

Anti-PGDH antibodies

This application claims priority from GR 20230101061 filed 20 December 2023 and GB 2400120.8 filed 04 January 2024, the contents and elements of each of which are herein incorporated by reference for all purposes.

5 ***Field of the Disclosure***

The present invention relates to antibodies capable of binding and inhibiting 15-PGDH and particularly, although not exclusively, to novel therapeutic antibodies. Methods for using anti-PGDH antibodies in therapy, including for the treatment of Parkinson's Disease and inflammatory conditions, are also described.

10 ***Background***

Parkinson's Disease (PD) is a progressive neurodegenerative disease. It is an age-dependent disease characterised by a progressive loss of dopaminergic neurons in the *substantia nigra*, *locus coeruleus*, and other neuronal populations that leads to a broad spectrum of non-motor and motor symptoms. Non-motor symptoms include rapid eye movement sleep behaviour disorder (RBD), anosmia, constipation, depression, dementia, and psychosis. Motor symptoms include tremor, stiffness, impaired posture, slowness of movement, falls, freezing, and muscle cramps (Jankovic et al., 2020). RBD has emerged as one of the most specific predictors of the synuclein-mediated neurodegenerative diseases including Parkinson's disease. It is now estimated that up to 90% of patients with RBD will eventually develop one of the α -synucleinopathies, although the delay from RBD to diagnosis of PD is variable (Roguski et al., 2020).

20 The neuropathological hallmark of PD is the abnormal accumulation and aggregation of alpha synuclein protein (α -Syn) in the form of Lewy bodies and Lewy neurites. Pathological aggregation of α -Syn is a common feature of PD and other diseases referred to as alpha-synucleinopathies, such as dementia with Lewy bodies (Lewy body disease), and multiple-system atrophy (MSA). Chronic neuroinflammation is an important driver in the pathogenesis of PD, and prostaglandins have been implicated in this process

25 (Tansey et al., 2010; Corwin et al., 2018). Prostaglandins are generated from arachidonic acid (AA) that is liberated from membrane phospholipids catalysed by phospholipase A2. The AAs are subsequently oxygenated to form prostaglandin H2 (PGH2) by cyclooxygenase-1 and 2 (COX1, 2). PGH2 is transformed into PGE2, PGF2 α , PGD2, and PGI2 via terminal prostaglandin synthases (PGES, PGFS, PGDS and PGIS respectively for each prostaglandin) that differ in their cell type distribution (Smyth et al., 2009). Different

30 prostaglandins have different context-dependent effects. For example, while PGD2 is neurotoxic and has been shown to promote neurodegeneration, PGE2 (also referred to as PGE₂) signalling reduces inflammatory neurodegeneration (Corwin et al., 2018; Liu et al., 2019). Further, whether PGD2 or PGE2 is beneficial or not is dependent on disease state and spatial (tissue and cell-type) and temporal factors (acute vs. chronic).

35 PGE2 acts through four downstream G-protein-coupled prostaglandin E receptors: EP1; EP2; EP3; and EP4. The effect of PGE2 signalling depends on the expression of each EP receptor and the strength of each EP signal. EP1 (couple to Gq) and EP3 (couple to Gi) mediate PGE2-induced intracellular calcium

mobilization. The EP2 and EP4 receptors coupled to Gs activate adenylate cyclase (AC) and increase cAMP production, whereas the EP3 receptor inhibits cAMP signalling (Cheng et al., 2021). The PGE2 signalling pathway has been implicated in neuroinflammation, mitochondrial function, oxidative stress, apoptosis, tissue regeneration, and neuronal signalling (Funk et al., 2001; Ho et al., 2017; Montalban et al., 2022; Palla et al., 2021). In addition, reduced PGE2 signalling contributes to muscle wasting in sarcopenia, an age-related skeletal muscle wasting disease. These findings therefore implicate PGE2 in peripheral ageing-associated diseases (Palla et al., 2021; Guo et al., 2022). EP4 signalling has been shown to have a neuroprotective effect in a model of Parkinson's disease (Pradhan et al. 2016).

15-hydroxyprostaglandin dehydrogenase (15-PGDH) is an enzyme responsible for the biological inactivation of eicosanoids such as prostaglandins, in particular prostaglandin E2 (PGE2). 15-PGDH negatively regulates the PGE2 signalling pathway and degrades PGE2 by catalysing its NAD⁺-dependent dehydrogenation into 15-keto-PGE2 which is unable to bind prostaglandin receptors (Tai et al., 2002). 15-PGDH is mostly an intracellular protein, however small concentrations have been found in the extracellular space as well. Notably, inhibition of 15-PGDH promotes mitochondrial function and autophagy through increased PGE2 signalling, and this increased muscle mass and strength in aged mice (Palla et al., 2021).

Small molecule inhibitors of 15-PGDH have been described for the treatment of inflammatory conditions and peripheral ageing-associated diseases (Zhang et al., 2015; Antczak et al., 2017; Huang et al., 2023). WO 2023/009618 describes bicyclic PGDH inhibitors and methods of using these in a range of conditions.

Summary of the Invention

The present inventors have shown that the antibody repertoire of resilient individuals can be used to identify disease-specific antibody sequences. In the present work, the inventors sought to identify candidate protective antibodies from patients resilient to Parkinson's disease (PD). A proteome-wide interaction study of serum derived from PD patients revealed strong reactivity against 15-PGDH in patients resilient to PD and PD patients without cognitive impairment. These findings indicate that 15-PGDH autoreactivity has a protective role in PD pathology. Mass spectrometry-based proteomics of serum antibodies and phage display of antibody repertoires subsequently identified five monoclonal antibodies derived from these patients that bind and inhibit 15-PGDH. 15-PGDH-detecting antibodies for research purposes have previously been described (see, for example, Kahnt et al., 2022). However, to the best of the inventors' knowledge, no therapeutic antibody or antibody capable of modulating the enzymatic activity of 15-PGDH have been described.

In a first aspect, the present disclosure provides an isolated antibody that specifically binds and inhibits 15-PGDH.

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Antibodies according to the present aspect may have any one or more of the following optional features.

The antibody may comprise a heavy chain variable domain with the following CDRs:

CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 12 (ATL_6027); SEQ ID NO: 13 (ATL_6058; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 14 (ATL_6074); SEQ ID NO: 15 (ATL_6075); SEQ ID NO: 112 (ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932) or SEQ ID NO: 191 (ATL_7471);

CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); SEQ ID NO: 16 (ATL_6026; ATL_7925; ATL_7450; ATL_7819; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7919; ATL_7920; ATL_7923); SEQ ID NO: 17 (ATL_6027); SEQ ID NO: 18 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 19 (ATL_6074); SEQ ID NO: 20 (ATL_6075); SEQ ID NO: 96 (ATL_7952; ATL_7917; ATL_7918; ATL_7921; ATL_7922; ATL_7924); SEQ ID NO: 97 (ATL_7953); SEQ ID NO: 154 (ATL_7820); SEQ ID NO: 155 (ATL_7821); SEQ ID NO: 156 (ATL_7822); or SEQ ID NO: 157 (ATL_7823), and

CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955; ATL_7952; ATL_7953; ATL_7829); SEQ ID NO: 21 (ATL_6026; ATL_7925; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7918; ATL_7919; ATL_7921; ATL_7924); SEQ ID NO: 22 (ATL_6027); SEQ ID NO: 23 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 24 (ATL_6074); SEQ ID NO: 25 (ATL_6075); or SEQ ID NO: 162 (ATL_7917; ATL_7920; ATL_7922; ATL_7923);

or a set of CDRs containing one to six (for example one, two, or three) amino acid mutations, compared with the above set of CDRs. The mutations may be substitutions compared with the above set of CDRs.

In a second aspect, the disclosure provides an isolated antibody that specifically binds and inhibits 15-PGDH comprising a heavy chain variable domain with the following CDRs:

CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953);

CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); SEQ ID NO: 16 (ATL_6026; ATL_7925); SEQ ID NO: 96 (ATL_7952); or SEQ ID NO: 97 (ATL_7953); and

CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955; ATL_7952; ATL_7953); or SEQ ID NO: 21 (ATL_6026; ATL_7925);

or a set of CDRs containing one to six, or one to three amino acid mutations compared with the above set of CDRs. The mutations may be substitutions compared with the above set of CDRs. The mutation may

be at position 62, for example N62A or N62Q; and/or at position 63, for example G63A; and/or at position 64, for example N64A; and/or at position 65, for example T65A or T65S; and/or at position 111C, for example D111CE; and/or at position 112D, for example S122DA.

- 5 The heavy chain variable domain (VH) may have the following framework sequences: HFWR1 of SEQ ID NO: 41 (ATL_6026) or SEQ ID NO: 95 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); HFWR2 of SEQ ID NO: 42 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955); HFWR3 of SEQ ID NO: 43 (ATL_6026); SEQ ID NO: 99 (ATL_7925; ATL_7953); SEQ ID NO: 100 (ATL_7952); or SEQ ID NO: 101 (ATL_7955); and HFWR4 of SEQ ID NO: 44 (ATL_6026); or SEQ ID NO: 103 (ATL_7925; ATL_7952;
- 10 ATL_7953; ATL_7955); or framework sequences with one to nine or one to six mutations (e.g. one, two, three, four, five or six mutations) compared with the framework sequences above. The mutations may be substitutions compared with the above set of CDRs. The mutation may be at position 5, for example Q5V; and/or at position 53, for example M53A; and/or at position 78, for example M78I or M78A; and/or at position 81, for example D81E; and/or at position 89, for example M89A; and/or at position 97, for example D97E; and/or at position 98, for example D98E; and/or at position 99, for example T99A; and/or at position 123, for example M123T. The antibody may bind to an epitope that comprises one or more (or all of) residues Met143; Pro144; Val145; Ala146; Gln147; Phe185; Tyr206; Asp208; His209; Asp212; Met213; Lys215; Tyr216; Tyr217; Gly218; Thr246; Thr247; Ser248; Arg163; Leu167; Asn170; Leu171; Ala237; Asn239; Thr258; Thr259; Pro260; Phe261; Gln262 of 15 PGDH, provided as SEQ ID NO: 82.
- 15 The antibody may have a heavy chain variable domain with the following CDRs: CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955); CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); and CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955). The antibody may have a heavy chain variable domain with the following framework sequences: HFWR1 of SEQ ID NO: 95 (ATL_7955); HFWR2 of SEQ ID NO: 42 (ATL_7955); HFWR3 of SEQ ID NO: 101 (ATL_7955); and HFWR4 of SEQ ID NO: 103 (ATL_7955).
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In a third aspect, the disclosure provides an isolated antibody that specifically binds and inhibits 15-PGDH comprising a heavy chain variable domain with the following CDRs:

- CDRH1 comprising an amino acid sequence of SEQ ID NO: 13 (ATL_6058); or SEQ ID NO: 112 (ATL_7933; ATL_7956);
- 30 CDRH2 comprising an amino acid sequence of SEQ ID NO: 18 (ATL_6058; ATL_7933; ATL_7956); and
- CDRH3 comprising an amino acid sequence of SEQ ID NO: 23 (ATL_6058; ATL_7933; ATL_7956);
- 35 or a set of CDRs containing one, two, or three amino acid mutations compared with the above set of CDRs. The mutations may be substitutions. The substitution may be at position 28, for example D28E and/or at position 29, for example S29A. The heavy chain variable domain (VH) may comprise the following framework sequences: HFWR1 of SEQ ID NO: 57 (ATL_6058; ATL_7933; ATL_7956); HFWR2 of SEQ ID NO: 58 (ATL_6058) or SEQ ID NO: 113 (ATL_7933; ATL_7956); HFWR3 of SEQ ID NO: 59 (ATL_6058) or SEQ ID NO: 114 (ATL_7933; ATL_7956); and HFWR4 of SEQ ID NO: 60 (ATL_6058; ATL_7933) or SEQ ID NO: 115 (ATL_7956); or framework sequences with one to eight, for example one to six (e.g. one, two, three, four, five, or six) mutations, compared with the framework sequences above.
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The mutations may be substitutions compared with the framework sequences above. The mutation may be at position 40, for example A40S; and/or at position 49, for example R49G; and/or at position 66, for example S66N; and/or at position 78, for example M78I; and/or at position 81, for example D81E; and/or at position 85, for example K85N; and/or at position 92, for example T92S; and/or at position 122, for example M122T. The antibody may bind to an epitope that comprises one or more (or all of) residues Asp221; Leu224; Asn227; Thr231; Asp235; Ala237; Leu238; Thr246; Thr247; Ser248; Lys249; Gly250; Ile251; His252; Phe253; Asp255 of 15 PGDH, provided as SEQ ID NO: 82. The antibody may have a heavy chain variable domain with the following CDRs: CDRH1 comprising an amino acid sequence of SEQ ID NO: 112 (ATL_7933); CDRH2 comprising an amino acid sequence of SEQ ID NO: 18 (ATL_7933), and CDRH3 comprising an amino acid sequence of SEQ ID NO: 23 (ATL_7933). The antibody may have a heavy chain variable domain (VH) with the following framework sequences: HFWR1 of SEQ ID NO: 57 (ATL_7933); HFWR2 of SEQ ID NO: 113 (ATL_7933); HFWR3 of SEQ ID NO: 114 (ATL_7933); and HFWR4 of SEQ ID NO: 60 (ATL_7933).

Embodiments of any of the above aspects may have any one or more of the following optional features

The antibody may comprise a heavy chain variable domain (VH) with the following framework sequences: HFWR1 of SEQ ID NO: 41 (ATL_6026); SEQ ID NO: 49 (ATL_6027); SEQ ID NO: 57 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 65 (ATL_6074); SEQ ID NO: 73 (ATL_6075); or SEQ ID NO: 95 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); HFWR2 of SEQ ID NO: 42 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_7450; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 50 (ATL_6027); SEQ ID NO: 58 (ATL_6058; ATL_7469; ATL_7927); SEQ ID NO: 66 (ATL_6074); SEQ ID NO: 74 (ATL_6075); SEQ ID NO: 113 (ATL_7933; ATL_7956; ATL_7467; ATL_7468; ATL_7470; ATL_7471; ATL_7472; ATL_7473; ATL_7926; ATL_7930; ATL_7931; ATL_7932); or SEQ ID NO: 153 (ATL_7819); SEQ ID NO: 192 (ATL_7928); or SEQ ID NO: 193 (ATL_7929); HFWR3 of SEQ ID NO: 43 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7922); SEQ ID NO: 51 (ATL_6027); SEQ ID NO: 59 (ATL_6058; ATL_7469); SEQ ID NO: 67 (ATL_6074; ATL_7472); SEQ ID NO: 75 (ATL_6075); SEQ ID NO: 99 (ATL_7925; ATL_7953; ATL_7919); SEQ ID NO: 100 (ATL_7952; ATL_7917; ATL_7920; ATL_7921); SEQ ID NO: 101 (ATL_7955); SEQ ID NO: 114 (ATL_7933; ATL_7956; ATL_7926; ATL_7928; ATL_7929); SEQ ID NO: 158 (ATL_7824); SEQ ID NO: 159 (ATL_7825; ATL_7918; ATL_7923; ATL_7924); SEQ ID NO: 160 (ATL_7826); SEQ ID NO: 161 (ATL_7827); SEQ ID NO: 194 (ATL_7931);

SEQ ID NO: 195 (ATL_7932); SEQ ID NO: 196 (ATL_7467, ATL_7468; ATL_7470; ATL_7471); SEQ ID NO: 197 (ATL_7473); SEQ ID NO: 198 (ATL_7927); or SEQ ID NO: 199 (ATL_7930); and HFWR4 of SEQ ID NO: 44 (ATL_6026); SEQ ID NO: 52 (ATL_6027); SEQ ID NO: 60 (ATL_6058; ATL_7933; ATL_7469; ATL_7927); SEQ ID NO: 68 (ATL_6064); SEQ ID NO: 76 (ATL_6075); SEQ ID NO: 103 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); or SEQ ID NO: 115 (ATL_7956; ATL_7467; ATL_7468; ATL_7470; ATL_7471; ATL_7472; ATL_7473; ATL_7926; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932)

or framework sequences with one to five mutations (e.g. one, two, or three mutations), compared with the framework sequences above. The mutations may be substitutions compared with the framework sequences above. The mutations may be at position 78, for example M78I or M78A; and/or at position 81; for example D81E; and/or at position 97, for example D97E; and/or at position 98, for example D98E; and/or at position 98, for example D98E; and/or at position 99, for example T99A. Compared with the framework sequences for ATL_6026, the mutations may be at position 78, for example M78I or M78A; and/or at position 81; for example D81E; and/or at position 97, for example D97E; and/or at position 98, for example D98E; and/or at position 98, for example D98E; and/or at position 99, for example T99A. Compared with the framework sequences for ATL_6058, the mutations may be at position 78, for example M78I; and/or at position 81; for example D81E.

