## *Claims:*

Claim 1. An isolated antibody which specifically binds to a CD33 protein, wherein the antibody comprises:

a heavy chain variable domain (VH) with the following CDRs:

a CDRH1 comprising the amino acid sequence set forth in SEQ ID NO:44;

a CDRH2 comprising an amino acid sequence set forth in SEQ ID NO: 52; and

a CDRH3 comprising an amino acid sequence set forth in SEQ ID NO: 59; and

a light chain variable domain (VL) with the following CDRs:

CDRL1 comprising the amino acid sequence set forth in SEQ ID NO: 110.

CDRL2 comprising the amino acid sequence set forth in SEQ ID NO:119; and

CDRL3 comprising the amino acid sequence set forth in SEQ ID NO: 129;

and wherein:

a) the antibody increases phagocytosis of a cell expressing CD33 compared to a comparative antibody and/or

b) wherein the antibody binding to a human CD33 protein comprising mutations at positions 20, 21, 22 and 24 is increased compared to the antibody binding to a human CD33 protein without said mutations.

Claim 2. The isolated antibody of claim 1, wherein

a) the antibody binding to a human CD33 protein comprising mutations at positions 20, 21, 22, 24 and 132 is increased compared to the antibody binding to a human CD33 protein without said mutations, and/or

b) wherein the antibody binding to a human CD33 protein comprising mutations at positions 47, 50, 51 and 52 is reduced compared to the antibody binding to a human CD33 protein without said mutations, and/or

c) wherein the antibody does not bind to a human CD33 protein comprising mutations at positions 47, 50, 51 and 52, and/or

d) wherein the antibody binding to a human CD33 protein comprising mutations at positions 47, 50, 51, 52 and 122 is reduced compared to the antibody binding to a human CD33 protein without said mutations, and/or

e) wherein the antibody does not bind to a human CD33 protein comprising mutations at positions 47, 50, 51, 52 and 122, and/or

f) wherein the antibody binding to a human CD33 protein comprising mutations at positions 83 is reduced compared to the antibody binding to a human CD33 protein without said mutations.

Claim 3. The isolated antibody of claim 1 or claim 2, wherein the mutations are selected from:

a. at position 20: N20R,
b. at position 21: F21V,
c. at position 22: W22R,
d. at position 24: Q24E,
e. at position 47: I47V,
f. at position 50: Y50H,

g. at position 51: D51T,
h. at position 52: K52R,
i. at position 83: Q83R,
j. at position 122: R122K, and
k. at position 132: P132T.

Claim 4. The isolated antibody of any preceding claim, wherein the binding is as measured using a single point ELISA and/or the human CD33 protein comprises residues 18-232 of human CD33, and/or the human CD33 protein is CD33M2_ECD_18-232_WT, wherein the amino acid sequence of CD33M2_ECD_18-232_WT is SEQ ID NO: 226.

Claim 5. The isolated antibody of any preceding claim, wherein the antibody has one or more, or all of:

a. increased binding to a protein comprising the sequence of CD33M2_ECD_18-232_MutPos1[P1] set forth in SEQ ID NO: 227 compared to a protein comprising the sequence of CD33M2_ECD_18-232_WT set forth in SEQ ID NO: 226,
b. increased binding to a protein comprising the sequence of CD33M2_ECD_18-232_MutPos1_MutPos6 [P6+1] set forth in SEQ ID NO: 228 compared to a protein comprising the sequence of CD33M2_ECD_18-232_WT set forth in SEQ ID NO: 226,
c. reduced binding to a protein comprising the sequence of CD33M2_ECD_18-232_MutPos2 [P2] set forth in SEQ ID NO: 229 compared to a protein comprising the sequence of CD33M2_ECD_18-232_WT set forth in SEQ ID NO: 226,
d. reduced binding to a protein comprising the sequence of CD33M2_ECD_18-232_MutPos2_MutPos5 [P2+5] set forth in SEQ ID NO: 230 compared to a protein comprising the sequence of CD33M2_ECD_18-232_WT set forth in SEQ ID NO: 226, and
e. reduced binding to a protein comprising the sequence of CD33M2_ECD_18-232_MutPos4 [P4] set forth in SEQ ID NO: 232 compared to a protein comprising the sequence of CD33M2_ECD_18-232_WT set forth in SEQ ID NO: 226.

