

eof-seql

<221> V\_region  
 <222> (166)..(186)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (283)..(309)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 170  
 gat att gtg atg act caa tca cca gac tcc ctg gct gtg tct ctg ggc 48  
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
 1 5 10 15  
 gag agg gcc acc atg acc tgc aag tcc agc cag agt ctt ttc tac agt 96  
 Glu Arg Ala Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Tyr Ser  
 20 25 30  
 tac aac aat gag aac tac tta gcc tgg tat cag cag aga cca gga cag 144  
 Tyr Asn Asn Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln  
 35 40 45  
 cct cct aag ttg ctc att tac tgg gca tct acc cgg gaa tcc ggg gtc 192  
 Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val  
 50 55 60  
 cct gac cga ttc agt ggc agc ggg tct ggg aca gat ttc act ctc acc 240  
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 65 70 75 80  
 atc agc agc ctg cag gct gaa gat gtg gca gtt tat tac tgt cag caa 288  
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln  
 85 90 95  
 tat tat agt act cct cag acg ttc ggc caa ggg acc aag gtg gaa atc 336  
 Tyr Tyr Ser Thr Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu Ile  
 100 105 110  
 aaa 339  
 Lys

<210> 171  
 <211> 113  
 <212> PRT  
 <213> Homo sapiens

<400> 171  
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly  
 1 5 10 15  
 Glu Arg Ala Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Tyr Ser  
 20 25 30  
 Tyr Asn Asn Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln  
 35 40 45  
 Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val  
 50 55 60  
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 65 70 75 80

eof-seq1

I l e Ser Ser Leu G l n A l a G l u A s p V a l A l a V a l T y r T y r C y s G l n G l n  
85 90 95

T y r T y r Ser Thr Pro G l n Thr P h e G l y G l n G l y Thr L y s V a l G l u I l e  
100 105 110

Lys

<210> 172  
<211> 357  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(357)  
<223> NI-302.7D8-VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(324)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 172  
cag gtg cag ctg gtg caa tct gga tct gag ttg aag aag cct ggg gcc 48  
G l n V a l G l n L e u V a l G l n S e r G l y S e r G l u L e u L y s L y s P r o G l y A l a  
1 5 10 15

tca gtg aag gtt tcc tgc aag gct tct gga tac aac ttc aat aac tat 96  
S e r V a l L y s V a l S e r C y s L y s A l a S e r G l y T y r A s n P h e A s n A s n T y r  
20 25 30

gcc atc aat tgg ttg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
A l a I l e A s n T r p L e u A r g G l n A l a P r o G l y G l n G l y L e u G l u T r p M e t  
35 40 45

gga tgg atc aac acc atc act ggg cac cca acg tat gcc cag ggc ttc 192  
G l y T r p I l e A s n T h r I l e T h r G l y H i s P r o T h r T y r A l a G l n G l y P h e  
50 55 60

aaa gga cga ttt gtc ttc tcc ttg gac acc tct gtc agc acg gca tat 240  
L y s G l y A r g P h e V a l P h e S e r L e u A s p T h r S e r V a l S e r T h r A l a T y r  
65 70 75 80

ctg cag atc agc agc cta aag cct gag gac act gcc gtc tat tac tgt 288  
L e u G l n I l e S e r S e r L e u L y s P r o G l u A s p T h r A l a V a l T y r T y r C y s  
85 90 95

gcg aga act tac agt aac tac ggc gaa ttt gac tac tgg ggc cag gga 336  
A l a A r g T h r T y r S e r A s n T y r G l y G l u P h e A s p T y r T r p G l y G l n G l y  
100 105 110

eof-seql

357

acc ctg gtc acc gtc tcc tcg  
Thr Leu Val Thr Val Ser Ser  
115

<210> 173  
<211> 119  
<212> PRT  
<213> Homo sapiens

<400> 173

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

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

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

Gly Trp Ile Asn Thr Ile Thr Gly His Pro Thr Tyr Ala Gln Gly Phe  
50 55 60

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

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

Ala Arg Thr Tyr Ser Asn Tyr Gly Glu Phe Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210> 174  
<211> 333  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(333)  
<223> NI-302.7D8 VL variable light-lambda chain (VL) sequence

<220>  
<221> V\_region  
<222> (67)..(108)  
<223> complementarity determining region (CDR) VL-CDR1