The antibody may have a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence identity with the with the amino acid sequence selected from the group consisting of:

SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID NO: 5; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 109; SEQ ID NO: 110; SEQ ID NO: 118; SEQ ID NO: 119; SEQ ID NO: 120; SEQ ID NO: 121; SEQ ID NO: 122; SEQ ID NO: 123; SEQ ID NO: 124; SEQ ID NO: 125; SEQ ID NO: 126; SEQ ID NO: 127; SEQ ID NO: 128; SEQ ID NO: 129; SEQ ID NO: 130; SEQ ID NO: 131; SEQ ID NO: 132; SEQ ID NO: 133; SEQ ID NO: 134; SEQ ID NO: 178; SEQ ID NO: 179; SEQ ID NO: 180; SEQ ID NO: 181; SEQ ID NO: 182; SEQ ID NO: 183; SEQ ID NO: 184; SEQ ID NO: 185; SEQ ID NO: 186; SEQ ID NO: 187; and SEQ ID NO: 188. For example the antibody may have a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence identity with the with the amino acid sequence selected from the group consisting of: SEQ ID NO: 1; SEQ ID NO: 3; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 109; SEQ ID NO: 110. For example the antibody may have a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence identity with the with the amino acid sequence selected from the group consisting of: SEQ ID NO: 93 and SEQ ID NO: 109.

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The antibody may have a heavy chain variable domain (VH) comprising CDRH1, CDRH2, and CDRH3 within a human framework, and/or within a germline framework.

The antibody may comprise a light chain variable domain (VL), with the following CDRs:

- CDRL1 comprising an amino acid sequence of SEQ ID NO: 26 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 27 (ATL_6027); SEQ ID NO: 28 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 29 (ATL_6074), or SEQ ID NO: 30 (ATL_6075).
- CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955; ATL_7925; ATL_7952; ATL_7953; ATL_7900; ATL_7919; ATL_7923); SEQ ID NO: 31 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7901; ATL_7902; ATL_7920); SEQ ID NO: 32 (ATL_6027); SEQ ID NO: 33 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 34 (ATL_6074); SEQ ID NO: 35 (ATL_6075); SEQ ID NO: 166 (ATL_7917; ATL_7918); or SEQ ID NO: 167 (ATL_7899; ATL_7921; ATL_7922; ATL_7924); and
- CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955; ATL_7925; ATL_7952; ATL_7953; ATL_7902; ATL_7917; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 36 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7918); SEQ ID NO: 37 (ATL_6027); SEQ ID NO: 38 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 39 (ATL_6074); SEQ ID NO: 40 (ATL_6075); SEQ ID NO: 168 (ATL_7901; ATL_7919; ATL_7921); or SEQ ID NO: 169 (ATL_7920); or a set of CDRs containing one to four (e.g. one, two, three or four) amino acid mutations, such as substitutions, compared with the above set of CDRs. The mutation may be at position 57, for example N57A or N57Q; and/or at position 65, for example S65N or S65A; and/or at position 109, for example N109A or N109Q; and/or at position 113, for example S113N or S113A.

The antibody may comprise a light chain variable domain (VL) with the following CDRs: CDRL1

- comprising an amino acid sequence of SEQ ID NO: 26 (ATL_7955); CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955); and CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955). The light chain variable domain (VL) may comprise the following framework sequences: LFWR1 of SEQ ID NO: 104 (ATL_7955); LFWR2 of SEQ ID NO: 46 (ATL_7955); LFWR3 of SEQ ID NO: 106 (ATL_7955); and LFWR4 of SEQ ID NO: 108 (ATL_7955).

- The antibody may comprise a light chain variable domain (VL) with the following CDRs: CDRL1 comprising an amino acid sequence of SEQ ID NO: 28 (ATL_6058; ATL_7933; ATL_7956); CDRL2 comprising an amino acid sequence of SEQ ID NO: 33 (ATL_6058; ATL_7933; ATL_7956); and CDRL3

comprising an amino acid sequence of SEQ ID NO: 38 (ATL_6058; ATL_7933; ATL_7956); or a set of CDRs containing one, two, or three amino acid mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs. The light chain variable domain (VL) may comprise the following framework sequences: LFWR1 of SEQ ID NO: 61 (ATL_6058; ATL_7933; ATL_7956);

5 LFWR2 of SEQ ID NO: 62 (ATL_6058) or SEQ ID NO: 116 (ATL_7933; ATL_7956); LFWR3 of SEQ ID NO: 63 (ATL_6058) or SEQ ID NO: 117 (ATL_7933; ATL_7956); and LFWR4 of SEQ ID NO: 64 (ATL_6058; ATL_7933; ATL_7956), or framework sequences with one to four mutations compared with the framework sequences above. The mutations may be substitutions, optionally wherein the substitution is at position 49, optionally wherein the substitution is P49A; and/or at position 52, optionally wherein the substitution is R52L; and/or at position 74, optionally wherein the substitution is G74D; and/or at position

10 90, optionally wherein the substitution is S90T.

The antibody may comprise a light chain variable domain (VL) with the following CDRs: CDRL1 comprising an amino acid sequence of SEQ ID NO: 28 (ATL_7933); CDRL2 comprising an amino acid

15 sequence of SEQ ID NO: 33 (ATL_7933); and CDRL3 comprising an amino acid sequence of SEQ ID NO: 38 (ATL_7933); and wherein the light chain variable domain (VL) comprises the following framework sequences: LFWR1 of SEQ ID NO: 61 (ATL_7933); LFWR2 of SEQ ID NO: 116 (ATL_7933); LFWR3 of SEQ ID NO: 117 (ATL_7933); and LFWR4 of SEQ ID NO: 64 (ATL_7933).

20 The antibody may comprise a light chain variable domain (VL) with the following framework sequences: LFWR1 of SEQ ID NO: 45 (ATL_6026; ATL_0007450; ATL_0007819; ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824; ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007892; ATL_0007893; ATL_0007899; ATL_0007900; ATL_0007901; ATL_0007902; ATL_0007917); SEQ ID NO: 53 (ATL_6027); SEQ ID NO: 61 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 69 (ATL_6074); SEQ ID NO: 77 (ATL_6075); SEQ ID NO: 104 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_0007896; ATL_0007920; ATL_0007921; ATL_0007922); SEQ ID NO: 163 (ATL_0007889; ATL_0007895; ATL_0007919; ATL_0007924); or SEQ ID NO: 164 (ATL_0007890; ATL_0007918; ATL_0007923);

25 30 LFWR2 of SEQ ID NO: 46 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_0007450; ATL_0007819; ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824; ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007889; ATL_0007890; ATL_0007892; ATL_0007893; ATL_0007896; ATL_0007899; ATL_0007900; ATL_0007901; ATL_0007902; ATL_0007920); SEQ ID NO: 54 (ATL_6027); SEQ ID NO: 62 (ATL_6058; ATL_7468);

35 40 SEQ ID NO: 70 (ATL_6074); SEQ ID NO: 78 (ATL_6075); SEQ ID NO: 116 (ATL_7933; ATL_7956; ATL_7467; ATL_7469; ATL_7470; ATL_7471; ATL_7472; ATL_7473; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932); SEQ ID NO: 165 (ATL_0007895; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007921; ATL_0007922; ATL_0007923; ATL_0007924); SEQ ID NO: 200 (ATL_7927); or SEQ ID NO: 201 (ATL_7926);

LFWR3 of SEQ ID NO: 47 (ATL_6026; ATL_0007450; ATL_0007819; ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824; ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007889; ATL_0007890; ATL_0007893; ATL_0007899; ATL_0007900;

ATL_0007901; ATL_0007902; ATL_0007921); SEQ ID NO: 55 (ATL_6027); SEQ ID NO: 63 (ATL_6058; ATL_7468); SEQ ID NO: 71 (ATL_6074); SEQ ID NO: 79 (ATL_6075); SEQ ID NO: 106 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_0007892; ATL_0007895; ATL_0007896; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007920; ATL_0007922; ATL_0007923; ATL_0007924); or SEQ ID NO: 117 (ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7469; ATL_7472; ATL_7473); and LFWR4 of SEQ ID NO: 48 (ATL_6026; ATL_0007450; ATL_0007819; ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824; ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007889; ATL_0007890; ATL_0007892; ATL_0007899; ATL_0007900; ATL_0007901; ATL_0007902; ATL_0007922); SEQ ID NO: 56 (ATL_6027); SEQ ID NO: 64 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 72 (ATL_6074; ATL_0007893; ATL_0007895; ATL_0007896; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007920; ATL_0007921; ATL_0007923; ATL_0007924); SEQ ID NO: 80 (ATL_6075); or SEQ ID NO: 108 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); or framework sequences with one, two, or three mutations, such as substitutions, compared with the framework sequences above.

The antibody may comprise a light chain variable domain (VL) with the following framework sequences: LFWR1 of SEQ ID NO: 45 (ATL_6026) or SEQ ID NO: 104 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); LFWR2 of SEQ ID NO: 46 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955); LFWR3 of SEQ ID NO: 47 (ATL_6026) or SEQ ID NO: 106 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); and LFWR4 of SEQ ID NO: 48 (ATL_6026) or SEQ ID NO: 108 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); or framework sequences with one to five mutations (e.g. one, two, three, four, or five mutations), compared with the framework sequences above. The mutations may be substitutions compared with the framework sequences above. The mutation may be at position 2, for example A2S; and/or at position 8, for example S8P; and/or at position 52, for example P52L; and/or at position 90, for example V90A; and/or at position 124, for example V124L. Alternatively, the mutation may be at a position other than position 52, that is, P52 may be maintained. The antibody may have a light chain variable domain (VL) with the following CDRs: CDRL1 comprising an amino acid sequence of SEQ ID NO: 26 (ATL_7955); CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955); and CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955). The antibody may have a light chain variable domain (VL) comprising the following framework sequences: LFWR1 of SEQ ID NO: 104 (ATL_7955); LFWR2 of SEQ ID NO: 46 (ATL_7955); LFWR3 of SEQ ID NO: 106 (ATL_7955); and LFWR4 of SEQ ID NO: 108 (ATL_7955).

The antibody may comprise a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence identity with the amino acid sequence selected from the group consisting of: SEQ ID NO: 6; SEQ ID NO: 7; SEQ ID NO: 8; SEQ ID NO: 9; SEQ ID NO: 10; SEQ ID NO: 94; SEQ ID NO: 111; SEQ ID NO: 135; SEQ ID NO: 136; SEQ ID NO: 137; SEQ ID NO: 138; SEQ ID NO: 139; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 143; SEQ ID NO: 144; SEQ ID NO: 145; SEQ ID NO:

146, SEQ ID NO: 147; SEQ ID NO: 148; SEQ ID NO: 149; SEQ ID NO: 150; SEQ ID NO: 151; SEQ ID NO: 152; SEQ ID NO: 189; and SEQ ID NO: 190; optionally the group consisting of: SEQ ID NO: 6; SEQ ID NO: 8; SEQ ID NO: 94; and SEQ ID NO: 111; optionally the group consisting of: SEQ ID NO: 94 and SEQ ID NO: 111.

5

The antibody may comprise:

- (a) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 1 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 6; or
- (b) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 2 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 7; or
- (c) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 3 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 8; or
- (d) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 4 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 9; or
- (e) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 5 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 10 or
- (f) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 90 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (g) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 91 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or

- (h) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 92 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (i) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 93 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (j) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 109 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 111; or
- (k) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 110 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 111.

The antibody may comprise a light chain variable domain (VL) comprising CDRL1, CDRL2, and CDRL3 within a human framework, and/or within a germline framework. The antibody may bind 15-PGDH in the active site. The antibody may bind 15-PGDH at an allosteric site. The antibody may be a monoclonal antibody. The antibody may be an IgG1, or a modified version thereof, such as a LALA IgG1, for example a LALA IgG1 variant according to SEQ ID NO: 87.

The antibody may bind human PGDH, wherein the antibody binds human PGDH with a K_d of at most 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, preferably at most 10^{-9} M, as measured by ELISA, and/or wherein the antibody binds human PGDH with an EC_{50} below 100 nM, below 50 nM, or below 10 nM as measured by titration ELISA. The antibody may inhibit PGDH as determined using a 15-PGDH enzyme activity assay. In embodiments, the antibody inhibits human PGDH with an IC_{50} below 200 nM or below 150 nM.

The antibody may alter PGE2 levels in an *in vitro* cell culture. The antibody may alter one or more of autophagy, neuronal activity, oxidative stress, and apoptosis of dopaminergic neurons *in vitro*. The antibody may alter microglia inflammatory state *in vitro*. The antibody may reduce inflammation, optionally neuroinflammation, in an *in vitro* cell culture, optionally wherein a reduction in inflammation is determined by measuring the levels of one or more pro-inflammatory cytokines. The pro-inflammatory cytokines may include IL-6, IL-1 β , and/or TNF α . An *in vitro* cell culture may comprise cells exposed to a proinflammatory condition, optionally comprising exposure to α Syn fibrils. The antibody may alter the levels of circulating PGE2 *in vivo*. The antibody may alter 15-PGDH levels in an *in vitro* cell culture. The antibody may alter phospho- α Syn129 levels in an *in vitro* cell culture comprising cells exposed to α Syn fibrils. The antibody

may alter mitochondrial function in an *in vitro* cell culture, optionally wherein an alteration in mitochondrial function is determined by measuring the mitochondrial membrane potential (MMP) comprising cells exposed to α Syn fibrils. The antibody may decrease the levels of one or more pro-inflammatory cytokines *in vivo*. The pro-inflammatory cytokines may include IL-6, IL-1 β , and/or TNF α . The antibody may
5 decrease the levels of one or more pro-inflammatory cytokines in an animal model and/or in a subject exposed to pro-inflammatory conditions, optionally comprising exposure to LPS

The antibody may be an isolated VH domain according to any embodiment of any preceding embodiment or any embodiment described herein.

10

In a fourth aspect, the disclosure provides an isolated nucleic acid comprising a nucleotide sequence encoding an antibody according to the first, second, or third aspect.

In a fifth aspect, the disclosure provides a vector or set of vectors comprising the nucleic acid according
15 to the fourth aspect.

In a sixth aspect, the disclosure provides a host cell comprising the vector or set of vectors according to the fifth aspect, or a host cell *in vitro* transformed with a nucleic acid according to the fourth aspect.

20 In a seventh aspect, the disclosure provides a composition comprising the antibody or fragment thereof according to the first, second, or third aspect, and at least one additional component, optionally comprising a pharmaceutically acceptable excipient, vehicle or carrier.

In an eighth aspect, the disclosure provides antibody according to the first, second, or third aspect, or a
25 composition according to the seventh aspect, for use as a therapeutic.

In a ninth aspect, the disclosure provides antibody according to the first, second, or third aspect, or a composition according to the seventh aspect, for use in the treatment of a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a
30 synuclein-mediated neurodegenerative disease. The disease may be selected from Parkinson's Disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Alzheimer's Disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS). The disease may be Parkinson's Disease.

35 In a tenth aspect, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition according to the seventh aspect, or an antibody according to the first, second, or third aspect. The subject may have or may be at risk of developing a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a synuclein-mediated neurodegenerative disease. The
40 disease may be selected from Parkinson's Disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Alzheimer's Disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS). The disease may be Parkinson's Disease.

In an eleventh aspect, the disclosure provides the use of an antibody according to the first, second, or third aspect in the manufacture of a medicament. The medicament may be for the treatment of a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a synuclein-mediated neurodegenerative disease. The disease may be selected from Parkinson's Disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Alzheimer's Disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS). The disease may be Parkinson's Disease.

The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

Summary of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures in which:

Figure 1 shows the results of high-throughput proteome screening for autoreactivity in PD subject. The figure shows the hit fold change for autoreactive proteins to each subject sample. Points highlighted in green represent autoreactivity to 15-PGDH within subject SU_478 sample. All other data points in black and across all patient samples represent autoreactivity to a diverse range of human proteins.

Figure 2 shows 15-PGDH activity measured in the presence of 15-PGDH reactive and non-reactive serum. Plot shows fluorescence signal over time, where the fluorescence signal is generated by reduction of a fluorescent probe upon oxidation of NADH generated by 15-PGDH mediated substrate oxidation. The activity of 15-PGDH is proportional to the fluorescent signal (fluorescence signal proportional to NADH concentration).