Claim 6. The isolated antibody of any preceding claim, wherein

a) the comparative antibody is selected from: an isotype control antibody, another CD33-binding antibody, and an antibody with the heavy chain variable sequence of ATL_5909 set forth in SEQ ID NO: 11 and the light chain variable sequence of ATL_5909 set forth in SEQ ID NO: 31, and/or

b) the phagocytosis is assessed by measuring a fluorescence signal associated with uptake of a labelled particle by imaging or flow cytometry, and/or

c) the cell is a monocyte or a microglial cell, optionally wherein the cell is a human cell and/or an iPSC derived microglial cell and/or a cell that has been stimulated with an inflammatory signal prior to exposure to the antibody, optionally wherein the inflammatory signal is LPS, and/or

d) the antibody binds to a CD33 protein that comprises the V domain of CD33, and/or

e) the antibody does not bind to a CD33 protein that does not comprise the V domain of CD33, and/or

f) the antibody does not bind to a CD33 protein that has the sequence of protein CD33_HUMAN_ECD_Cdomain_His_007 set forth in SEQ ID NO: 175.

Claim 7. The isolated antibody according to any preceding claim, wherein the antibody has a heavy chain variable domain (VH) with the following framework sequences:

HFWR1 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 70, ATL_0005853 set forth in SEQ ID NO: 235, ATL_0005854 set forth in SEQ ID NO: 75, ATL_0005807 set forth in SEQ ID NO: 71, ATL_0005808 set forth in SEQ ID NO: 72, ATL_0005809 set forth in SEQ ID NO: 73, ATL_0005810 set forth in SEQ ID NO: 74,

HFWR2 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 83, ATL_0005853 set forth in SEQ ID NO: 83, ATL_0005854 set forth in SEQ ID NO: 83, ATL_0005807 set forth in SEQ ID NO: 84, ATL_0005808 set forth in SEQ ID NO: 84, ATL_0005809 set forth in SEQ ID NO: 85, ATL_0005810 set forth in SEQ ID NO: 86,

HFWR3 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 91, ATL_0005853 set forth in SEQ ID NO: 96, ATL_0005854 set forth in SEQ ID NO: 97, ATL_0005807 set forth in SEQ ID NO: 92, ATL_0005808 set forth in SEQ ID NO: 93, ATL_0005809 set forth in SEQ ID NO: 94, ATL_0005810 set forth in SEQ ID NO: 95, and

HFWR4 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 101, ATL_0005853 set forth in SEQ ID NO: 101, ATL_0005854 set forth in SEQ ID NO: 101, ATL_0005807 set forth in SEQ ID NO: 104, ATL_0005808 set forth in SEQ ID NO: 104, ATL_0005809 set forth in SEQ ID NO: 106, ATL_0005810 set forth in SEQ ID NO: 105, or

framework sequences with one to six substitutions compared to the framework sequences above optionally wherein the substitutions in the framework sequences of the heavy chain variable domain are located at any position other than position 40 in standard IMGT numbering.

Claim 8. The isolated antibody according to any preceding claim, wherein the antibody has a heavy chain variable domain (VH) with a framework sequence HFWR2 of ATL_0005802 set forth in SEQ ID NO: 83 and/or wherein the antibody has a heavy chain variable domain (VH) with a framework sequence comprising a A at position 40 in standard IMGT numbering.

Claim 9. The isolated antibody according to any preceding claim, wherein the antibody has a heavy chain variable domain (VH) comprising a sequence that has a least 95% sequence identity with a sequence selected from the VH sequence of antibodies: ATL_0005802 set forth in SEQ ID NO: 4, ATL_0005853 set forth in SEQ ID NO: 9, ATL_0005854 set forth in SEQ ID NO: 10, ATL_0005807 set forth in SEQ ID NO: 5, ATL_0005808 set forth in SEQ ID NO: 6, ATL_0005809 set forth in SEQ ID NO: 7, ATL_0005810 set forth in SEQ ID NO: 8, ATL_0006040 set forth in SEQ ID NO: 12,
ATL_0006041 set forth in SEQ ID NO: 13, ATL_0006042 set forth in SEQ ID NO: 14, ATL_0006043 set forth in SEQ ID NO: 15, ATL_0006044 set forth in SEQ ID NO: 16, ATL_0006045 set forth in SEQ ID NO: 17, ATL_0006046 set forth in SEQ ID NO: 18, ATL_0006047 set forth in SEQ ID NO: 19, and ATL_0006048 set forth in SEQ ID NO: 20, or wherein the antibody has a heavy chain variable domain (VH) comprising a sequence that has at most 3 mutations in each framework region compared with a sequence selected from said VH sequences; optionally wherein the antibody has a heavy chain variable domain (VH) comprising a sequence that has a least 95% sequence identity with a sequence selected from the VH sequence of antibodies ATL_0005802 set forth in SEQ ID NO: 4, ATL_0005853 set forth in

SEQ ID NO: 9, or ATL_0005854 set forth in SEQ ID NO: 10 or a sequence that has at most 3 mutations in each framework region compared with a sequence selected from said VH sequences.