<220>  
<221> V\_region  
<222> (154)..(174)  
<223> complementarity determining region (CDR) VL-CDR2

<220>  
<221> V\_region



eof-seql

<222> (271)..(303)

<223> complementarity determining region (CDR) VL-CDR3

<400> 174

cag tct gcc ctg act cag cct gcc tcc gtg tct ggg tct cgt gga cag 48  
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Arg Gly Gln  
1 5 10 15

tcg atc acc atc tcc tgc act gga acc agc agt gat gtt gga agt tat 96  
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr  
20 25 30

aac ctt gtc tcc tgg tac caa cag tac cca ggc aag gcc ccc aag ctc 144  
Asn Leu Val Ser Trp Tyr Gln Gln Tyr Pro Gly Lys Ala Pro Lys Leu  
35 40 45

ata att cat gag ggc agt gag cgg ccc tca ggg gtt tct aat cgc ttc 192  
Ile Ile His Glu Gly Ser Glu Arg Pro Ser Gly Val Ser Asn Arg Phe  
50 55 60

tct ggc tcc aag tct ggc aac acg gcc tcc ctg aca att tct ggg ctc 240  
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
65 70 75 80

cag gct gag gac gag gct gat tat tac tgc tgc tca tat gca ggt act 288  
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Thr  
85 90 95

act act ttc gtg cta ttc ggc gga ggg acc aag ctg acc gtc ctc 333  
Thr Thr Phe Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105 110

<210> 175

<211> 111

<212> PRT

<213> Homo sapiens

<400> 175

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Arg Gly Gln  
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr  
20 25 30

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

Ile Ile His Glu Gly Ser Glu Arg Pro Ser Gly Val Ser Asn Arg Phe  
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Thr  
85 90 95

Thr Thr Phe Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
100 105 110

eof-seq1

<210> 176  
 <211> 357  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(357)  
 <223> NI-302.72F10-VH variable heavy chain (VH) sequence

<220>  
 <221> V\_region  
 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (295)..(324)  
 <223> complementarity determining region (CDR) VH-CDR2

<400> 176	
gag gtg cag ctg gtg gag act ggg gga ggc ttc gta cag cct ggg ggg	48
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Phe Val Gln Pro Gly Gly	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc aac ttc ggc agt tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Gly Ser Tyr	
20 25 30	
gcc atg agc tgg gtc cgc cag gct cca ggg aag gga ctg gag tgg gtg	144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
tca gat atc agt ggt att ggt agt aac aca tac tac gca gac tcc gtg	192
Ser Asp Ile Ser Gly Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cgt ttc acc att tcc aga gac aat tcc gac aat acg ttg tac	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Asp Asn Thr Leu Tyr	
65 70 75 80	
ctg gac atg agc agc ctg aga gcc gag gac acg gcc aga tat tac tgt	288
Leu Asp Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr Tyr Cys	
85 90 95	
gcg aag gat cga aag cgc agt ggc tgg tac gaa cag tgg ggc cag ggc	336
Ala Lys Asp Arg Lys Arg Ser Gly Trp Tyr Glu Gln Trp Gly Gln Gly	
100 105 110	
acc ctg gtc acc gtc tcc tcg	357
Thr Leu Val Thr Val Ser Ser	
115	

<210> 177  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<400> 177

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Phe Val Gln Pro Gly Gly

eof-seq1

1	5	10	15
Ser	Leu	Arg	Leu
	20	Ser	Cys
Ala	Ala	Ser	Gly
		25	Phe
Asn	Phe	Gly	Ser
		30	Tyr
Ala	Met	Ser	Trp
	35	Val	Arg
Gln	Ala	Pro	Gly
	40	Lys	Gly
Leu	Glu	Trp	Val
	45		
Ser	Asp	Ile	Ser
	50	Gly	Ile
Gly	Ser	Asn	Thr
	55	Tyr	Tyr
Ala	Asp	Ser	Val
Lys	Gly	Arg	Phe
	65	Thr	Ile
Ser	Arg	Asp	Asn
	70	Ser	Asp
Asn	Ser	Asp	Asn
	75	Thr	Leu
Tyr			80
Leu	Asp	Met	Ser
		85	Ser
Leu	Arg	Ala	Glu
		90	Asp
Thr	Ala	Arg	Tyr
		95	Tyr
Cys			
Ala	Lys	Asp	Arg
	100	Lys	Arg
Ser	Gly	Trp	Tyr
		105	Glu
Gln	Trp	Gly	Gln
		110	Gly
Thr	Leu	Val	Thr
	115	Val	Ser
Ser			