Figure 3 shows the results of serum and plasma screening by ELISA across a panel of Parkinson's Disease and healthy control patients (subjects). **Fig. 3A** shows raw absorbances demonstrating the level of binding to 15-PGDH across these patient samples. **Fig. 3B** shows z-scores demonstrating the level of autoreactivity to 15-PGDH across these patient samples. Z-score is calculated as $[\text{raw signal} - \text{mean signal}] / \text{Standard deviation (SD)}$. Dotted line at $y=1.5$. Lysozyme was included as negative control. 15-PGDH antigen was an in-house recombinant human 15-PGDH with additional C-terminal Avi and hexahistidine tag (rhPGDH-Avi-His). 84 serum or plasma samples were screened for binding to 15-PGDH. Subjects SU1271 (healthy, no prodromal PD), SU478 (late onset at 90 years old with severe motor progression but no cognitive impairment), SU1238 (resilient, RBD 7 years no progression to PD), SU1242 (resilient, RBD 12 years, no progression to PD), and SU1264 (healthy, no prodromal PD) are the top 5 subjects and with clear higher z-scores, showing serum/plasma reactivity against at least one form of 15-PGDH. SU1286 (PD 6.8 years + RBD, no cognitive impairment) was also selected for further characterisation as it was just outside the threshold for determining reactivity, but found not to inhibit 15-PGDH during serum inhibition tests (**Fig. 2**).

Figure 4 shows the principles and results of a PGDH inhibition assay. **Fig. 4A** shows a schematic of a 15-PGDH inhibition assay. 15-PGDH inactivation of PGE2 modulates inflammatory signalling. A biochemical assay was adapted to measure 15-PGDH inhibition following incubation with 15-PGDH reactive serum or 15-PGDH binding monoclonal antibodies. **Fig. 4B** shows results of experiments where diluted patient serum from PGDH-reactive subjects SU1238, SU1242, SU1264, SU478, and SU1286 and an age-matched control (SU477) was incubated with active recombinant 15-PGDH and then added to the reaction mix from a commercial fluorometric PGDH activity assay (ab273327). Mean increase in fluorescence at 587 nm across three replicate samples for each subject was measured at the endpoint of the assay. PGDH-reactive subject means were compared to the SU477 mean by ordinary one-way ANOVA. SU1286 sample did not show significant enzyme inhibition in this format, validating the z-score cutoff used to select serum for screening.

Figure 5 shows the results of a PGDH inhibition assay in the presence of the antibody ATL6058. Activity is reported as a percentage of activity in the presence of an equal concentration of isotype control antibody. Error bars show Standard Error of the Mean (SEM) for three technical replicates in one assay run. Data were fit using non-linear regression [inhibitor] vs response function in Graphpad Prism. ATL6058 was identified from PD patient SU478 via serum proteomics.

Figure 6 shows the results of a single point ELISA for antibodies identified from PD patients SU1242 and SU1271. **Fig. 6A** shows the raw absorbance data of antibodies ATL_0006026 and ATL_0006027 binding to 15-PGDH (rhPGDH-Avi-His). **Fig. 6B** shows binding of antibodies ATL_0006026 and ATL_0006027 as fold change over lysozyme control. Both include anti-His antibody to confirm antigen coating and anti-human-15-PGDH (Goat IgG) as a positive control.

Figure 7 shows the results of a single point ELISA for antibodies identified from PD patients SU1238 and SU1286. **Fig. 7A** shows the raw absorbance of antibodies ATL_0006074, and ATL_0006075 binding to Neutravidin captured NLB-rhPGDH-Avi-His or plated PGDH (both full length). **Fig. 7B** shows the raw absorbance of ATL_0006058 binding to Neutravidin captured NLB-rhPGDH-Avi-His or plated PGDH (both full length). **Fig. 7C** shows binding of antibodies ATL_0006058 to Neutravidin-captured biotinylated PGDH or plated PGDH as fold change over background lysozyme binding. **Fig. 7D** shows binding of antibodies ATL_0006074, and ATL_0006075 to Neutravidin-captured biotinylated PGDH or plated PGDH as fold change over background lysozyme binding.

Figure 8 shows the results of a multipoint ELISA binding of IgG to 15-PGDH, either plated (ATL_0006026, ATL_0006027, ATL_0005338 (isotype control) or Neutravidin captured 15-PGDH (ATL_0006058, ATL_0006074, ATL_0006075). EC50s shown calculated using non-linear regression (curve fit) function on GraphPad Prism.

Figure 9 shows the results of a PGDH inhibition assays in the presence of anti-PGDH antibodies identified using phage display. **Fig. 9A** shows the percentage of activity for ATL6026. **Fig. 9B** shows the percentage of activity for ATL6027. **Fig. 9C** shows the percentage of activity for ATL6074. **Fig. 9D** shows the percentage of activity for ATL6075. Activity is reported as a percentage of activity in the presence of an

equal concentration of isotype control antibody. Error bars show SEM for three technical replicates in one assay run. Data were fit using non-linear regression [inhibitor] vs response function in Graphpad Prism.

Figure 10 shows the results of a kinetics analysis of 15-PGDH binding antibodies using biolayer interferometry (BLI). Figs. 10A-E show binding to human 15-PGDH; and Fig. F-J show binding to mouse 15-PGDH. Each plot shows BLI raw data collected for each antibody concentration (represented by different colours) and 1:1 binding fit shown in red. **Figs. 10A and F** show results for ATL_6026. **Figs. 10B and G** show results for ATL_6027. **Figs. 10C and H** show results for ATL_6058. **Figs. 10D and I** show results for ATL_6074. **Figs. 10E and J** show results for ATL_6075.

Figure 11 shows the results of kinetic analysis of 15-PGDH binding antibodies using surface plasmon response (SPR). **Fig. 11A** shows binding of ATL6026 to human 15-PGDH. **Fig. 11B** shows binding of ATL6027 (**B**) to human 15-PGDH. **Fig. 11C** shows binding of ATL6058 to human 15-PGDH. **Fig. 11D** shows binding of ATL6074 to human 15-PGDH. **Fig. 11E** shows binding of ATL6075 to human 15-PGDH. Each plot shows SPR raw data collected for each antigen concentration (represented by different colours) and 1:1 binding fit shown in red. For antibodies other than ATL6027 (shown in **B**) data shown were collected at two sensor locations at four capture densities. For ATL6027 data shown were collected at two sensor locations at the highest capture density only.

Figure 12 shows the results of a thermal stability assay for the indicated antibodies tested on freshly thawed material over a temperature gradient. FF= Full spectrum fluorescence; SLS= Static light scattering; Tm1 = Unfolding at 50%; Tonset = unfolding at 10%.

Figure 13 shows sequence alignments showing antibodies of the disclosure aligned using the IMGT sequence numbering. **Fig. 13A** shows VH sequences. **Fig. 13B** shows VL sequences

Figure 14 shows *in silico* predicted protein structure of (**A**) ATL6026 and (**B**) ATL6058 and their binding to a PGDH dimer. **Fig. 14A** shows predicted binding of ATL6026 to the active site via its CDR3 loop. **Fig. 14B** shows predicted binding of ATL6058 to a different epitope, suggesting allosteric inhibition.

Figure 15 shows the experimental design of an α Synuclein fibrils-induced model. This is used to determine the effects of antibodies of the disclosure on IL6 production and PGDH activity upon exposure of dopaminergic neurons, astrocytes and microglia to α Synuclein fibrils. IL-6 in the CNS is secreted by astrocytes, microglia, oligodendrocytes, neurons, and endothelial cells. Each of these cell types can contribute to the overall IL-6 levels in response to various stimuli, playing roles in both normal physiology and in pathological conditions.

Figure 16 shows results demonstrating effective target engagement, with ATL-6026 specifically inhibiting 15-PGDH and subsequently eliciting significant anti-inflammatory effects in an alpha-synuclein-induced model. The figure shows the results of an ELISA for 15-PGDH and IL-6 at day 11 of the α Synuclein fibrils-induced PD-model. **Fig. 16A** shows the concentration of 15-PGDH in cell lysates obtained from the triculture. Bars show mean $\pm$ standard error of the mean. 3 wells per condition. Fisher's LSD pairwise comparisons versus isotype (ATL5338) control with α Synuclein preformed fibrils (α Syn PFFs). * $p < 0.05$. **Fig. 16B** shows the concentration of 15-PGDH in cell culture supernatants obtained from the triculture. Bars show mean $\pm$ standard error of the mean. 3 wells per condition. **Fig. 16C** shows the concentration

of IL-6 in the cell culture supernatants obtained from the triculture. Bars show mean $\pm$ standard error of the mean for two experiments. Each data point represents mean of 3-4 wells from each experiment. Two way ANOVA with Tukey's multiple comparisons comparing all means with each other, * $p < 0.05$, ** $p < 0.01$.

Figure 17 shows results demonstrating the restoration of mitochondrial function by ATL-6026 and ATL-605. The figure shows the results of an experiment measuring the red/green fluorescence intensity ratio using JC-1 dye to indicate mitochondrial membrane potential (MMP) of the α Synuclein fibrils-induced PD-model. Bars show mean $\pm$ standard error of the mean for each well. 4 wells per condition each with 3-4 fields of view. Two way ANOVA with Tukey's multiple comparisons versus Isotype control (ATL5338) with α Synuclein preformed fibrils (α Syn PFFs), ** $p < 0.01$, **** $p < 0.0001$.

Figure 18 shows data demonstrating effective reduction of α Syn seeding by ATL-6026. The figure shows the results of immunostaining the α Synuclein fibrils-induced PD-model. **Fig. 18A** shows images obtained using DAPI nuclear stain, immunostaining with MAP2 antibody, and immunostaining with Phospho- α Syn129 antibody. **Fig. 18B** shows the quantification of the images in Fig. 18A. Bars show mean $\pm$ standard error of the mean for each well. 3 wells per condition each with 3-4 fields of view. Two way ANOVA with Tukey's multiple comparisons versus Isotype control (ATL5338) with α Synuclein preformed fibrils (α Syn PFFs), * $p < 0.05$, **** $p < 0.0001$.

Figure 19 shows the results of an experiment measuring the cytokine levels in plasma and brain samples obtained from a LPS-induced mouse model of inflammation treated with isotype control (ATL5338; white), ATL6026 (dark grey) or positive control SW033291 small molecule inhibitor of 15-PGDH (SW; light grey). Results are shown as bar graphs of indicated cytokine concentrations showing mean $\pm$ standard error of the mean (SEM) for 5-8 mice per group. **Fig. 19A** shows data for IL-6. **Fig. 19B** shows data for IL-1 β . **Fig. 19C** shows data for TNF- α .

Figure 20 shows the results of an experiment measuring the gait and postural stability of aged mice treated with isotype control (ATL5338), ATL6026, positive control SW033291, or vehicle control. Kinematic parameters measured were: (A) speed, (B) hind stance time, (C) diagonal interlimb coordination, (D) double support, (E) maximum knee angle, and (F) peak hind leg swing speed. Mean $\pm$ SEM for $n=12-13$ mice per group. * p -value=0.0262 ATL5338 vs ATL6026 using an unpaired t test. **Fig. 20A** shows the results for speed measurements. **Fig. 20B** shows the results for hind stance time measurements. **Fig. 20C** shows the results for diagonal interlimb coordination measurements. **Fig. 20D** shows the results for double support measurements. **Fig. 20E** shows the results for maximum knee angle measurements. **Fig. 20F** shows the results for peak hind leg swing speed measurements.

Figure 21 shows overall gait score obtained by combining the above kinematic parameters of Figure 20A-F. **Fig. 21A** shows gait score results for mice treated with ATL6026 vs vehicle. **Fig. 21B** shows gait score results for mice treated with a small molecule inhibitor of 15-PGDH (SW033291) vs vehicle. The results show mice treated with (A) ATL6026 have a more profound effect in gait and stability vs isotype control than (B) the small molecule inhibition of 15-PGDH vs vehicle. Pairwise comparison using Unpaired t test with Welch's correction, * $p < 0.05$, ** $p < 0.01$.

Figure 22 shows sequence alignments showing antibodies of the disclosure aligned using the IMGT sequence numbering. Fig.22A. VH sequences. Fig.22B. VL sequences.

Figure 23 shows the results of a kinetics analysis of 15-PGDH binding antibodies using biolayer interferometry (BLI). (A-H) binding to human 15-PGDH. Each plot shows BLI raw data collected for each antibody concentration (each line representing a different concentration as indicated below the graph). Fig. 23A shows results for ATL_6058. Fig. 23B shows results for ATL_7956. Fig. 23C shows results for ATL_7933. Fig. 23D shows results for ATL_6026. Fig. 23E shows results for ATL_7953. Fig. 23F shows results for ATL_7952. Fig. 23G shows results for ATL_7955. Fig. 23H shows results for ATL_7925.

Figure 24 shows the results of a fluorescence-based enzyme inhibition assay testing the inhibition of 15-PGDH binding antibodies as measured by the reduction in fluorescence intensity (RFU). Fig. 24A shows results of a four-point 10-fold dilution series of antibodies ATL_6026, ATL_7925, ATL_7952, ATL_7953, and ATL_7955 compared to isotype control (ATL_5338) (one point per antibody, one set of points on the x-axis for each dilution series). Fig. 24B-F show fluorescence intensity data across time shown for dilution series of 15-PGDH binding antibodies (each data series corresponding to a different dilution of the antibody on the specific plot). Fig. 24B shows results for ATL_5338. Fig. 24C: shows results for ATL_6026. Fig. 24D shows results for ATL_7925. Fig. 24E shows results for ATL_7952. Fig. 24F shows results for ATL_7953. Fig. 24G shows results for ATL_7955.

Figure 25 shows the results of a fluorescence-based enzyme inhibition assay testing the inhibition of 15-PGDH binding antibodies as measured by the reduction in fluorescence intensity (RFU). A-C: fluorescence intensity data across time shown for a dilution series of 15-PGDH binding antibodies (each data series corresponding to a different dilution of the antibody on the specific plot). Fig. 25A shows results for ATL_6058. Fig. 25B shows results for ATL_7933. Fig. 25C shows results for ATL_7956.

Figure 26 shows sequence alignments showing antibodies of the disclosure aligned using the IMGT sequence numbering. Fig.26A: HFWR1 and HCDR1 sequences. Fig.26B: HFWR2 and HCDR2 sequences. Fig.26C: HFWR3 sequences Fig.26D: HCDR3 and HFWR4 sequences. Fig.26E: LFWR1 and LCDR1 sequences. Fig.26F: LFWR2 and LCDR2 sequences. Fig.26G: LFWR3 sequences Fig.26H: LCDR3 and LFWR4 sequences.

Detailed Description of the Disclosure

Aspects and embodiments of the present invention will now be discussed with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

The present disclosure refers to antibodies described herein using references specified as "ATL_000xxxx", "ATL_xxxx", "ATLxxxx" or "xxxx", where "xxxx" is a four digits reference number specific to an antibody described herein. All of the above notations are used interchangeably to refer to the same antibody or a portion thereof (e.g. a VH, VL or part thereof, of the antibody). For example, antibody ATL_0006026 is

interchangeably referred to herein as ATL_6026, ATL6026 and 6026. Unless otherwise specified, reference to a position within an antibody domain refers to the position according to IMGT numbering.

Disclosed herein are antibodies and fragments thereof that are capable of specifically binding to 15-hydroxyprostaglandin dehydrogenase (15-PGDH) or a fragment thereof. As used herein, an antibody capable of specifically binding or specifically binding a target is one able to bind through the association of the epitope recognition site with an epitope within the target. It is distinct from non-specific binding, for example Fc mediated binding, ionic and/or hydrophobic interactions. In other words, an antibody which specifically binds a target recognised and binds to a specific protein structure within it rather than to proteins generally.

10 Binding to PGDH

The notations "15-PGDH" and "PGDH" are used interchangeably herein to refer to 15-hydroxyprostaglandin dehydrogenase or a fragment thereof. The fragment may include amino acids 3-266 of the human sequence of 15-hydroxyprostaglandin dehydrogenase, or equivalents in a homologous sequence such as the mouse 15-hydroxyprostaglandin dehydrogenase sequence or the cynomolgus monkey 15-hydroxyprostaglandin dehydrogenase sequence.

An antibody according to the present disclosure may bind human 15-PGDH. An antibody according to the present disclosure may bind human 15-PGDH as set out in SEQ ID NO: 82 (Uniprot ID P15428) or an antigen derived therefrom, such as e.g. as set out in SEQ ID NOs: 173, 83, and 81. An antibody according to the present disclosure may bind orthologs of human 15-PGDH found in a non-human primate (e.g. *Macaca fascicularis*) and/or a rodent (e.g. mouse - *Mus musculus* and/or rat - *Rattus norvegicus*) species. For example, an antibody or fragment thereof may bind to one or more of: *Macaca fascicularis* 15-PGDH as set out in SEQ ID NO: 84 (Uniprot ID: Q8MJY8), or an antigen derived therefrom with the amino acid sequence set forth in SEQ ID NO: 170, *Mus musculus* 15-PGDH as set out in SEQ ID NO: 86 (Uniprot ID: Q8VCC1) or an antigen derived therefrom with the amino acid sequence set forth in SEQ ID NO: 85, and/or *Rattus norvegicus* 15-PGDH as set out in SEQ ID NO: 171 (Uniprot ID: O08699) or an antigen derived therefrom with the amino acid sequence set forth in SEQ ID NO: 172. Binding of an antibody of the disclosure to one or more of the above antigens may be determined by biolayer interferometry (BLI), such as e.g. as described in examples of the present disclosure. For example, cross-reactivity of an antibody as described herein binding human 15-PGDH with mouse 15-PGDH antigen may be determined by BLI, for example BLI performed as described herein (Materials and Methods).