Claim 10. The isolated antibody of any preceding claim, wherein the antibody: (i) has a heavy chain variable domain (VH) comprising CDRH1, CDRH2, and CDRH3 within a germline framework, provided that position 40 in standard IMGT numbering is A, and/or (ii) is an scFv antibody molecule, or a whole antibody, and/or wherein the antibody comprises an antibody constant region, and/or wherein the antibody is a whole antibody and/or wherein the antibody is an IgG1 or variant thereof, optionally wherein the antibody is an IgG1 variant L234A/L235A (LALA).

Claim 11. The isolated antibody of any preceding claim, wherein:

a) the antibody binds human CD33, optionally wherein the antibody binds human CD33 with an EC50 of at most 2e-08 M, or at most 3e-09 M, as assessed by ELISA, optionally wherein the ELISA measures binding of plated rhCD33, and/or

b) the antibody selectively binds to CD33 over other one or more siglecs, optionally wherein the antibody selectively binds to CD33 over one or more: siglec-6, siglec-7, siglec-8, and siglec-9, optionally wherein the antibody selectively binds to CD33 over all of: siglec-6, siglec-7, siglec-8, and siglec-9, and/or

c) the antibody selectively binds to human CD33 over other one or more homologs, optionally wherein the antibody selectively binds to human CD33 over mouse CD33 and cyno CD33, and/or.

d) the antibody depletes CD33 on the cell surface of human monocytes by less than 50%, or less than 80% after 5 hours of incubation with the antibody, and/or

e) the antibody depletes CD33 on the cell surface of human monocytes after 5 hours of incubation with the antibody to a lower extent than a comparative antibody at the same concentration, and/or

f) the antibody has lower peripheral clearance when administered to a subject, compared to a comparative anti-CD33 antibody, and/or

g) the antibody increases phagocytosis of Aβ by microglial cells in vivo compared to a control, and/or

h) the antibody increases the phagocytosis of tau aggregates by microglia with inflammatory phenotype compared to a control, optionally wherein the microglia with inflammatory phenotype are LPS treated iPSC microglia, and/or

i) the antibody increases the phagocytosis of tau aggregates by microglia with inflammatory phenotype to a larger extent than a comparative anti-CD33 antibody, and/or

j) the antibody does not induce release of one or more cytokines including IL-6 and/or MCP-1 by microglia in vitro and/or in vivo, and/or

k) the antibody reduces the levels of IL-6 and/or MCP-1 released by microglia with an inflammatory phenotype in vitro, optionally wherein the microglia with inflammatory phenotype are LPS treated iPSC derived microglia, and/or in vivo, and/or

l) the antibody reduces inflammation induced release of one or more markers of inflammation in a human neural cell culture assay and/or in the central nervous system of a subject, optionally wherein the one or more markers of inflammation are selected from: MCP-1, IP-10, GFAP and IL-6.

Claim 12. The isolated antibody according to any preceding claim, wherein:

a) the CDRL1, CDRL2 and CDRL3 of the VL domain are within a germline framework, and/or

b) the antibody has a light chain variable domain (VL) with the following framework sequences:

LFWR1 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 138, ATL_0005853 set forth in SEQ ID NO: 143, ATL_0005854 set forth in SEQ ID NO: 140, ATL_0005807 set forth in SEQ ID NO: 139, ATL_0005808 set forth in SEQ ID NO: 140, ATL_0005809 set forth in SEQ ID NO: 141, ATL_0005810 set forth in SEQ ID NO: 142;

LFWR2 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 151, ATL_0005853 set forth in SEQ ID NO: 156, ATL_0005854 set forth in SEQ ID NO: 153, ATL_0005807 set forth in SEQ ID NO: 152, ATL_0005808 set forth in SEQ ID NO: 153, ATL_0005809 set forth in SEQ ID NO: 154, ATL_0005810 set forth in SEQ ID NO: 155;