<210> 178  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <223> NI-302.72F10-PIMC VH variable heavy chain (VH) sequence

<220>  
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 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
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 <222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
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 <223> complementarity determining region (CDR) VH-CDR3

<400>	178	
gag	gtg	cag
Glu	Val	Gln
1		5
gtg	gag	tct
Val	Glu	Ser
5		10
ggg	gga	ggc
Gly	Gly	Phe
10		15
ttc	gta	cag
Val	Gln	Pro
15		20
ggg	ggg	ggg
Gly	Gly	Gly

48

tcc	ctg	aga	ctc	tcc	tgt	gca	gcc	tct	gga	ttc	aac	ttc	ggc	agt	tat
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Phe	Gly	Ser	Tyr
		20						25					30		

96

gcc	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggg	aag	gga	ctg	gag	tgg	gtg
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val

144

eol f-seql

35	40	45	
tca gat atc agt ggt att ggt agt aac aca tac tac gca gac tcc gtg Ser Asp Ile Ser Gly Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val			192
	50	55	
aag ggc cgt ttc acc att tcc aga gac aat tcc gac aat acg ttg tac Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Asp Asn Thr Leu Tyr			240
	65	70	
ctg gac atg agc agc ctg aga gcc gag gac acg gcc aga tat tac tgt Leu Asp Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr Tyr Cys			288
	85	90	
gcg aag gat cga aag cgc agt ggc tgg tac gaa cag tgg ggc cag ggc Ala Lys Asp Arg Lys Arg Ser Gly Trp Tyr Glu Gl n Trp Gly Gl n Gly			336
	100	105	
acc ctg gtc acc gtc tcc tcg Thr Leu Val Thr Val Ser Ser			357
	115		

<210> 179  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens  
 <400> 179

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Phe Val Gl n Pro Gly Gly	1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Gly Ser Tyr	20	25	30	
Ala Met Ser Trp Val Arg Gl n Ala Pro Gly Lys Gly Leu Gl u Trp Val	35	40	45	
Ser Asp Ile Ser Gly Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val	50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Asp Asn Thr Leu Tyr	65	70	75	80
Leu Asp Met Ser Ser Leu Arg Ala Gl u Asp Thr Ala Arg Tyr Tyr Cys	85	90	95	
Ala Lys Asp Arg Lys Arg Ser Gly Trp Tyr Gl u Gl n Trp Gly Gl n Gly	100	105	110	
Thr Leu Val Thr Val Ser Ser	115			

<210> 180  
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 <213> Homo sapiens

eof-seql

<220>  
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 <223> NI-302.72F10 VK variable light-kappa chain (VK) sequence

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 <223> complementarity determining region (CDR) VK-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(168)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (265)..(291)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 180  
 gaa att gtg atg aca cag tct cca gcc acc ctg act ttg tct cca ggg 48  
 Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Thr Leu Ser Pro Gly  
 1 5 10 15  
 gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt att agc gcc tac 96  
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ala Tyr  
 20 25 30  
 tta ggc tgg tat caa caa aaa cct ggc cag gct ccc agg ctc ctc atc 144  
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35 40 45  
 tat gat gca tcc att agg gcc act ggc att cca gac agg ttt agt ggc 192  
 Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly  
 50 55 60  
 agt ggg tct ggg aca gac ttc act ctc acc atc agc agc cta gag cct 240  
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
 65 70 75 80  
 gaa gat tct gca gtt tat tac tgt cac cag cgt agc aag tgg cct ctt 288  
 Glu Asp Ser Ala Val Tyr Tyr Cys His Gln Arg Ser Lys Trp Pro Leu  
 85 90 95  
 act ttc ggc gga ggg acc aag gtg gaa atc aaa 321  
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 181  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 181  
 Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Thr Leu Ser Pro Gly  
 1 5 10 15  
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ala Tyr  
 20 25 30  
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35 40 45

eof-seq1

Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
65 70 75 80

Glu Asp Ser Ala Val Tyr Tyr Cys His Gln Arg Ser Lys Trp Pro Leu  
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 182  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1)..(321)  
<223> NI-302.72F10-PIMC VK variable kappa-light chain (VK) sequence