Human 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is encoded by *HPCD* (NCBI gene ID: 3248). 15-PGDH is located on chromosome 4 (4q34.1) and comprises 10 exons. Multiple transcript variants encoding different isoforms have been found for this gene. The PGDH protein is 266 amino acids in length, available under the Uniprot identifier P15428 and Ensembl ID ENSG00000164120. 15-PGDH is a member of the short-chain non-metaloenzyme alcohol dehydrogenase protein family and catalyses the NAD-dependent dehydrogenation (oxidation) of hydroxylated polyunsaturated fatty acids. These include prostaglandins (PGs; mainly PGE2, PGD2, and PGF2α), which function in a variety of physiologic and cellular processes such as inflammation (Sun et al., 2021).

- The antibodies described herein inhibit 15-PGDH. As used herein, inhibition of 15-PGDH refers to the blocking, suppression or reduction of its enzymatic activity. In other words, the antibody according to the present disclosure may prevent or decrease the enzymatic activity of 15-PGDH, that is its NAD-dependent oxidation function may be reduced or abolished by binding to a binding site on 15-PGDH, compared with unbound 15-PGDH. The skilled person will be familiar with assays for measuring 15-PGDH activity, such as assays measuring the oxidation of a substrate as described in Tai, 1976. Inhibition of 15-PGDH may be determined using any assay known in the art, such as e.g. assays used in examples of the present disclosure. For example, inhibition of 15-PGDH may be determined using an assay based on the conversion of non-fluorescent NAD⁺ to fluorescent NADH catalyzed by 15-PGDH in the presence of substrate PGE₂.
- 5 Inhibition of 15-PGDH (e.g. mouse and/or human PGDH) may be assessed by measuring the half-maximal inhibitory concentration (IC₅₀). Antibodies described herein may inhibit 15-PGDH with an IC₅₀ below 1.5E-07 M, below 2.5E-07 M, below 5 E-07 M, or below 1E-08 M. In some embodiments, the IC₅₀ is about 1 E-08 M, about 1 E-09 M, about 3 E-09 M about 4 E-09 M. In some embodiments, the IC₅₀ below 1 E-09 M.
- 10 Antibodies described herein may bind 15-PGDH (e.g. mouse and/or human) with high affinity. High affinity binding may be assessed by measuring the EC₅₀ value, the concentration at which the antibody produces a half-maximal binding, for example via titration ELISA, as described herein. For example, affinity of the antibody may be assessed by binding to plate-bound recombinant human 15-PGDH as described herein.
- 15 High affinity as referred to herein means an EC₅₀ value of at most 1E-06 M, at most 2E-06 M, at most 3E-06M, at most 4E-06, at most 5E-06 M, at most 6E-06 M, at most 7E-06, at most 8E-06 M, at most 9E-06 M, at most 1E-07 M, at most 5E-07 M, at most 1 E-08 M, at most 2 E-08 M, at most 3 E-08 M, at most 4 E-08 M, at most 5 E-08 M, at most 6 E-08 M, at most 7 E-08 M, at most 8 E-08 M, at most 9 E-08 M, at most 1 E-09 M, at most 2 E-09 M, at most 3 E-09 M, at most 4 E-09 M, at most 5E-09 M, at most 6 E-09 M, at most 7 E-09 M, at most 8 E-09 M, at most 9 E-09 M, at most 1E-10 M, at most 2 E-10 M, at most 3 E-10 M, at most 4 E-10 M, at most 5E-10 M, at most 6 E-10 M, at most 7 E-10 M. at most 8 E-10 M, at most 9 E-10 M, at most 1E-11M, at most 2 E-11M, at most 3 E-11M, at most 4E-11M, at most 5 E-11M, at most 6E-11M, at most 7 E-11M, at most 8 E-11M, at most 9 E-11M, at most 1E-12M, at most 2 E-12M, at most 3 E-12M, at most 4 E-12M, 5E-12M, at most 6 E-12M, at most 7 E-12M, at most 8 E-12M, at most 9 E-12M or 1E-13M.
- 20 M, at most 1E-07 M, at most 5E-07 M, at most 1 E-08 M, at most 2 E-08 M, at most 3 E-08 M, at most 4 E-08 M, at most 5 E-08 M, at most 6 E-08 M, at most 7 E-08 M, at most 8 E-08 M, at most 9 E-08 M, at most 1 E-09 M, at most 2 E-09 M, at most 3 E-09 M, at most 4 E-09 M, at most 5E-09 M, at most 6 E-09 M, at most 7 E-09 M, at most 8 E-09 M, at most 9 E-09 M, at most 1E-10 M, at most 2 E-10 M, at most 3 E-10 M, at most 4 E-10 M, at most 5E-10 M, at most 6 E-10 M, at most 7 E-10 M. at most 8 E-10 M, at most 9 E-10 M, at most 1E-11M, at most 2 E-11M, at most 3 E-11M, at most 4E-11M, at most 5 E-11M, at most 6E-11M, at most 7 E-11M, at most 8 E-11M, at most 9 E-11M, at most 1E-12M, at most 2 E-12M, at most 3 E-12M, at most 4 E-12M, 5E-12M, at most 6 E-12M, at most 7 E-12M, at most 8 E-12M, at most 9 E-12M or 1E-13M.
- 25 In some embodiments, the antibody binds 15-PGDH with an EC₅₀ of at most 5E-09M, at most 9E-09M, at most 9.50E-09M, at most 1E-10, at most 1.5E-10, at most 2E-10, at most 2.5E-10, at most 3 E-10, as measured by titration ELISA. In some embodiments, the antibody binds 15-PGDH with an EC₅₀ below 1E-07M, below 5E-07M, or below 1E-08M by titration ELISA.
- 30 High affinity binding may also be assessed by measuring the K_d value (the dissociation constant) as described herein, for example via titration ELISA or BLI, as described herein. Accordingly, in some embodiments antibodies described herein may bind human PGDH with a K_d of at most 10⁻⁶M, 10⁻⁷M, 10⁻⁸M, 10⁻⁹M, preferably at most 10⁻⁹M, as measured by ELISA. Accordingly, in some embodiments antibodies described herein may bind human PGDH with a K_d of at most 1E-6, 1E-7, 1E-8, 3E-9, 1E-9, preferably at most 3E-9 or 1E-9 as measured by BLI.
- 35

Antibodies described herein may bind to and inhibit 15-PGDH through allosteric inhibition. Antibodies described herein may inhibit 15-PGDH through binding directly to the active site of the enzyme. Antibodies described herein may also block the substrate or cofactor entry sites of 15-PGDH. 15-PGDH residues involved in cofactor binding and enzyme activity include Gly12; Ala13; Ala14; Gln15; Gly16; Ile17; Gly18; Arg19; Ala20; Asp36; Trp37; Asn38; Cys63; Asp64; Val65; Asn91; Lys98; Asn 99; Lys102; Val186; Asn187; Thr188; Ala189; Glu198 of human 15-PGDH or homologous residues in homologous proteins. Accordingly, antibodies described herein may bind one or more, or all of the following 15-PGDH residues: Gly12; Ala13; Ala14; Gln15; Gly16; Ile17; Gly18; Arg19; Ala20; Asp36; Trp37; Asn38; Cys63; Asp64; Val65; Asn91; Lys98; Asn 99; Lys102; Val186; Asn187; Thr188; Ala189; Glu198 of human 15-PGDH or corresponding residues in homologous proteins. 15-PGDH residues involved in substrate binding (as well as enzyme activity) include Ser138; Leu139; Gln148; Phe185; Phe217. Accordingly, antibodies described herein may bind one or more, or all of the following 15-PGDH residues: Ser138; Leu139; Gln148; Phe185; Tyr217 of human 15-PGDH or corresponding residues in homologous proteins. Antibodies described herein may inhibit 15-PGDH through binding to an allosteric site of the enzyme. Allosteric as used herein refers to a site other than the active site of the enzyme. Accordingly, antibodies described herein may inhibit 15-PGDH allosterically, e.g. by reducing substrate affinity. Antibodies of the present disclosure may bind one or more active site residues of 15-PGDH. Antibodies of the present disclosure may bind one or more or all of the residues in Table 8, or corresponding residues in homologous proteins. This may be the case for e.g. antibodies having the VH CDRs of ATL6026 (and optionally also the VL CDRs or ATL6026) and variants and derivatives thereof, such as e.g. ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955. Antibodies of the present disclosure may bind one or more residues of 15-PGDH outside of the active site of the protein (e.g. allosteric site residues). Antibodies of the present disclosure may bind one or more or all of the residues in Table 9, or corresponding residues in homologous proteins. This may be the case for e.g. antibodies having the VH CDRs of ATL6058 (and optionally also the VL CDRs or ATL6058) and variants and derivatives thereof, such as e.g. ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473.

As used herein, the term "PGDH" encompasses truncations, derivatives, and variants of the sequence of human PGDH provided herein as SEQ ID NO: 82 or a homolog thereof (such as e.g. mouse PGDH provided as SEQ ID NO: 86), and it may refer to any protein with at least 80%, at least 90%, or at least 95% sequence identity with said sequence. The protein may be a protein that has the stated sequence identity with 15-PGDH or homologue thereof, and that has the enzymatic activity of the 15-PGDH or homologue thereof. The PGDH sequence may be a human PGDH sequence. The term "PGDH" encompasses any protein that is a fragment of human 15-PGDH or a homologue thereof that maintains at least some of the enzymatic activity of the corresponding full protein, as well as any derivative thereof with at least 80%, at least 90%, or at least 95% sequence identity with the sequence of such a fragment, provided that the variant maintains

at least some of the enzymatic activity of the fragment. The term "PGDH" encompasses any protein that is a fragment of human 15-PGDH or a homologue thereof that maintains the enzymatic activity of the corresponding full protein, as well as any derivative thereof with at least 80%, at least 90%, or at least 95% sequence identity with the sequence of such a fragment, provided that the variant maintains the enzymatic activity of the fragment.

Structural properties

Antibodies of the present disclosure may specifically bind to an epitope on 15-PGDH. The term epitope, also known as antigenic determinant, as used herein refers to any protein determinant capable of specific binding by an immunoglobulin or fragment thereof. Epitopic, or antigenic, determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics.

Antibodies described herein may bind to an epitope that comprises one or more of the following residues of 15-PGDH, provided as SEQ ID NO: 82: Met143; Pro144; Val145; Ala146; Gln147; Phe185; Tyr206; Asp208; His209; Asp212; Met213; Lys215; Tyr216; Tyr217; Gly218; Asp221; Leu224; Asn227; Thr231; Asp235; Ala237; Leu238; Thr246; Thr247; Ser248; Lys249; Arg163; Leu167; Asn170; Leu171; Ala237; Asn239; Gly250; Ile251; His252; Phe253; Asp255; Thr258; Thr259; Pro260; Phe261; Gln262, or corresponding residues in a homologous sequence. In some embodiments, the antibody binds to an epitope that comprises Thr246; Thr247; and Ser248.

In some embodiments, e.g. in instances where the antibody comprises the HCDR1-3 of ATL6026, the antibody binds to an epitope that comprises one or more (or all) of residues Met143; Pro144; Val145; Ala146; Gln147; Phe185; Tyr206; Asp208; His209; Asp212; Met213; Lys215; Tyr216; Tyr217; Gly218; Thr246; Thr247; Ser248; Arg163; Leu167; Asn170; Leu171; Ala237; Asn239; Thr258; Thr259; Pro260; Phe261; Gln262 of 15 PGDH, provided as SEQ ID NO: 82, or corresponding residues in a homologous sequence. In some embodiments, e.g. in instances where the antibody comprises the HCDR1-3 of ATL6058, the antibody binds to an epitope that comprises one or more (or all of) residues Asp221; Leu224; Asn227; Thr231; Asp235; Ala237; Leu238; Thr246; Thr247; Ser248; Lys249; Gly250; Ile251; His252; Phe253; Asp255 of 15 PGDH, provided as SEQ ID NO: 82, or corresponding residues in a homologous sequence.

An "antigen binding domain" describes the part of a molecule that binds to all or part of the target antigen. An antibody generally comprises six complementarity-determining regions (CDRs); three in the VH region: HCDR1, HCDR2 and HCDR3, and three in the VL region: LCDR1, LCDR2, and LCDR3. The six CDRs together (or specific residues therein) typically define the paratope of the antigen binding domain, which is the part of the antigen binding domain which binds to the target antigen. The paratope of an antibody as described herein may comprise any one or more or all of the VH residues in Table 10, in IMGT numbering.

The paratope of an antibody as described herein selected from ATL6026 or a variant or derivative thereof as described herein (including e.g. ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007896,

- ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955) may comprise any one or more or all of the VH residues listed in Table 10 for ATL6026, in IMGT numbering. The paratope of an antibody as described herein selected from ATL6058 or a variant or derivative thereof as described herein (including e.g. ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473) may comprise any one or more or all of the VH residues listed in Table 10 for ATL6058, in IMGT numbering. The paratope of an antibody as described herein selected from ATL6026 or a variant or derivative thereof as described herein (including e.g. ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955) may comprise any one or more or all of the VL residues listed in Table 10 for ATL6026, in IMGT numbering. The paratope of an antibody as described herein selected from ATL6058 or a variant or derivative thereof as described herein (including e.g. ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473) may comprise any one or more or all of the VL residues listed in Table 10 for ATL6058, in IMGT numbering. The paratope of an antibody as described herein may comprise the following VH residues 29, 35, 36, 37, 38, 55, 57, 59, 62, 64, 66, 107, 108, 109, 110, 111, 111A, 111B, 111C, 112D, 112C, 112B, 112A, 113, 114 in IMGT numbering. In embodiments, the paratope comprises one or more or all of the following VH residues: at position 29, T or S or A; at position 35, T; at position, 36, S; at position 37, Y, at position 38, G or F, at position 55, W; at position 57, S or Y; at position 59, Y or S; at position 62, N or A or Q; at position 64, N or S or A; at position 66, N or S; at position 107, D; at position 108, L; at position 109, G or F; at position 110, P or F; at position 111 Y or G; at position 111, Y or G; at position 111A, Y; at position 111B, Y; at position 111C, D or E; at position 112D, S or A; at position 112C, S; at position 112B, G; at position 112A, Y or S; at position 113, Y; at position 114, H.
- In some embodiments, the paratope comprises the following VH residues 29, 36, 37, 38, 55, 57, 59, 62, 64, 66, 107, 109, 110, 111, 111A, 111B, 111C, 112D, 112C, 112B, 112A, 113, in IMGT numbering. In some embodiments, the paratope comprises the following VH residues: at position 29, T; at position, 36, S; at position 37, Y, at position 38, G; at position 55, W; at position 57, S; at position 59, Y; at position 62, N or A or Q; at position 64, N or A; at position 66, N; at position 107, D; at position 109, G; at position 110, P; at position 111, Y; at position 111A, Y; at position 111B, Y; at position 111C, D or E; at position 112D, S or A; at position 112C, S; at position 112B, G; at position 112A, Y; at position 113, Y. This may be particularly the case for antibodies of the disclosure that are selected from ATL6026 and variants and derivatives thereof.

In some embodiments, the paratope comprises the following VH residues 29, 35, 36, 37, 38, 57, 59, 64, 108, 109, 110, 111, 112A, 114 in IMGT numbering. In some embodiments, the paratope comprises the following VH residues: at position 29, S or A; at position 35, T; at position 36, S; at position 37, Y; at position 38, F; at position 57, Y; at position 59, S; at position 64, S; at position 108, L; at position 109, F; at position 110, F; at position 111, G; at position 112A, S; Y; at position 114, H. This may be particularly the case for antibodies of the disclosure that are selected from ATL6058 and variants and derivatives thereof.

The paratope described herein may comprise the following VL residues: 35, 36, 37, 38, 52, 55, 109, 113, 114 in IMGT numbering. In embodiments, the paratope comprises the following VL residues: at position 35, A; at position 36, G or S; at position 37, Y or S; at position 38, Y or D; at position 52, R or P or L; at position 55, Y; at position 109, N or S or Q or A; at position 113, S or N or A, at position 114, L or S.

In embodiments, the paratope comprises VL residues 35, 36, 37, 109, 113, 114 in IMGT numbering. In embodiments, the paratope comprises the following VL residues: at position 35, A; at position 36, G; at position 37, Y; at position 109, N or Q or A; at position 113, S or N or A, at position 114, L. This may be particularly the case for antibodies of the disclosure that are selected from ATL6026 and variants and derivatives thereof.