LFWR3 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 160, ATL_0005853 set forth in SEQ ID NO: 165, ATL_0005854 set forth in SEQ ID NO: 166, ATL_0005807 set forth in SEQ ID NO: 161, ATL_0005808 set forth in SEQ ID NO: 162, ATL_0005809 set forth in SEQ ID NO: 163, ATL_0005810 set forth in SEQ ID NO: 164; and

LFWR4 of any of antibodies ATL_0005802 set forth in SEQ ID NO: 172, ATL_0005853 set forth in SEQ ID NO: 174, ATL_0005854 set forth in SEQ ID NO: 173, ATL_0005807 set forth in SEQ ID NO: 173, ATL_0005808 set forth in SEQ ID NO: 173, ATL_0005809 set forth in SEQ ID NO: 172, ATL_0005810 set forth in SEQ ID NO: 172; or

a set of FWRs which contains one to six amino acid substitutions compared with the above set of FWR, and/or

c) the antibody has a light chain variable domain (VL) comprising a sequence selected that has a least 95% sequence identity with a sequence selected from the VL sequence of antibodies: ATL_0005802 set forth in SEQ ID NO: 24, ATL_0005853 set forth in SEQ ID NO: 29, ATL_0005854 set forth in SEQ ID NO: 30, ATL_0005807 set forth in SEQ ID NO: 25, ATL_0005808 set forth in SEQ ID NO: 26, ATL_0005809 set forth in SEQ ID NO: 27, ATL_0005810 set forth in SEQ ID NO: 28, ATL_0006040 set forth in SEQ ID NO: 32, ATL_0006041 set forth in SEQ ID NO: 33, ATL_0006042 set forth in SEQ ID NO: 34, ATL_0006043 set forth in SEQ ID NO: 35, ATL_0006044 set forth in SEQ ID NO: 36, ATL_0006045 set forth in SEQ ID NO: 37, ATL_0006046 set forth in SEQ ID NO: 38, ATL_0006047 set forth in SEQ ID NO: 39, and ATL_0006048 set forth in SEQ ID NO: 40, or wherein the antibody has a light chain variable domain (VL) comprising a sequence that has at most 3 mutations in each framework region compared with a sequence selected from said VL sequences; optionally wherein the antibody has a light chain variable domain (VL) comprising a sequence that has a least 95% sequence identity with a sequence selected from the VL sequence of antibodies ATL_0005802 set forth in SEQ ID NO: 24, ATL_0005853 set forth in SEQ ID NO: 29, or ATL_0005854 set forth in SEQ ID NO: 30, or a sequence that has at most 3 mutations in each framework region compared with a sequence selected from said VL sequences.

Claim 13. An isolated nucleic acid, vector or set of vectors which comprises a nucleotide sequence encoding an antibody, including a VH or VL domain, according to any preceding claim, or a fragment thereof.

Claim 14. A host cell comprising the vector(s) of claim 13, or a host cell *in vitro* transformed with a nucleic acid of claim 13.

Claim 15. An antibody according to any of claims 1 to 12, for use in the treatment of a disease or disorder selected from:

(i) a disease associated with dysfunction of microglial cells;

(ii) a neurodegenerative disease or disorder, optionally wherein the neurodegenerative disease or disorder is a tauopathy or a disease or disorder selected from: frontotemporal dementia (FTD), Alzheimer's disease (AD), Huntington's Disease (HD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), human immunodeficiency virus (HIV)-induced encephalitis, Chronic traumatic encephalopathy (CTE), vascular dementia, prion diseases, Lewy body disease, Spinal muscular atrophy (SMA), Motor Neuron Disease (MND), such as amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), spinocerebellar ataxias (SCA) types 1, 2, 6, 7 and 17, Machado–Joseph disease (MJD/SCA3), dentatorubral pallidoluysian atrophy (DRPLA), spinal bulbar muscular atrophy X-linked type 1 (SMAX1/SBMA), Anderson-Fabry (X-linked Fabry Disease), and DNAJB6 Myopathies, optionally wherein the neurodegenerative disease is selected from FTD, AD, HD, and PD;

(iii) a cancer, optionally wherein the cancer is AML or a cancer associated with hypersyalilation of tumour cells and/or overexpression of CD33 by tumour cells; and

(iv) a disease characterised by insufficient macrophage phagocytosis and/or macrophage dysfunction, optionally wherein the disease is COPD or IPF.