<220>  
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<222> (70)..(102)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (148)..(168)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (265)..(291)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 182  
gaa att gtg ctg act cag tct cca gcc acc ctg act ttg tct cca ggg 48  
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Thr Leu Ser Pro Gly  
1 5 10 15

gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt att agc gcc tac 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ala Tyr  
20 25 30

tta ggc tgg tat caa caa aaa cct ggc cag gct ccc agg ctc ctc atc 144  
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

tat gat gca tcc att agg gcc act ggc att cca gac agg ttt agt ggc 192  
Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly  
50 55 60

agt ggg tct ggg aca gac ttc act ctc acc atc agc agc cta gag cct 240  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
65 70 75 80

gaa gat tct gca gtt tat tac tgt cac cag cgt agc aag tgg cct ctt 288  
Glu Asp Ser Ala Val Tyr Tyr Cys His Gln Arg Ser Lys Trp Pro Leu  
85 90 95

act ttc ggc gga ggg acc aag gtg gaa atc aaa  
 Thr Phe Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 183  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens  
 <400> 183

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ala Tyr  
 20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35 40 45

Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro  
 65 70 75 80

Glu Asp Ser Ala Val Tyr Tyr Cys His Gln Arg Ser Lys Trp Pro Leu  
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 184  
 <211> 378  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(378)  
 <223> NI-302.4A6-VH variable heavy chain (VH) sequence

<220>  
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 <222> (91)..(105)  
 <223> complementarity determining region (CDR) VH-CDR1

<220>  
 <221> V\_region  
 <222> (148)..(198)  
 <223> complementarity determining region (CDR) VH-CDR2

<220>  
 <221> V\_region  
 <222> (295)..(324)  
 <223> complementarity determining region (CDR) VH-CDR3

<400> 184  
 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg ggg  
 Page 115

eol f-seql

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
tcc	ctg	aga	ctc	tcc	tgt	gca	gcc	tct	gga	ttc	acc	ttt	agc	gct	tat		96
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ala	Tyr		
			20					25					30				
gcc	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggg	aag	ggg	ctg	gag	tgg	gtc		144
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
tca	act	att	agt	ggc	agt	ggc	ggc	agt	aca	tac	tac	gca	gac	tcc	gtg		192
Ser	Thr	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val		
	50					55					60						
aag	ggc	cgg	ttc	tcc	atc	tcc	aga	gac	aac	tcc	aaa	aac	acc	ctg	tat		240
Lys	Gly	Arg	Phe	Ser	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
	65				70				75					80			
ctg	caa	atg	aac	agc	ctg	aga	gcc	gag	gac	acg	gcc	gta	tat	ttc	tgt		288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys		
				85					90					95			
gcg	aaa	gtt	acc	acg	gaa	ctc	tac	ggc	gct	aac	tcc	tac	tac	tac	tac		336
Ala	Lys	Val	Thr	Thr	Glu	Leu	Tyr	Gly	Ala	Asn	Ser	Tyr	Tyr	Tyr	Tyr		
			100					105					110				
atg	gac	gtc	tgg	ggc	aaa	ggg	acc	acg	gtc	acc	gtc	tcc	tcg				378
Met	Asp	Val	Trp	Gly	Lys	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				
		115					120					125					

<210> 185  
 <211> 126  
 <212> PRT  
 <213> Homo sapiens  
 <400> 185

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ala	Tyr		
			20					25					30				
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ser	Thr	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val		
	50					55					60						
Lys	Gly	Arg	Phe	Ser	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
	65				70				75					80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys		
			85					90					95				
Ala	Lys	Val	Thr	Thr	Glu	Leu	Tyr	Gly	Ala	Asn	Ser	Tyr	Tyr	Tyr	Tyr		
			100					105					110				
Met	Asp	Val	Trp	Gly	Lys	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				



115

120

125

<210> 186  
 <211> 321  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)..(321)  
 <223> NI-302.4A6 VK variable light-kappa chain (VK) sequence

<220>  
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<220>  
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 <222> (151)..(171)  
 <223> complementarity determining region (CDR) VK-CDR2

<220>  
 <221> V\_region  
 <222> (286)..(291)  
 <223> complementarity determining region (CDR) VK-CDR3