In embodiments, the paratope comprises VL residues 36, 38, 52, 55 in IMGT numbering. In embodiments, the paratope comprises the following VL residues: at position 36, S; at position 38, S; at position 52, R; at position 55, Y. This may be particularly the case for antibodies of the disclosure that are selected from ATL6058 and variants and derivatives thereof.

The present disclosure relates primarily to antibody molecules, whether whole antibody (e.g. IgG, such as IgG1) or antibody fragments (e.g. single-chain variable fragment (scFv), antibody fragments (Fab) or bivalent antibody fragments (F(ab')₂), single-domain antibody (sdAb). Antibody antigen binding regions (also referred to as "antigen binding portions") are provided, as are antibody heavy chain variable (VH) and light chain variable (VL) domains. Within VH and VL domains are provided complementarity determining regions (CDRs), which may be provided within different framework regions (FRs), to form VH or VL domains, as the case may be. An antigen binding site may consist of an antibody VH domain and/or a VL domain. Thus, the term "isolated antibody" and "antibody" encompass whole antibody, and fragments thereof that maintain the binding functionality of the full antibody.

Antibodies according to the present disclosure may be provided in isolated form. The term "antibody" encompasses a fragment or derivative thereof, or a synthetic antibody or antibody fragment.

The antibody may be an scFv antibody molecule, a nanobody, or a whole antibody. The antibody may comprise an antibody constant region. The antibody may be a whole antibody. The antibody may be an IgG1 or variant thereof. The antibody may be an IgG1 variant L234A/L235A (LALA) (such as an antibody comprising a constant region as set out in SEQ ID NO: 87). IgG1 variant may have reduced effector function. The antibody may comprise a human IgG1 lambda or kappa constant region. The antibody may comprise a constant region as set out in SEQ ID NO: 88 or SEQ ID NO: 89.

An antibody or fragment thereof may be a monoclonal antibody (mAb). mAbs are homogenous populations of antibodies specifically targeting a single epitope on an antigen. Antibodies and methods for their

construction and use are well-known in the art and are described in, for example, Holliger & Hudson, Nature Biotechnology 23(9), 1126-1136 (2005). In view of today's techniques in relation to monoclonal antibody technology, antibodies can be prepared to most targets. It is possible to take monoclonal and other antibody molecules and use techniques of recombinant DNA technology to produce other antibody or chimeric molecules which retain the specificity of the original antibody. Such techniques may involve introducing CDRs or variable regions of one antibody into a different antibody molecule (see e.g. GB 2188638A and EP0239400).

A monoclonal monospecific IgG antibody molecule contains two antigen binding domains, each of which are able to bind the same target (i.e. it is bivalent for a single target). A Fab fragment generally comprises a VH domain, a CH1 domain, a VL domain and a CL domain. A full antibody may comprise a pair of Fab fragments and an Fc fragment comprising a pair of chains each comprising a CH2 domain and a CH3 domain. An Fv fragment comprises a VH domain and a VL domain. The VH region and VL region comprise framework regions (FRs) either side of each CDR, which provide a scaffold for the CDRs. From N-terminus to C-terminus, VH regions comprise the following structure: N term-[HFR1]-[HCDR1]-[HFR2]-[HCDR2]-[HFR3]-[HCDR3]-[HFR4]-C term; and VL regions comprise the following structure: N term-[LFR1]-[LCDR1]-[LFR2]-[LCDR2]-[LFR3]-[LCDR3]-[LFR4]-C term.

The term "ScFv molecules" refers to molecules wherein the VH and VL partner domains are covalently linked, e.g. by a flexible oligopeptide. Fab, Fv, ScFv and sdAb antibody fragments can all be expressed and/or secreted from expression systems, such as *E.coli* and mammalian cells thus allowing the facile production of large amounts of the said fragments.

Whole antibodies, and F(ab')₂ fragments are "bivalent". The term "bivalent" means that the said antibodies and F(ab')₂ fragments have two antigen combining sites. In contrast, Fab, Fv, ScFv and sdAb fragments are monovalent, having only one antigen combining site.

Antibodies according to the present disclosure may be detectably labelled or, at least, capable of detection. For example, the antibody may be labelled with a radioactive atom or a coloured molecule or a fluorescent molecule or a molecule which can be readily detected in any other way. Suitable detectable molecules include fluorescent proteins, luciferase, enzyme substrates, and radiolabels. The binding moiety (antibody or fragment thereof) may be directly labelled with a detectable label or it may be indirectly labelled. For example, the binding moiety may be an unlabelled antibody which can be detected by another antibody which is itself labelled. Alternatively, the second antibody may have bound to it biotin and binding of labelled streptavidin to the biotin is used to indirectly label the first antibody.

A "fragment" of an antibody may comprise any number of residues of a "parental" antibody, whilst retaining target binding ability. A fragment may lack effector function, for example may be entirely unable to bind or show diminished binding to the Fc receptor, relative to the parent. A fragment is typically smaller than the parental antibody. A fragment may comprise 50%, 60%, 70%, 80%, 90%, 95% or more of the contiguous or non-contiguous amino acids of the parental antibody. A fragment may comprise 50, 100, 150, 200, 250, 300 or more contiguous or non-contiguous amino acids of the parental antibody. A fragment may comprise deletions in the Fc region, or of the Fc region. A fragment may retain the CDRs and/or the variable domains

of the parental antibody, unaltered. In some embodiments, a fragment is a Fab fragment or an F(ab')₂ fragment. CDR sequences are described herein using the IMGT numbering (Lefranc, M.-P., Immunology Today, 18, 509 (1997)).

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: (i) a CDRH1 comprising the sequence of HCDR1_ATL_0006026; HCDR1_ATL_0006027; HCDR1_ATL_0006058; HCDR1_ATL_0006074; HCDR1_ATL_0006075; HCDR1_ATL_0007925; HCDR1_ATL_0007952; HCDR1_ATL_0007953; HCDR1_ATL_0007955; HCDR1_ATL_0007933; HCDR1_ATL_0007956; HCDR1_ATL_0007450; HCDR1_ATL_0007819; HCDR1_ATL_0007820; HCDR1_ATL_0007821; HCDR1_ATL_0007822; HCDR1_ATL_0007823; HCDR1_ATL_0007824; HCDR1_ATL_0007825; HCDR1_ATL_0007826; HCDR1_ATL_0007827; HCDR1_ATL_0007829; HCDR1_ATL_0007889; HCDR1_ATL_0007890; HCDR1_ATL_0007892; HCDR1_ATL_0007893; HCDR1_ATL_0007895; HCDR1_ATL_0007896; HCDR1_ATL_0007899; HCDR1_ATL_0007900; HCDR1_ATL_0007901; HCDR1_ATL_0007902; HCDR1_ATL_0007917; HCDR1_ATL_0007918; HCDR1_ATL_0007919; HCDR1_ATL_0007920; HCDR1_ATL_0007921; HCDR1_ATL_0007922; HCDR1_ATL_0007923; HCDR1_ATL_0007924; HCDR1_ATL_0007926; HCDR1_ATL_0007927; HCDR1_ATL_0007928; HCDR1_ATL_0007929; HCDR1_ATL_0007930; HCDR1_ATL_0007931; HCDR1_ATL_0007932; HCDR1_ATL_0007933; HCDR1_ATL_0007956; HCDR1_ATL_0007467; HCDR1_ATL_0007468; HCDR1_ATL_0007469; HCDR1_ATL_0007470; HCDR1_ATL_0007471; HCDR1_ATL_0007472; or HCDR1_ATL_0007473; and (ii) a CDRH2 comprising the sequence of HCDR2_ATL_0006026; HCDR2_ATL_0006027; HCDR2_ATL_0006058; HCDR2_ATL_0006074; HCDR2_ATL_0006075; HCDR2_ATL_0007925; HCDR2_ATL_0007952; HCDR2_ATL_0007953; HCDR2_ATL_0007955; HCDR2_ATL_0007933; HCDR2_ATL_0007956; HCDR2_ATL_0007450; HCDR2_ATL_0007819; HCDR2_ATL_0007820; HCDR2_ATL_0007821; HCDR2_ATL_0007822; HCDR2_ATL_0007823; HCDR2_ATL_0007824; HCDR2_ATL_0007825; HCDR2_ATL_0007826; HCDR2_ATL_0007827; HCDR2_ATL_0007829; HCDR2_ATL_0007889; HCDR2_ATL_0007890; HCDR2_ATL_0007892; HCDR2_ATL_0007893; HCDR2_ATL_0007895; HCDR2_ATL_0007896; HCDR2_ATL_0007899; HCDR2_ATL_0007900; HCDR2_ATL_0007901; HCDR2_ATL_0007902; HCDR2_ATL_0007917; HCDR2_ATL_0007918; HCDR2_ATL_0007919; HCDR2_ATL_0007920; HCDR2_ATL_0007921; HCDR2_ATL_0007922; HCDR2_ATL_0007923; HCDR2_ATL_0007924; HCDR2_ATL_0007926; HCDR2_ATL_0007927; HCDR2_ATL_0007928; HCDR2_ATL_0007929; HCDR2_ATL_0007930; HCDR2_ATL_0007931; HCDR2_ATL_0007932; HCDR2_ATL_0007933; HCDR2_ATL_0007956; HCDR2_ATL_0007467; HCDR2_ATL_0007468; HCDR2_ATL_0007469; HCDR2_ATL_0007470; HCDR2_ATL_0007471; HCDR2_ATL_0007472; or HCDR2_ATL_0007473 and (iii) a CDRH3 comprising the sequence of HCDR3_ATL_0006026; HCDR3_ATL_0006027; HCDR3_ATL_0006058; HCDR3_ATL_0006074; HCDR3_ATL_0006075; HCDR3_ATL_0007925; HCDR3_ATL_0007952; HCDR3_ATL_0007953; HCDR3_ATL_0007955; HCDR3_ATL_0007933; HCDR3_ATL_0007956; HCDR3_ATL_0007450; HCDR3_ATL_0007819; HCDR3_ATL_0007820; HCDR3_ATL_0007821; HCDR3_ATL_0007822; HCDR3_ATL_0007823; HCDR3_ATL_0007824; HCDR3_ATL_0007825; HCDR3_ATL_0007826; HCDR3_ATL_0007827; HCDR3_ATL_0007829; HCDR3_ATL_0007889; HCDR3_ATL_0007890; HCDR3_ATL_0007892;

HCDR3_ATL_0007893; HCDR3_ATL_0007895; HCDR3_ATL_0007896; HCDR3_ATL_0007899;
 HCDR3_ATL_0007900; HCDR3_ATL_0007901; HCDR3_ATL_0007902; HCDR3_ATL_0007917;
 HCDR3_ATL_0007918; HCDR3_ATL_0007919; HCDR3_ATL_0007920; HCDR3_ATL_0007921;
 HCDR3_ATL_0007922; HCDR3_ATL_0007923; HCDR3_ATL_0007924; HCDR3_ATL_0007926;
 5 HCDR3_ATL_0007927; HCDR3_ATL_0007928; HCDR3_ATL_0007929; HCDR3_ATL_0007930;
 HCDR3_ATL_0007931; HCDR3_ATL_0007932; HCDR3_ATL_0007933; HCDR3_ATL_0007956;
 HCDR3_ATL_0007467; HCDR3_ATL_0007468; HCDR3_ATL_0007469; HCDR3_ATL_0007470;
 HCDR3_ATL_0007471; HCDR3_ATL_0007472; or HCDR3_ATL_0007473.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with
 10 the following CDRs: (i) a CDRH1 comprising the sequence of HCDR1_ATL_0006026;
 HCDR1_ATL_0006058; HCDR1_ATL_0007925; HCDR1_ATL_0007952; HCDR1_ATL_0007953;
 HCDR1_ATL_0007955; HCDR1_ATL_0007933; or HCDR1_ATL_0007956; and (ii) a CDRH2 comprising
 the sequence of HCDR2_ATL_0006026; HCDR2_ATL_0006058; HCDR2_ATL_0007925;
 HCDR2_ATL_0007952; HCDR2_ATL_0007953; HCDR2_ATL_0007955; HCDR2_ATL_0007933; or
 15 HCDR2_ATL_0007956; and (iii) a CDRH3 comprising the sequence of HCDR3_ATL_0006026;
 HCDR3_ATL_0006058; HCDR3_ATL_0007925; HCDR3_ATL_0007952; HCDR3_ATL_0007953;
 HCDR3_ATL_0007955; HCDR3_ATL_0007933; or HCDR3_ATL_0007956.

An antibody according to the present disclosure may have a CDRH1 that is 8 to 10 amino acids in length.
 An antibody according to the present disclosure may have a CDRH2 that is 7 or 8 amino acids in length.
 20 An antibody according to the present disclosure may have a CDRH3 that is 14 to 20 amino acids in length.

An antibody according to the present disclosure may have a CDRH1 comprising the sequence of
 HCDR1_ATL_0006058, or a sequence comprising 1 to 5 mutations, such as substitutions, compared to
 said sequence. The mutations, such as substitutions, may be at position 28 and/or position 29 (e.g. D28E
 and/or S29A).

25 An antibody according to the present disclosure may have a CDRH1 comprising the sequence of
 HCDR1_ATL_0006026, or a sequence comprising 1 to 4, mutations, such as substitutions, compared to
 said sequence. The mutations, such as substitutions, may be at any position that is not positions 27 and
 37 (IMGT numbering). An antibody according to the present disclosure may have a CDRH1 with a G at
 position 27 and a Y at position 37 (IMGT numbering).

30 An antibody according to the present disclosure may have a CDRH2 comprising the sequence of
 HCDR2_ATL_0006058, or a sequence comprising 1 to 6 substitutions compared to said sequence.

An antibody according to the present disclosure may have a CDRH2 comprising the sequence of
 HCDR2_ATL_0006026, or a sequence comprising 1 to 6 substitutions compared to said sequence. The
 antibody may have an I at position 56, a G at position 63, and/or a T at position 65. The mutations, such as
 35 substitutions may be at position 62 (e.g. N62A or N62Q), position 63 (e.g. G63A) position 64 (e.g. N64A)
 and/or position 65 (e.g. T65A or T65S).

An antibody according to the present disclosure may have a CDRH3 comprising the sequence of
 HCDR3_ATL_0006058, or a sequence comprising 1 to 5 substitutions compared to said sequence.

An antibody according to the present disclosure may have a CDRH3 comprising the sequence of HCDR3_ATL_0006026, or a sequence comprising 1 to 5 substitutions compared to said sequence. The substitutions may be at any position that is not positions 105, 115 and 166 (IMGT numbering). Position 105 may be a G. Position 106 may be an R. Position 115 may be a F. Position 116 may be a D. The mutations, such as substitutions may be at position 111C (e.g. D111CE) and/or at position 112D (e.g. S112DA).

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0006026, a CDRH2 comprising the sequence of HCDR2_ATL_0006026, and a CDRH3 comprising the sequence of HCDR3_ATL_0006026, or a set of CDRs comprising 1 to 6 mutations (total of 1 to 6 mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007925, a CDRH2 comprising the sequence of HCDR2_ATL_0007925, and a CDRH3 comprising the sequence of HCDR3_ATL_0007925, or a set of CDRs comprising 1 to 6 mutations (total of 1 to 6 mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007952, a CDRH2 comprising the sequence of HCDR2_ATL_0007952, and a CDRH3 comprising the sequence of HCDR3_ATL_0007952, or a set of CDRs comprising 1 to 6 mutations (total of 1 to 6 mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007953, a CDRH2 comprising the sequence of HCDR2_ATL_0007953, and a CDRH3 comprising the sequence of HCDR3_ATL_0007953, or a set of CDRs comprising 1 to 6 mutations (total of 1 to 6 mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007955, a CDRH2 comprising the sequence of HCDR2_ATL_0007955, and a CDRH3 comprising the sequence of HCDR3_ATL_0007955, or a set of CDRs comprising 1 to 6 mutations (total of 1 to 6 mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0006058, a CDRH2 comprising the sequence of HCDR2_ATL_0006058, and a CDRH3 comprising the sequence of HCDR3_ATL_0006058, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007933, a CDRH2 comprising the sequence of HCDR2_ATL_0007933, and a CDRH3 comprising the sequence of

HCDR3_ATL_0007933, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

An antibody according to the present disclosure may comprise a heavy chain variable domain (VH) with the following CDRs: a CDRH1 comprising the sequence of HCDR1_ATL_0007956, a CDRH2 comprising
5 the sequence of HCDR2_ATL_0007956, and a CDRH3 comprising the sequence of HCDR3_ATL_0007956, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

Mutations as used herein refers to amino acid substitutions, insertions, or deletions. Mutations may be introduced by standard techniques, such as site-directed mutagenesis, PCR-mediated mutagenesis and
10 gene synthesis.

The antibodies of the disclosure explicitly encompass combinations of any of the VH of antibodies
ATL_0006026, ATL_0006027, ATL_0006058, ATL_0006074, ATL_0006075, ATL_0007925,
ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450,
ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824,
15 ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890,
ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900,
ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920,
ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, ATL_0007926, ATL_0007927,
ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933,
20 ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471,
ATL_0007472, ATL_0007473 (i.e. ATL_0006026 VH, ATL_0006027 VH, ATL_0006058 VH, ATL_0006074
VH, ATL_0006075 VH, ATL_0007925 VH, ATL_0007952 VH, ATL_0007953 VH, ATL_0007955 VH,
ATL_0007933 VH, ATL_0007956 VH, ATL_0007450 VH, ATL_0007819 VH, ATL_0007820 VH,
ATL_0007821 VH, ATL_0007822 VH, ATL_0007823 VH, ATL_0007824 VH, ATL_0007825 VH,
25 ATL_0007826 VH, ATL_0007827 VH, ATL_0007829 VH, ATL_0007889 VH, ATL_0007890 VH,
ATL_0007892 VH, ATL_0007893 VH, ATL_0007895 VH, ATL_0007896 VH, ATL_0007899 VH,
ATL_0007900 VH, ATL_0007901 VH, ATL_0007902 VH, ATL_0007917 VH, ATL_0007918 VH,
ATL_0007919 VH, ATL_0007920 VH, ATL_0007921 VH, ATL_0007922 VH, ATL_0007923 VH,
ATL_0007924 VH, ATL_0007926 VH, ATL_0007927 VH, ATL_0007928 VH, ATL_0007929 VH,
30 ATL_0007930 VH, ATL_0007931 VH, ATL_0007932 VH, ATL_0007933 VH, ATL_0007956 VH,
ATL_0007467 VH, ATL_0007468 VH, ATL_0007469 VH, ATL_0007470 VH, ATL_0007471 VH,
ATL_0007472 VH, ATL_0007473 VH) with any of the VL of ATL_0006026, ATL_0006027, ATL_0006058,
ATL_0006074, ATL_0006075, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955,
ATL_0007933, ATL_0007956, ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821,
35 ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827,
ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007895,
ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007917,
ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923,
ATL_0007924, ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930,

ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473 (i.e. ATL_0006026 VL, ATL_0006027 VL, ATL_0006058 VL, ATL_0006074 VL, ATL_0006075 VL, ATL_0007925 VL, ATL_0007952 VL, ATL_0007953 VL, ATL_0007955 VL, ATL_0007933 VL, ATL_0007956 VL, 5 ATL_0007450 VL, ATL_0007819 VL, ATL_0007820 VL, ATL_0007821 VL, ATL_0007822 VL, ATL_0007823 VL, ATL_0007824 VL, ATL_0007825 VL, ATL_0007826 VL, ATL_0007827 VL, ATL_0007829 VL, ATL_0007889 VL, ATL_0007890 VL, ATL_0007892 VL, ATL_0007893 VL, ATL_0007895 VL, ATL_0007896 VL, ATL_0007899 VL, ATL_0007900 VL, ATL_0007901 VL, ATL_0007902 VL, ATL_0007917 VL, ATL_0007918 VL, ATL_0007919 VL, ATL_0007920 VL, 10 ATL_0007921 VL, ATL_0007922 VL, ATL_0007923 VL, ATL_0007924 VL, ATL_0007926 VL, ATL_0007927 VL, ATL_0007928 VL, ATL_0007929 VL, ATL_0007930 VL, ATL_0007931 VL, ATL_0007932 VL, ATL_0007933 VL, ATL_0007956 VL, ATL_0007467 VL, ATL_0007468 VL, ATL_0007469 VL, ATL_0007470 VL, ATL_0007471 VL, ATL_0007472 VL, ATL_0007473 VL).

The antibodies of the disclosure explicitly encompass antibodies comprising a VH with all 3 CDRH of 15 antibodies ATL_0006026, ATL_0006027, ATL_0006058, ATL_0006074, ATL_0006075, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900, 20 ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473 with a VL comprising all 3 CDRL any of the VL of ATL_0006026, 25 ATL_0006027, ATL_0006058, ATL_0006074, ATL_0006075, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956 ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, 30 ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473.

35 In an antibody according to the present disclosure, at least one of the VH CDR1-3 sequences may vary. A variant may have one, two, three, four, five or six (e.g. one, two, or three) amino acid mutations, such as substitutions, compared with the set of VH CDR1-3 described above. A variant may have one to six (e.g. one to three) amino acid mutations, such as substitutions, compared with the set of VH CDR1-3 described above. Substitutions may be present at any one or more of the following positions: in HCDR1: 28 (e.g.

D28E), 29 (e.g. S29A); and/or in HCDR2: 62 (e.g. N62A or N62Q), 63 (e.g. G63A), 64 (e.g. N64A), 65 (e.g. T65A or T65S); and/or in HCDR3: 111C (e.g. D111CE), 112D (e.g. S112DA). Substitutions in antibodies that have HCDRs based on the HCDRs of ATL_0006058 including one or more substitutions as described herein may include substitutions at the following positions: 28 (e.g. D28E), and/or 29 (e.g. S29A) (both in HCDR1). Substitutions in antibodies that have HCDRs based on the HCDRs of ATL_0006026 including one or more substitutions as described herein may include substitutions at the following positions: in HCDR2: 62 (e.g. N62A or N62Q), 63 (e.g. G63A), 64 (e.g. N64A), and/or 65 (e.g. T65A or T65S); and/or in HCDR3: 111C (e.g. D111CE), 112D (e.g. S112DA).

In embodiments, an antibody according to the present disclosure comprises CDRs with sequences that each have zero, one, two or three, mutations, such as substitutions compared with VH CDR sequences of any antibody described herein. For example, an antibody according to the disclosure may comprise VH CDRs with the sequences of any antibody above, except that one, two or each of the CDRs comprise a substitution, where the total number of substitutions across CDRs does not exceed 3. In embodiments, a variant may have one, two or three substitutions, preferably at most one or two substitutions in each of one or more of the VH CDR1-3 described above. CDRH1 regions of any antibodies or fragments described herein may have a length of 7 or 8 amino acids. CDRH2 regions of any antibodies or fragments described herein may have a length of 7 or 8 amino acids. CDRH3 regions of any antibodies or fragments described herein may have a length of 14, 15, 17, or 20 amino acids. In embodiments, a variant may have VH CDRs that have at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with any set of VH CDRs described herein.

An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: (i) a CDRL1 comprising the sequence of LCDR1_ATL_0006026; LCDR1_ATL_0006027; LCDR1_ATL_0006058; LCDR1_ATL_0006074; LCDR1_ATL_0006075; LCDR1_ATL_0007925; LCDR1_ATL_0007952; LCDR1_ATL_0007953; LCDR1_ATL_0007955; LCDR1_ATL_0007933; LCDR1_ATL_0007956; LCDR1_ATL_0007450; LCDR1_ATL_0007819; LCDR1_ATL_0007820; LCDR1_ATL_0007821; LCDR1_ATL_0007822; LCDR1_ATL_0007823; LCDR1_ATL_0007824; LCDR1_ATL_0007825; LCDR1_ATL_0007826; LCDR1_ATL_0007827; LCDR1_ATL_0007829; LCDR1_ATL_0007889; LCDR1_ATL_0007890; LCDR1_ATL_0007892; LCDR1_ATL_0007893; LCDR1_ATL_0007895; LCDR1_ATL_0007896; LCDR1_ATL_0007899; LCDR1_ATL_0007900; LCDR1_ATL_0007901; LCDR1_ATL_0007902; LCDR1_ATL_0007917; LCDR1_ATL_0007918; LCDR1_ATL_0007919; LCDR1_ATL_0007920; LCDR1_ATL_0007921; LCDR1_ATL_0007922; LCDR1_ATL_0007923; LCDR1_ATL_0007924; LCDR1_ATL_0007926; LCDR1_ATL_0007927; LCDR1_ATL_0007928; LCDR1_ATL_0007929; LCDR1_ATL_0007930; LCDR1_ATL_0007931; LCDR1_ATL_0007932; LCDR1_ATL_0007933; LCDR1_ATL_0007956; LCDR1_ATL_0007467; LCDR1_ATL_0007468; LCDR1_ATL_0007469; LCDR1_ATL_0007470; LCDR1_ATL_0007471; LCDR1_ATL_0007472; or LCDR1_ATL_0007473; and (ii) a CDRL2 comprising the sequence of LCDR2_ATL_0006026; LCDR2_ATL_0006027; LCDR2_ATL_0006058; LCDR2_ATL_0006074; LCDR2_ATL_0006075; LCDR2_ATL_0007925; LCDR2_ATL_0007952; LCDR2_ATL_0007953; LCDR2_ATL_0007955; LCDR2_ATL_0007933; LCDR2_ATL_0007956; LCDR2_ATL_0007450;

- LCDR2_ATL_0007819; LCDR2_ATL_0007820; LCDR2_ATL_0007821; LCDR2_ATL_0007822;
 LCDR2_ATL_0007823; LCDR2_ATL_0007824; LCDR2_ATL_0007825; LCDR2_ATL_0007826;
 LCDR2_ATL_0007827; LCDR2_ATL_0007829; LCDR2_ATL_0007889; LCDR2_ATL_0007890;
 LCDR2_ATL_0007892; LCDR2_ATL_0007893; LCDR2_ATL_0007895; LCDR2_ATL_0007896;
 5 LCDR2_ATL_0007899; LCDR2_ATL_0007900; LCDR2_ATL_0007901; LCDR2_ATL_0007902;
 LCDR2_ATL_0007917; LCDR2_ATL_0007918; LCDR2_ATL_0007919; LCDR2_ATL_0007920;
 LCDR2_ATL_0007921; LCDR2_ATL_0007922; LCDR2_ATL_0007923; LCDR2_ATL_0007924;
 LCDR2_ATL_0007926; LCDR2_ATL_0007927; LCDR2_ATL_0007928; LCDR2_ATL_0007929;
 LCDR2_ATL_0007930; LCDR2_ATL_0007931; LCDR2_ATL_0007932; LCDR2_ATL_0007933;
 10 LCDR2_ATL_0007956; LCDR2_ATL_0007467; LCDR2_ATL_0007468; LCDR2_ATL_0007469;
 LCDR2_ATL_0007470; LCDR2_ATL_0007471; LCDR2_ATL_0007472; or LCDR2_ATL_0007473; and
 (iii) a CDRL3 comprising the sequence of LCDR3_ATL_0006026; LCDR3_ATL_0006027;
 LCDR3_ATL_0006058; LCDR3_ATL_0006074; LCDR3_ATL_0006075; LCDR3_ATL_0007925;
 LCDR3_ATL_0007952; LCDR3_ATL_0007953; LCDR3_ATL_0007955; LCDR3_ATL_0007933;
 15 LCDR3_ATL_0007956; LCDR3_ATL_0007450; LCDR3_ATL_0007819; LCDR3_ATL_0007820;
 LCDR3_ATL_0007821; LCDR3_ATL_0007822; LCDR3_ATL_0007823; LCDR3_ATL_0007824;
 LCDR3_ATL_0007825; LCDR3_ATL_0007826; LCDR3_ATL_0007827; LCDR3_ATL_0007829;
 LCDR3_ATL_0007889; LCDR3_ATL_0007890; LCDR3_ATL_0007892; LCDR3_ATL_0007893;
 LCDR3_ATL_0007895; LCDR3_ATL_0007896; LCDR3_ATL_0007899; LCDR3_ATL_0007900;
 20 LCDR3_ATL_0007901; LCDR3_ATL_0007902; LCDR3_ATL_0007917; LCDR3_ATL_0007918;
 LCDR3_ATL_0007919; LCDR3_ATL_0007920; LCDR3_ATL_0007921; LCDR3_ATL_0007922;
 LCDR3_ATL_0007923; LCDR3_ATL_0007924; LCDR3_ATL_0007926; LCDR3_ATL_0007927;
 LCDR3_ATL_0007928; LCDR3_ATL_0007929; LCDR3_ATL_0007930; LCDR3_ATL_0007931;
 LCDR3_ATL_0007932; LCDR3_ATL_0007933; LCDR3_ATL_0007956; LCDR3_ATL_0007467;
 25 LCDR3_ATL_0007468; LCDR3_ATL_0007469; LCDR3_ATL_0007470; LCDR3_ATL_0007471;
 LCDR3_ATL_0007472; or LCDR3_ATL_0007473.

- An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: (i) a CDRL1 comprising the sequence of LCDR1_ATL_0006026; LCDR1_ATL_0006058; LCDR1_ATL_0007925; LCDR1_ATL_0007952; LCDR1_ATL_0007953; LCDR1_ATL_0007955;
 30 LCDR1_ATL_0007933; or LCDR1_ATL_0007956; and (ii) a CDRL2 comprising the sequence of LCDR2_ATL_0006026; LCDR2_ATL_0006058; LCDR2_ATL_0007925; LCDR2_ATL_0007952;
 LCDR2_ATL_0007953; LCDR2_ATL_0007955; LCDR2_ATL_0007933; or LCDR2_ATL_0007956; and (iii)
 a CDRL3 comprising the sequence of LCDR3_ATL_0006026; LCDR3_ATL_0006058;
 LCDR3_ATL_0007925; LCDR3_ATL_0007952; LCDR3_ATL_0007953; LCDR3_ATL_0007955;
 35 LCDR3_ATL_0007933; or LCDR3_ATL_0007956.

An antibody according to the present disclosure may have a CDRL1 that is 5 to 8 amino acids in length. An antibody according to the present disclosure may have a CDRL2 that is 3 amino acids in length. An antibody according to the present disclosure may have a CDRL3 that is 9 or 10 amino acids in length.

An antibody according to the present disclosure may have a CDRL1 comprising the sequence of LCDR1_ATL_0006058, or a sequence comprising 1 or 2 mutations, such as substitutions, compared to said sequence.

5 An antibody according to the present disclosure may have a CDRL1 comprising the sequence of LCDR1_ATL_0006026, or a sequence comprising 1 or 2 mutations, such as substitutions compared to said sequence. The antibody may have an S at position 28.

An antibody according to the present disclosure may have a CDRL2 comprising the sequence of LCDR2_ATL_0006058, or a sequence comprising 1 or 2 mutations, such as substitutions, compared to said sequence.

10 An antibody according to the present disclosure may have a CDRL2 comprising the sequence of LCDR2_ATL_0006026, or a sequence comprising 1 or 2 mutations, such as substitutions compared to said sequence. The antibody may have a substitution at position 57, e.g. N57A or N57Q and/or at position 65, e.g. S65N or S65A. The antibody may have a G at position 56 and/or an S at position 65.

15 An antibody according to the present disclosure may have a CDRL3 comprising the sequence of LCDR3_ATL_0006058, or a sequence comprising 1 to 5 mutations, such as substitutions compared to said sequence.

An antibody according to the present disclosure may have a CDRL3 comprising the sequence of LCDR3_ATL_0006026, or a sequence comprising 1 to 5 mutations, such as substitutions, compared to said sequence. The antibody may have a Q at position 105. The antibody may have a substitution at
20 position 109, e.g. N109Q or N109A, and/or at position 113, e.g. S113N or S113A.

In an antibody according to the present disclosure at least one of the VL CDR1-3 sequences may vary. A variant may have 1, 2, or 3 amino acid mutations, such as substitutions compared with the set of VL CDR1-3 described above. In embodiments, an antibody according to the disclosure comprises CDRs with sequences that have between 1 and 3 mutations, such as substitutions, compared with the VL CDR sequences of an antibody described herein. For example, an antibody according to the disclosure may
25 comprise a mutation, such as a substitution, where the total number of mutations, such as substitutions, does not exceed 3. In embodiments, a variant may have one, two or three, preferably at most one or two mutations, such as substitutions, in each of one or more of the VL CDR1-3 described above. The antibody may have substitutions at the following positions compared to the sequences described herein: (i) In the
30 LCDR2: position 57 (e.g. N57A or N57Q), position 65 (e.g. S65N or S65A); and/or (ii) in the LCDR3: position 109 (e.g. N109Q or N109A); position 113 (e.g. S113N or S113A).

An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0006026, a CDRL2 comprising the sequence of LCDR2_ATL_0006026, and a CDRL3 comprising the sequence of LCDR3_ATL_0006026,
35 or a set of CDRs comprising 1 to 4 mutations (total of 1 to 4 mutations over all CDRs) compared to these sequences.

5 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007925, a CDRL2 comprising the sequence of LCDR2_ATL_0007925, and a CDRL3 comprising the sequence of LCDR3_ATL_0007925, or a set of CDRs comprising 1 to 4 mutations (total of 1 to 4 mutations over all CDRs) compared to these sequences.

10 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007952, a CDRL2 comprising the sequence of LCDR2_ATL_0007952, and a CDRL3 comprising the sequence of LCDR3_ATL_0007952, or a set of CDRs comprising 1 to 4 mutations (total of 1 to 4 mutations over all CDRs) compared to these sequences.