<400> 186  
 gaa att gtg ttg aca cag tct cca ggc acc ctg tct ttg tct cca ggg 48  
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15  
 gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt gtc agc agg 96  
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Val Ser Arg  
 20 25 30  
 tat tta gcc tgg tac cag caa aaa cct ggc cag gct ccc agg ctc ctc 144  
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
 35 40 45  
 atc tat ggt gca tcc agc agg gcc act ggc atc cca gac agg ttc agt 192  
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
 50 55 60  
 ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag 240  
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
 65 70 75 80  
 cct gaa gat ttt gca atg tat tac tgt cag ctg tat ggt aac tca cag 288  
 Pro Glu Asp Phe Ala Met Tyr Tyr Cys Gln Leu Tyr Gly Asn Ser Gln  
 85 90 95  
 acg ttc ggc cag ggg acc aag gtg gag atc aaa 321  
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 187  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 187  
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

eof-seq1

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Val Ser Arg  
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

Pro Glu Asp Phe Ala Met Tyr Tyr Cys Gln Leu Tyr Gly Asn Ser Gln  
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 188  
<211> 375  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1)..(375)  
<223> NI-302.12H2-VH variable heavy chain (VH) sequence

<220>  
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<223> complementarity determining region (CDR) VH-CDR1

<220>  
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<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(342)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 188  
gag gtg cag ctg gtg cag tct ggg gga ggc ttg gta cag cct ggg ggg 48  
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
1 5 10 15

tcc ctg aga ctt tcc tgt gaa gcc tct gga ttc acc ttt agc aac tat 96  
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Asn Tyr  
20 25 30

gcc atg ggc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

tca gta att agt ggt act ggt ggt agc aca tac tac gca gac tcc gtc 192  
Ser Val Ile Ser Gly Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

eof-seql

aag ggc cgg ttc acc atc tcc aga gac aat tcc atg aac acg ctg tat 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Met Asn Thr Leu Tyr  
65 70 75 80

ctg caa atg aac agc ccg aga gcc gac gac acg gcc gta tat tac tgt 288  
Leu Gln Met Asn Ser Pro Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gcg aaa gat ctg agg aag att agc ggt cct tta tac tac tac ggt atg 336  
Ala Lys Asp Leu Arg Lys Ile Ser Gly Pro Leu Tyr Tyr Tyr Gly Met  
100 105 110

gac gtc tgg ggc caa ggg acc acg gtc acc gtc tcc tgc 375  
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

<210> 189  
<211> 125  
<212> PRT  
<213> Homo sapiens

<400> 189

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

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Asn Tyr  
20 25 30

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

Ser Val Ile Ser Gly Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Met Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Pro Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Lys Asp Leu Arg Lys Ile Ser Gly Pro Leu Tyr Tyr Tyr Gly Met  
100 105 110

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

<210> 190  
<211> 375  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1)..(375)  
<223> NI-302.12H2-PIMC VH variable heavy chain (VH) sequence

eof-seql

<220>  
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 <223> compl ementari ty determi ni ng regi on (CDR) VH-CDR1

<220>  
 <221> V\_rehi on  
 <222> (148).. (198)  
 <223> compl ementari ty determi ni ng regi on (CDR) VH-CDR2

<220>  
 <221> V\_rehi on  
 <222> (295).. (342)  
 <223> compl ementari ty determi ni ng regi on (CDR) VH-CDR3

<400> 190  
 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg ggg 48  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 tcc ctg aga ctt tcc tgt gaa gcc tct gga ttc acc ttt agc aac tat 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Asn Tyr  
 20 25 30  
 gcc atg ggc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 tca gta att agt ggt act ggt ggt agc aca tac tac gca gac tcc gtg 192  
 Ser Val Ile Ser Gly Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cgg ttc acc atc tcc aga gac aat tcc atg aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Met Asn Thr Leu Tyr  
 65 70 75 80  
 ctg caa atg aac agc ccg aga gcc gac gac acg gcc gta tat tac tgt 288  
 Leu Gln Met Asn Ser Pro Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aaa gat ctg agg aag att agc ggt cct tta tac tac tac ggt atg 336  
 Ala Lys Asp Leu Arg Lys Ile Ser Gly Pro Leu Tyr Tyr Tyr Gly Met  
 100 105 110  
 gac gtc tgg ggc caa ggg acc acg gtc acc gtc tcc tgc 375  
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120 125