15 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007953, a CDRL2 comprising the sequence of LCDR2_ATL_0007953, and a CDRL3 comprising the sequence of LCDR3_ATL_0007953, or a set of CDRs comprising 1 to 4 mutations (total of 1 to 4 mutations over all CDRs) compared to these sequences.

20 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007955, a CDRL2 comprising the sequence of LCDR2_ATL_0007955, and a CDRL3 comprising the sequence of LCDR3_ATL_0007955, or a set of CDRs comprising 1 to 4 mutations (total of 1 to 4 mutations over all CDRs) compared to these sequences.

25 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0006058, a CDRL2 comprising the sequence of LCDR2_ATL_0006058, and a CDRL3 comprising the sequence of LCDR3_ATL_0006058, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

30 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007933, a CDRL2 comprising the sequence of LCDR2_ATL_0007933, and a CDRL3 comprising the sequence of LCDR3_ATL_0007933, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

35 An antibody according to the present disclosure may comprise a light chain variable domain (VL) with the following CDRs: a CDRL1 comprising the sequence of LCDR1_ATL_0007956, a CDRL2 comprising the sequence of LCDR2_ATL_0007956, and a CDRL3 comprising the sequence of LCDR3_ATL_0007956, or a set of CDRs comprising one, two, or three mutations (total of one, two, or three mutations over all CDRs) compared to these sequences.

The VH CDRs 1-3 and optionally VL CDRs 1-3 of any of the antibodies described above may also be particularly useful in conjunction with a number of different framework regions.

Accordingly, light and/or heavy chains having CDRs 1-3 as described above may possess an alternative framework region. Suitable framework regions are known in the art and are described for example in M. Lefranc & G. Le Franc (2001) "The Immunoglobulin Facts Book", Academic Press.

An antibody of the disclosure may have the CDRH1, CDRH2 and CDRH3 of the VH domain within a germline framework. An antibody of the disclosure may have a light chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibodies ATL_0006026, ATL_0006027, ATL_0006074, ATL_0006075, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, or ATL_0007473, for example the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibodies ATL_0006026, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, or ATL_0007956, or a set of framework sequences with one to three mutations, such as substitutions, compared with these framework sequences. The antibody of the disclosure may have substitutions at one or more of the following positions compared to the sequences described herein: at position 5 (e.g. Q5V); and/or at position 40 (e.g. A40S); and/or at position 49 (e.g. R49G); and/or at position 53 (e.g. M53A); and/or at position 66 (e.g. S66N); and/or at position 78 (e.g. M78I or M78A); and/or at position 81 (e.g. D81E); and/or at position 85 (e.g. K85N); and/or at position 89 (e.g. M89A); and/or at position 92 (e.g. T92S); and/or at position 97 (e.g. D97E); and/or at position 98 (e.g. D98E); and/or at position 99 (e.g. T99A); and/or at position 122 (e.g. M122T); and/or at position 123 (e.g. M123T).

An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0006026, or framework sequences with one to nine substitutions compared to these framework sequences (a total of one to nine substitutions across all framework sequences).

An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007925, or framework sequences with one to nine substitutions compared to these framework sequences (a total of one to nine substitutions across all framework sequences).

An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007952, or framework sequences with one to nine substitutions compared to these framework sequences (a total of one to nine substitutions across all framework sequences).

An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007953, or framework sequences with one to nine substitutions compared to these framework sequences (a total of one to nine substitutions across all framework sequences).

- 5 An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007955, or framework sequences with one to nine substitutions compared to these framework sequences (a total of one to nine substitutions across all framework sequences).

- 10 An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0006058, or framework sequences with one to eight substitutions compared to these framework sequences (a total of one to eight substitutions across all framework sequences).

- 15 An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007933, or framework sequences with one to eight substitutions compared to these framework sequences (a total of one to eight substitutions across all framework sequences).

- 20 An antibody of the disclosure may have a heavy chain variable domain (VH) with the framework sequences HFWR1, HFWR2, HFWR3 and HFWR4 of antibody ATL_0007956, or framework sequences with one to eight substitutions compared to these framework sequences (a total of one to eight substitutions across all framework sequences). The antibody may have any one or more of (or all of):

- In the HFWR1: a Q at position 1, a V at position 2, a Q at position 3, a L at position 4, Q or V at position 5, Q or E at position 6, S or W at position 7, G at position 8, A or P at position 9, E or G at position 11, V or L at position 12, K at position 14, P at position 15, G or S at position 16, S or T at position 18, V or L at position 21, S or T at position 22, C at position 23, A or V at position 25, S or Y at position 26;
- In the HCDR1: G at position 27, T or S at position 29, F or I at position 30, S or G at position 36, Y at position 37;
- In the HFRW2: a I or W at position 39, S or A at position 40, W at position 41, V or I at position 42, R at position 43, Q at position 44, P or A at position 46, G at position 47, Q or K at position 48, R or G at position 49, L at position 50, E at position 51, W at position 52, M or I at position 53, G at position 54;
- In the HCDR2: I or V at position 56, G at position 63, T or A at position 65;
- In the HFWR3: Y at position 67, A or N at position 68, Q or P at position 69, K or S at position 70, L or F at position 71, Q or K at position 72, G or S at position 74, R at position 75, V at position 76, T at position 77, M or I at position 78, T or S at position 79, D at position 81, T or K at position 82, S at position 83, T or K at position 84, T or Q at position 86, A or F at position 87, M or L at position 89, E or K at position 90, L at position 91, L or V at position 94, R or T at position 95, S or A at

position 96, D at position 98, T at position 99, A at position 100, V at position 101, Y at position 102, Y at 103, C at position 104;

- In the HCDR3: A at position 105, R or S at position 106, F at position 115, D at position 116;
- In the HFWR4: W at position 118, G at position 119, A at position 120, G at position 121, T or M at position 122, V at 124, T at position 125, V at position 126, S at position 127, S at position 128.

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The antibody may have any one or more of (or all of):

- In the HFWR1: Q at position 1, V at position 2, Q at position 3, L at position 4, Q or V at position 5, Q or E at position 6, S at position 7, G at position 8, A or P at position 9, no position 10, E or G at position 11, V or L at position 12, K or V at position 13, K at position 14, P at position 15, G or S at position 16, A or E at position 17, S or T at position 18, V or L at position 19, K or S at position 20, V or L at position 21, S or T at position 22, C at position 23, K or T at position 24, A or V at position 25, S at position 26;
- In the HCDR1: G at position 27, Y or D or E at position 28, T or S or A at position 29, F or I at position 30, no position 31-34, T at position 35, S at position 36, Y at position 37, G or F at position 38;
- In the HFRW2: I or W at position 39, S or A at position 40, W at position 41, V or I at position 42, R at position 43, Q at position 44, P or A at position 45, P or A at position 46, G at position 47, Q or K at position 48, R or G at position 49, L at position 50, E at position 51, W at position 52, M or I or A at position 53, G at position 54, W or R at position 55;
- In the HCDR2: I or V at position 56, S or Y at position 57, A at position 58, Y or S at position 59, no position 60-61, N or A or Q or nothing at position 62, G or A at position 63, N or S or A at position 64, T or A or S at position 65;
- In the HFWR3: N or S at position 66, Y at position 67, A or N at position 68, Q or P at position 69, K or S at position 70, L at position 71, Q or K at position 72, no position 73, G or S at position 74, R at position 75, V at position 76, T at position 77, M or I or A at position 78, T or S at position 79, T or V at position 80, D or E at position 81, T at position 82, S at position 83, T or K at position 84, S or K or N at position 85, T or Q at position 86, A or F at position 87, Y or S at position 88, M or L or A at position 89, E or K at position 90, L at position 91, R or T or S at position 92, S at position 93, L or V at position 94, R or T at position 95, S or A at position 96, D or A or E at position 97, D or E at position 98, T or A at position 99, A at position 100, V at position 101, Y at position 102, Y at position 103, C at position 104;
- In the HCDR3: A at position 105, R at position 106, D at position 107, L at position 108, G or F at position 109, P or F at position 110, Y or G at position 111, Y or nothing at position 111A, Y or nothing at position 111B, D or E or nothing at position 111C, S or A or nothing at position 112D, S or nothing at position 112C, G or nothing at position 112B, Y or S at position 112A, Y or G at position 112, Y or S at position 113, G or H at position 114, F at position 115, D at position 116, I or P at position 117;

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- In the HFWR4: W at position 118, G at position 119, Q at position 120, G at position 121, T or M at position 122, M or L or T at position 123, V at position 124, T at position 125, V at position 126, S at position 127, S at position 128.

The antibody of the disclosure may have a D at position 98 and/or a T at position 99. The presence of these residues may positively affect stability and/or binding. A computational structure prediction (AlphaFold2) of antibody ATL_0006058 indicated that D98 makes a salt bridge with R75 and T99 is involved in beta-sheet structure. Therefore, based on this prediction maintaining these residues (or residues that are able to establish the same interactions, such as e.g. R, H, K, E instead of D at position 98) is likely to be beneficial (although not strictly necessary), particularly in ATL_0006058 and antibodies derived therefrom (including e.g. including e.g. ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, ATL_0007473). A computational structure prediction (AlphaFold2) of antibody ATL_0006026 indicated that D98 makes a salt bridge with R75, however T99 was not indicated to involved in beta-sheet structure in ATL_0006026. Therefore, based on this prediction maintaining D98 is likely to be beneficial (although not strictly necessary, and the amino acid can be replaced by other amino acids that are able to form salt bridges, such as R, H, K, E, as evidenced by the binding of e.g. ATL_7925, which has E98), particularly in ATL_0006026 and antibodies derived therefrom (including e.g. ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955).

An antibody of the disclosure may have the CDRL1, CDRL2 and CDRL3 of the VL domain within a germline framework. An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibodies ATL_0006026, ATL_0006027, ATL_0006074, ATL_0006075, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890, ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, ATL_0007926, ATL_0007927, ATL_0007928, ATL_0007929, ATL_0007930, ATL_0007931, ATL_0007932, ATL_0007933, ATL_0007956, ATL_0007467, ATL_0007468, ATL_0007469, ATL_0007470, ATL_0007471, ATL_0007472, or ATL_0007473, for example the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibodies ATL_0006026, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, or ATL_0007956 or a set of framework sequences with one to three mutations, such as substitutions, compared with these framework sequences. The antibody of the disclosure may have substitutions at one or more of the following positions compared to the sequences described herein: position 2 (e.g. A2S);

and/or at position 8 (e.g. S8P); and/or position 49 (e.g. P49A); and/or at position 52 (e.g. P52L or R52L); and/or at position 74 (e.g. G74D); and/or at position 90 (e.g. V90A or S90T); and/or at position 124 (e.g. V124L).

5 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0006026, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

10 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007925, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

15 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007952, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007953, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

20 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007955, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

25 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0006058, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

30 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007933, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

35 An antibody of the disclosure may have a light chain variable domain (VL) with the framework sequences LFWR1, LFWR2, LFWR3 and LFWR4 of antibody ATL_0007956, or framework sequences with one to five substitutions compared to these framework sequences (a total of one to five substitutions across all framework sequences).

The antibody may have any one or more of (or all of):

- In the LFWR1: an L at position 4, T at position 5, Q at position 6, S at position 12, G at position 16, S or R at position 22, C at position 23, G or A at position 25;
- In the CDRL1: S at position 28, G or – at position 31, D or Y at position 36;
- In the LFRW2: W at position 41, Y at position 42, Q at position 43, Q or H at position 44, P at position 46, a G at position 47, an A or P at position 49, a P at position 50, a K or R at position 51, a I or F at position 54, a Y or S at position 55;
- In the LCDR2: 3 amino acids;
- In the LFWR3: a R at position 67, a R or A at position 68, a S or T at position 69, a G at position 70, V or I at position 71, P or S at position 72, R at position 75, F at position 76, S at position 77, G or A at position 78, S at position 79, S at position 83, G at position 84, T or N at position 85, F or A at position 87, S or T at position 88, L at position 89, I at position 91, T or S at position 92, G or R at position 93, L or A at position 94, E or D at position 97, D at position 98, F or E at position 99, A at position 100, Y at position 102, A at position 103, C at position 104,
- In the LCDR3: Q or S at position 105, Q or S at position 106, Y or R at position 107;
- In the LFWR4: F at position 118, G at position 119, G or Q at position 120, G at position 121, T at position 122, V or L at position 124, T or E at position 125, V or I at position 126, L or K at position 127.

The antibody may have any one or more of (or all of):

- In the LFWR1: Q or E at position 1, A or I or S at position 2, V at position 3, L at position 4, T at position 5, Q at position 6, P or S at position 7, P or S at position 8, S or G at position 9, T or nothing at position 10, V or L at position 11, S at position 12, G or L at position 13, A or S at position 14, P at position 15, G at position 16, Q or E at position 17, R at position 18, V or A at position 19, T at position 20, I or L at position 21, S at position 22, C at position 23, T or R at position 24, G or A at position 25, S at position 26;
- In the CDRL1: S or Q at position 27, S at position 28, N or V at position 29, I or T at position 30, G or nothing at position 31, nothing at positions 32-34, A or nothing at position 35, G or S at position 36, Y or S at position 37, D or Y at position 38;
- In the LFRW2: V or L at position 39, H or A at position 40, W at position 41, Y at position 42, Q at position 43, Q at position 44, L or K at position 45, P at position 46, G at position 47, T or Q at position 48, A or P at position 49, P at position 50, K or R at position 51, P or R or L at position 52, L at position 53, I at position 54, Y at position 55;
- In the LCDR2: G at position 56, N or T or A or Q at position 57, nothing at positions 58-64, S or N at position 65;
- In the LFWR3: N or S at position 66, R at position 67, a P or A at position 68, a S or T at position 69, a G at position 70, V or I at position 71, P at position 72, nothing at position 73, D or G at position 74, R at position 75, F at position 76, S at position 77, G at position 78, S at position 79,

5 K or G at position 80, nothing at positions 81-82, S at position 83, G at position 84, T at position 85, S or D at position 86, F or A at position 87, S or T at position 88, L at position 89, V or S or A or T at position 90, I at position 91, T or S at position 92, G or R at position 93, L at position 94, Q or E at position 95, A or P at position 96, E at position 97, D at position 98, F or E at position 99, A at position 100, D or V at position 101, Y at position 102, Y at position 103, C at position 104;

- In the LCDR3: Q at position 105, Q or S at position 106, Y at position 107, D or G at position 108, N or S or Q or A at position 109, nothing at positions 110-112, S or N or nothing at position 113, L or S at position 114, S or P at position 115, V or P at position 116, A or T at position 117;
- 10 - In the LFWR4: F at position 118, G at position 119, G or Q at position 120, G at position 121, T at position 122, K or R at position 123, V or L at position 124, T or E at position 125, V or I at position 126, L or K at position 127.

An antibody of the disclosure may have a sequence comprising any or all of the amino acids that are conserved across (i.e. present in all of) ATL_0006026, ATL_0006027, ATL_0006074, ATL_0006075;
15 ATL_0006058, when comparing sequences using IMGT numbering (see Fig. 13).