<210> 191  
 <211> 125  
 <212> PRT  
 <213> Homo sapi ens

<400> 191  
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Asn Tyr  
 20 25 30  
 Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

eol f-seql

Ser Val Ile Ser Gly Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Met Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Pro Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Lys Asp Leu Arg Lys Ile Ser Gly Pro Leu Tyr Tyr Tyr Gly Met  
100 105 110

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

<210> 192  
<211> 324  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(324)  
<223> NI-302.12H2 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(105)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (151)..(171)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (268)..(294)  
<223> complementarity determining region (CDR) VK-CDR2

<400> 192  
gaa att gtg ttg acg cag tct cca ggc acc ctg tct ttg tct cca ggg 48  
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt agc agc ggc 96  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Gly  
20 25 30

tac tta gcc tgg tac cag cag aaa cct ggc cag gct ccc agg ctc ctc 144  
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
35 40 45

atc tat ggt gca tcc acc agg gcc act ggc atc cca gac agg ttc agt 192  
Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
50 55 60

ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag 240  
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

cct gaa gat ttt gca gtg tat tac tgt cag cac tat ggt gcc tca tcg 288

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ala Ser Ser  
85 90  
tac act ttt ggc cag ggg acc aag ctg gag atc aaa  
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
100 105

324

<210> 193  
<211> 108  
<212> PRT  
<213> Homo sapiens

<400> 193

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Gly  
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser  
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ala Ser Ser  
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 194  
<211> 363  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(363)  
<223> NI-302.8M1-VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(330)  
<223> complementarity determining region (CDR) VH-CDR3

eol f-seql

<400> 194  
gag gtc cag ctg gtg cag tct ggg gct gag gtg aag aag cct ggg gcc  
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 48  
1 5 10 15  
tca gtg aaa gtt tcc tgc aag gca tcc gga tac acc ttc acc atc tac 96  
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile Tyr  
20 25 30  
tat atg cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45  
gga gga atc agc ccg agt ggt gcc cac aca atg tac gca cag aat ttc 192  
Gly Gly Ile Ser Pro Ser Gly Ala His Thr Met Tyr Ala Gln Asn Phe  
50 55 60  
cag ggc aga gtc acc gtg acc agg gac acg tcc acg agc aca gtc tac 240  
Gln Gly Arg Val Thr Val Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
65 70 75 80  
atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt 288  
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
gcg aga ggg agc acg gtg act aac tat cga ccc ttt gac tac tgg ggc 336  
Ala Arg Gly Ser Thr Val Thr Asn Tyr Arg Pro Phe Asp Tyr Trp Gly  
100 105 110  
cag gga acc ctg gtc acc gtc tcc tcg 363  
Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 195  
<211> 121  
<212> PRT  
<213> Homo sapiens

<400> 195  
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
1 5 10 15  
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile Tyr  
20 25 30  
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45  
Gly Gly Ile Ser Pro Ser Gly Ala His Thr Met Tyr Ala Gln Asn Phe  
50 55 60  
Gln Gly Arg Val Thr Val Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
65 70 75 80  
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
Ala Arg Gly Ser Thr Val Thr Asn Tyr Arg Pro Phe Asp Tyr Trp Gly  
100 105 110

eof-seq1

Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 196  
<211> 363  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(363)  
<223> NI-302.8M1-PIMC VH variable heavy chain (VH) sequence

<220>  
<221> V\_region  
<222> (91)..(105)  
<223> complementarity determining region (CDR) VH-CDR1

<220>  
<221> V\_region  
<222> (148)..(198)  
<223> complementarity determining region (CDR) VH-CDR2

<220>  
<221> V\_region  
<222> (295)..(330)  
<223> complementarity determining region (CDR) VH-CDR3

<400> 196	
cag gtg cag ctg gtg caa tct ggg gct gag gtg aag aag cct ggg gcc	48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
1 5 10 15	
tca gtg aaa gtt tcc tgc aag gca tcc gga tac acc ttc acc atc tac	96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile Tyr	
20 25 30	
tat atg cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg	144
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga gga atc agc ccg agt ggt gcc cac aca atg tac gca cag aat ttc	192
Gly Gly Ile Ser Pro Ser Gly Ala His Thr Met Tyr Ala Gln Asn Phe	
50 55 60	
cag ggc aga gtc acc gtg acc agg gac acg tcc acg agc aca gtc tac	240
Gln Gly Arg Val Thr Val Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr	
65 70 75 80	
atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt	288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga ggg agc acg gtg act aac tat cga ccc ttt gac tac tgg ggc	336
Ala Arg Gly Ser Thr Val Thr Asn Tyr Arg Pro Phe Asp Tyr Trp Gly	
100 105 110	
cag ggc acc ctg gtc acc gtc tcc tcg	363
Gln Gly Thr Leu Val Thr Val Ser Ser	
115 120	

<210> 197  
<211> 121



eof-seq1

<212> PRT  
<213> Homo sapiens  
<400> 197

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 Ile Tyr  
20 25 30  
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45  
Gly Gly Ile Ser Pro Ser Gly Ala His Thr Met Tyr Ala Gln Asn Phe  
50 55 60  
Gln Gly Arg Val Thr Val Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
65 70 75 80  
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
Ala Arg Gly Ser Thr Val Thr Asn Tyr Arg Pro Phe Asp Tyr Trp Gly  
100 105 110  
Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 198  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(321)  
<223> NI-302.8M1 VK variable light-kappa chain (VK) sequence

<220>  
<221> V\_region  
<222> (70)..(102)  
<223> complementarity determining region (CDR) VK-CDR1

<220>  
<221> V\_region  
<222> (148)..(168)  
<223> complementarity determining region (CDR) VK-CDR2

<220>  
<221> V\_region  
<222> (265)..(291)  
<223> complementarity determining region (CDR) VK-CDR3

<400> 198  
gac atc cag atg acc cag tct cca tcc tcc ctg tct gca tct gta gga  
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1 5 10 15

48

eol f-seql

gac	aga	gtc	act	atc	act	tgc	cgg	gcg	agt	cag	gac	att	agc	aat	tat		96
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr		
			20					25					30				
tta	gcc	tgg	tat	cag	cag	aaa	cca	ggg	aaa	gtt	cct	aaa	ctc	ctg	atc		144
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Val	Pro	Lys	Leu	Leu	Ile		
		35					40					45					
ttt	gct	gca	tcc	act	ttg	caa	tca	ggg	gtc	ccg	tct	cgg	ttc	ggg	ggc		192
Phe	Ala	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Gly	Gly		
	50					55					60						
agt	gga	tct	ggg	aca	gat	ttc	act	ctc	acc	atc	agc	agc	ctg	cag	cct		240
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro		
	65				70					75					80		
gaa	gat	gtt	gca	act	tat	tac	tgt	caa	aac	tat	aac	agt	ggc	cct	ccg		288
Glu	Asp	Val	Ala	Thr	Tyr	Tyr	Cys	Gln	Asn	Tyr	Asn	Ser	Gly	Pro	Pro		
				85					90					95			
cct	ttc	ggc	cct	ggg	acc	aaa	gtg	gat	atc	aaa							321
Pro	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys							
			100					105									

<210> 199  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 199

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly		
1				5					10					15			
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr		
			20					25					30				
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Val	Pro	Lys	Leu	Leu	Ile		
		35					40					45					
Phe	Ala	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Gly	Gly		
	50					55					60						
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro		
	65				70					75				80			
Glu	Asp	Val	Ala	Thr	Tyr	Tyr	Cys	Gln	Asn	Tyr	Asn	Ser	Gly	Pro	Pro		
				85					90					95			
Pro	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys							
			100					105									

<210> 200  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Epitope recognized by NI-302.64E5

eol f-seql

<400> 200

Pro Gln Pro Pro Pro Gln Ala Gln Pro Leu  
1 5 10

<210> 201

<211> 10

<212> PRT

<213> Arti fici al Sequence

<220>

<223> Epi tope recogni zed by NI -302. 7D8

<400> 201

Gln Gln Gln Gln Gln Gln Gln Pro Pro Pro  
1 5 10

<210> 202

<211> 13

<212> PRT

<213> Arti fici al Sequence

<220>

<223> Epi tope recogni zed by NI -302. 72F10

<400> 202

Pro Pro Pro Gly Pro Ala Val Ala Glu Glu Pro Leu His  
1 5 10