An antibody of the disclosure may have a sequence comprising any or all of the amino acids that are conserved across (i.e. present in all of) ATL_0006026, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956 when comparing sequences using IMGT numbering (see Fig. 22, Fig. 26). An antibody of the disclosure may have a VH sequence comprising any
20 or all of the amino acids of the VH of ATL_0006026 that are conserved across ATL_0006026, ATL_0007925, ATL_0007952, ATL_0007953, and ATL_0007955. An antibody of the disclosure may have a VL sequence comprising any or all of the amino acids of the VL of ATL_0006026 that are conserved across ATL_0006026, ATL_0007925, ATL_0007952, ATL_0007953, and ATL_0007955. An antibody of the disclosure may have a VH sequence comprising any or all of the amino acids of the VH of ATL_0006058
25 that are conserved across ATL_0006058, ATL_0007933, and ATL_0007956. An antibody of the disclosure may have a VL sequence comprising any or all of the amino acids of the VL of ATL_0006058 that are conserved across ATL_0006058, ATL_0007933, and ATL_0007956. Thus, an antibody of the disclosure may have a VH sequence based on the VH sequence of ATL_0006026 and including one or more substitutions provided that the sequence maintains the identity of the amino acids at positions 1-4, 6-9, 11-
30 30, 35-59, 64, 66-72, 74-80, 82-96, 100-111C, 112C-122, and 124-128 in IMGT numbering. An antibody of the disclosure may have a VL sequence based on the VL sequence of ATL_0006026 and including one or more substitutions provided that the sequence maintains the identity of the amino acids at positions 1, 3-7, 9, 11-31, 35-57, 66-72, 74-80, 83-89, 91-109, 114-123, and 125-127 in IMGT numbering. In embodiments, an antibody of the disclosure may have a VL sequence based on the VL sequence of
35 ATL_0006026 and including one or more substitutions provided that the sequence maintains the identity of the amino acid at position 52 (proline 52; P52) in IMGT numbering. Based on the binding data provided herein, P52 appears beneficial (although not strictly necessary, as evidenced by the binding of numerous variants disclosed herein with the P52L mutation) for binding to 15-PGDH for variants of ATL_6026 (but not variants of ATL_6058). An antibody of the disclosure may have a VH sequence based on the VH

sequence of ATL_0006058 and including one or more substitutions provided that the sequence maintains the identity of the amino acids at positions 1-9, 11-27, 29-30, 35-39, 41-48, 50-59, 63-65, 67-72, 74-77, 79-80, 82-84, 86-91, 93-111, 112A-121, and 123-128 in IMGT numbering. An antibody of the disclosure may have a VL sequence based on the VL sequence of ATL_0006058 and including one or more substitutions
5 provided that the sequence maintains the identity of the amino acids at positions 1-30, 36-48, 50-51, 53-57, 65-72, 74-80, 83-89, 91-109, and 114-127 in IMGT numbering. In embodiments, an antibody of the disclosure has a VH sequence of ATL_0006026 or ATL_0006058 with one or more substitutions, provided that the substitutions are not at positions conserved amongst the variants in Fig. 26. In embodiments, an antibody of the disclosure has a VH sequence of ATL_0006026 with one or more substitutions provided
10 that the substitutions are not at positions 1-4, 7-8, 10, 14-15, 23, 26-27, 31-37, 41, 43-44, 47, 50-51, 54, 60-61, 63, 67, 71, 73, 75-77, 82-83, 91, 100, 101-104, 105-108, 115-116, 118-121, 124-128 in IMGT numbering. In embodiments, an antibody of the disclosure has a VH sequence of ATL_0006058 with one or more substitutions provided that the substitutions are not at positions 1-4, 7-8, 10, 14-15, 23, 26-27, 31-37, 41, 43-44, 47, 50-51, 54, 60-61, 63, 67, 71, 73, 75-77, 82-83, 91, 100, 101-104, 105-108, 115-116, 118-
15 121, 124-128 in IMGT numbering. In embodiments, an antibody of the disclosure has a VL sequence of ATL_0006026 or ATL_0006058 with one or more substitutions, provided that the substitutions are not at positions conserved amongst the variants in Fig. 26. In embodiments, an antibody of the disclosure has a VL sequence of ATL_0006026 with one or more substitutions provided that the substitutions are not at positions 3-6, 12, 15-16, 18, 22-23, 26, 28, 41-44, 46-47, 50, 53-56, 58-64, 67, 70, 72-73, 75-79, 81-85, 89,
20 91, 94, 97-100, 102-105, 107, 110-112, 118-122 in IMGT numbering. In embodiments, an antibody of the disclosure has a VL sequence of ATL_0006058 with one or more substitutions provided that the substitutions are not at positions 3-6, 12, 15-16, 18, 22-23, 26, 28, 41-44, 46-47, 50, 53-56, 58-64, 67, 70, 72-73, 75-79, 81-85, 89, 91, 94, 97-100, 102-105, 107, 110-112, 118-122 in IMGT numbering.

In this specification, antibodies may have VH (and optionally VL) regions comprising an amino acid
25 sequence that are identical or have a high percentage sequence identity to the VH and/or VL amino acid sequences of ATL_0006026, ATL_0006027, ATL_0006074; ATL_0006075; ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450, ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824, ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890,
30 ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900, ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920, ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, for example ATL_0006026, ATL_0006058 ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956. For example, antibodies according to the present invention include antibodies that bind PGDH and have a VH region that
35 comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the VH region amino acid sequence of ATL_0006026, ATL_0006058, ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, or ATL_0007956.

An antibody according to the disclosure may have a heavy chain variable domain (VH) comprising a sequence that has a least 95% sequence identity with the sequence of one or more of SEQ ID NO:1-5, SEQ ID NO:90-93, SEQ ID NO:109-110, SEQ ID NO: 118-134.

5 Antibodies according to the present invention include antibodies that bind PGDH and have a VL region that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the VL region amino acid sequence of
ATL_0006026, ATL_0006027, ATL_0006074, ATL_0006075, ATL_0006058, ATL_0007925,
ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956, ATL_0007450,
ATL_0007819, ATL_0007820, ATL_0007821, ATL_0007822, ATL_0007823, ATL_0007824,
10 ATL_0007825, ATL_0007826, ATL_0007827, ATL_0007829, ATL_0007889, ATL_0007890,
ATL_0007892, ATL_0007893, ATL_0007895, ATL_0007896, ATL_0007899, ATL_0007900,
ATL_0007901, ATL_0007902, ATL_0007917, ATL_0007918, ATL_0007919, ATL_0007920,
ATL_0007921, ATL_0007922, ATL_0007923, ATL_0007924, for example ATL_0006026, ATL_0006058
ATL_0007925, ATL_0007952, ATL_0007953, ATL_0007955, ATL_0007933, ATL_0007956.

15 An antibody according to the disclosure may have a light chain variable domain (VL) comprising a sequence that has a least 95% sequence identity with the sequence of one or more of SEQ ID NO: 6-10, SEQ ID NO: 94, SEQ ID NO:111, SEQ ID NO: 135-152.

An antibody according to the present disclosure may comprise:

- 20 (a) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 1 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 6; or
- 25 (b) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 2 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 7; or
- 30 (c) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 3 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 8; or
- 35 (d) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 4 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 9; or
- (e) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 5 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 10;
- 40 (f) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 90 and a light

- chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (g) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 91 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (h) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 92 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (i) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 93 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 94; or
- (j) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 109 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 111; or
- (k) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 110 and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 111.

The antibodies of the disclosure are derived from human antibodies and may therefore be referred to as human antibodies. Antibodies of the disclosure were obtained by pairing the VH and VL of a human VH domain with a human VL domain library, or through serum proteomics followed by native VH-VL pairing. Thus, antibodies of the disclosure may differ from naturally occurring antibodies at least by their VH-VL pairing. Antibodies of the disclosure may comprise human VH and/or VL sequences. Antibodies of the disclosure may be formulated as human IgG1 antibodies or variants thereof, such as e.g. LALA IgG1. Antibodies of the disclosure may have a human framework sequence and/or a human Fc domain.

Antibodies of the disclosure may have a lambda (λ) (e.g. that of SEQ ID NO: 88) or kappa (κ) (e.g. that of SEQ ID NO: 89) light chain.

Overall percentage identity of a variable region or full-length heavy/light chain sequence may be combined with specific CDR sequences from the same antibody. Percentage (%) sequence identity is defined as the percentage of amino acid residues in a candidate sequence that are identical with residues in a comparative sequence after aligning the sequences and introducing gaps if necessary, to achieve the maximum sequence identity, and not considering any conservative substitutions as part of the sequence identity. Sequence identity is preferably calculated over the entire length of the respective sequences. Where the aligned sequences are of different length, sequence identity of the shorter comparison sequence may be determined over the entire length of the longer given sequence or, where the comparison sequence is longer than the given sequence, sequence identity of the comparison sequence may be determined over

the entire length of the shorter given sequence. Sequence identity may be defined with reference to the algorithm GAP (Wisconsin GCG package, Accelrys Inc, San Diego USA).

Also described herein are single domain antibodies (sdAbs), otherwise known as nanobodies, comprising the heavy chain CDRs and/or the VH sequence of any antibody described herein. Isolated nucleic acids
5 encoding an antibody, antigen binding fragment, or polypeptide as described herein are provided. Also provided is a vector comprising a nucleic acid described herein, and a host cell comprising the vector. For example, the host cell may be a eukaryotic, or mammalian, e.g. Chinese Hamster Ovary (CHO), cell or may be a prokaryotic cell, e.g. *E. coli*. In some embodiments, the vector is a viral vector, for example a bacteriophage. Further provided are methods for making an antibody, or antibody fragment as described
10 herein, the method comprising culturing a host cell as described herein under conditions suitable for the expression of a vector encoding the antibody, or antibody fragment, and isolating and/or purifying the antibody, or antibody fragment. The method further comprises formulating the antibody or antibody fragment into a composition including at least an additional component.

Therapeutic uses and in vitro and in vivo effects

15 Antibodies described herein may inhibit 15-PGDH thereby altering, such as restoring and/or increasing, circulating PGE2 levels. Antibodies described herein may alter PGE2 levels in an *in vitro* cell culture. Antibodies described herein may increase levels of circulating PGE2. Antibodies described herein may increase the half-life of circulating PGE2 *in vivo*. In turn, this increases PGE2-induced signaling pathways implicated in PD, including neuroinflammation, mitochondrial function, oxidative stress, striatal projection
20 neuron activity and/or apoptosis through both EP-receptor and/or non-receptor mediated mechanisms, e.g. via organic anion transporting polypeptides as described in Roth et al., 2012. Accordingly, antibodies described herein may be useful in the treatment of Parkinson's disease.

The antibodies described herein are expected to act on the central nervous system indirectly through modulation of extracellular (also referred to as "circulating") PGE2, which, due to its low molecular weight
25 is able to cross the blood-brain barrier (Delvi et al., 2015). For example, inhibition of 15-PGDH may increase the availability and/or half-life of PGE2, thus resulting in more PGE2 crossing the blood-brain barrier. The half-life of PGE2 in human circulation has been reported to be extremely short, less than 30 seconds. Any increase in half-life of PGE2 in circulation may therefore have a significant effect. Further, as PGE2 and its precursors have been shown to be increased in the brain after peripheral delivery (Dalvi et al. 2015),
30 increasing the availability and/or half-life of PGE2 in the periphery is expected to have an effect on brain levels.

Antibodies described herein may reduce inflammation, such as neuroinflammation. This may be tested in an *in vitro* cell culture, for example using iPSC-derived neuronal cells, e.g. iPSC-derived dopaminergic neurons; and/or astrocytes, and/or microglia as described herein. Inflammation may be measured, for
35 example, by measuring the levels of pro-inflammatory cytokines, such as IL-6, present in the cell culture IL-6. The levels of IL-6 (and other pro-inflammatory cytokines) may be measured by ELISA, wherein a decrease in IL-6 is indicative of reduced inflammation.

Antibodies described herein may reduce the abundance of phospho- α Syn129 in cells pre-treated with α Synuclein fibrils, compared to a control condition. This may be tested in an *in vitro* cell culture, for example using iPSC-derived neuronal cells, e.g. iPSC-derived dopaminergic neurons; and/or astrocytes, and/or microglia as described herein. Antibodies described herein may restore or at least partially restore mitochondrial function after mitochondrial dysfunction induced by exposure of cells to α Synuclein fibrils. This may be tested in an *in vitro* cell culture, for example using iPSC-derived neuronal cells, e.g. iPSC-derived dopaminergic neurons; and/or astrocytes, and/or microglia as described herein. Mitochondrial function may be tested using a decrease of mitochondrial membrane potential as an indicator of mitochondrial dysfunction. Thus, an antibody described herein may at least partially rescue mitochondrial membrane depolarization induced by exposure to α Synuclein fibrils.

Antibodies described herein may alter microglial inflammatory state. For example, the antibody may alter, for example reduce, the inflammatory state of microglia *in vitro*. This may be tested by determining expression of the activation marker CD68 on the surface of microglia, for example by flow cytometry. Suitable models include a dopaminergic neurons, astrocytes and microglia triculture as described herein.

Antibodies described herein may reduce neuroinflammation *in vivo*. Antibodies described herein may reduce the levels of one or more inflammatory markers in mouse model (e.g. a C57BL/6 mouse) of neuroinflammation induced by lipopolysaccharide (LPS) (e.g. LPS exposure via intraperitoneal (i.p.) injection). This may be measured by treating an animal with an antibody and measuring levels of one or more inflammatory markers in the brain and/or plasma of the animal after exposure to LPS. The one or more inflammatory markers may be selected from: interleukin- 1β (IL- 1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α).

Antibodies described herein may improve one or more metrics of gait and/or postural stability in a model animal, compared to a control. Antibodies of the present disclosure may improve movement and/or postural stability in a model animal. Movement and/or postural stability may be determined using one or more metrics selected from: speed, hind stance time, diagonal interlimb coordination, double support, maximum knee angle, and peak hind leg swing speed. The animal model may be an aged animal, such as e.g. a 22-month old mouse. Effects on movement and/or posture can be determined using the methods described in examples of the present disclosure.

The antibodies and fragments thereof may find use in therapy.

A subject to be treated or diagnosed may be any animal or human. The subject is preferably mammalian, more preferably human. The subject may be male or female. The subject may be a patient. Therapeutic uses may be in human or animals (veterinary use). Unless, specified otherwise, the subject is a human

Medicaments and pharmaceutical compositions according to aspects of the present invention may be formulated for administration by a number of routes, including but not limited to, parenteral, intravenous, intra-arterial, intramuscular, oral and nasal. The medicaments and compositions may be formulated for injection.

Pharmaceutical compositions may be prepared using a pharmaceutically acceptable "carrier" composed of materials that are considered safe and effective. "Pharmaceutically acceptable" refers to molecular entities

and compositions that are "generally regarded as safe", e.g., that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In some embodiments, this term refers to molecular entities and compositions approved by a regulatory agency of the US federal or a state government, as the GRAS list under section 5204(s) and 409 of the Federal Food, Drug and Cosmetic Act, that is subject to premarket review and approval by the FDA or similar lists, the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to diluents, binders, lubricants and disintegrants. Those with skill in the art are familiar with such pharmaceutical carriers and methods of compounding pharmaceutical compositions using such carriers.

- 10 The pharmaceutical compositions provided herein may include one or more excipients, e.g., solvents, solubility enhancers, suspending agents, buffering agents, isotonicity agents, antioxidants or antimicrobial preservatives. When used, the excipients of the compositions will not adversely affect the stability, bioavailability, safety, and/or efficacy of the active ingredients, i.e. the anti-PGDH antibodies used in the composition. Thus, the skilled person will appreciate that compositions are provided wherein there is no incompatibility between any of the components of the dosage form. Excipients may be selected from the group consisting of buffering agents, solubilizing agents, tonicity agents, chelating agents, antioxidants, antimicrobial agents, and preservatives.

Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

Antibodies according to the present disclosure may find uses in a variety of medical contexts. Thus, antibodies according to the present disclosure may be used as a medicament, and may be used in the fabrication of a medicament comprising an antibody of the disclosure. Antibodies of the present disclosure may be used in a method of treatment of a disease or disorder, the method comprising administering to a subject an effective amount of an antibody according to the disclosure. Thus, also described herein are antibodies according to the disclosure, for use in a method of treating a subject.

Pathological aggregation of α -Syn in the form of Lewy bodies and Lewy neurites is a common feature of Parkinson's Disease (PD) and other synucleinopathies, or synuclein-mediated neurodegenerative diseases, such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) (Goedert et al., 2017), as well Alzheimer's disease (AD), and chronic traumatic encephalopathy (CTE).

Accordingly, the subject may be a subject who has been diagnosed as having or being at risk of a synuclein-mediated neurodegenerative disease. The synuclein-mediated neurodegenerative disease may be PD. Subjects deemed at risk of developing PD may be subjects having REM Sleep Behaviour Disorder (RBD).

Antibodies of the disclosure have been shown to be able to reduce effects of aging on neurodegeneration, and specifically gait and postural stability. Thus, the subject may be an older subject, such as e.g. a subject over the age of 60, 70, or 80 years old. The subject may be a subject who has been diagnosed as having one or more symptoms of neurodegeneration and/or neuromuscular degeneration. The symptoms of neurodegeneration and/or neuromuscular degeneration may be associated with normal ageing or with a neurodegenerative condition. The subject may be a subject who has been diagnosed as having a neuroinflammation, or a neurodegenerative condition associated with neuroinflammation, for example Parkinson's Disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Alzheimer's Disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS). Thus, also described herein is the use of antibodies of the disclosure in the treatment of neurological symptoms associated with aging and/or neurodegeneration and/or neuroinflammation.

PGDH-15 has been reported to play a role in the development of inflammation (Sun et al., 2021). Accordingly, the subject may be a subject who has been diagnosed as having or being at risk of an inflammatory disease such as rheumatoid arthritis, skin inflammation such as spontaneous atopic dermatitis and hidradenitis suppurativa, and lung inflammation, such as chronic obstructive pulmonary disease, acute lung injury and acute respiratory distress syndrome (ALI/ARDS), and bronchiolitis obliterans. The antibodies of the disclosure may be used in therapy with further therapeutic agents. As used herein, a "further therapeutic agent" is an additional compound, protein, vector, antibody, cell or entity with a therapeutic effect. The antibodies may be co-administered with a further therapeutic agent. The antibodies may be co-formulated with a further therapeutic agent. The antibodies may be sequentially administered before or after a further therapeutic agent.

The present disclosure also provides methods of treatment of a subject who has been diagnosed as having or being at risk of a synuclein-mediated neurodegenerative disease, the methods comprising administering to the subject a therapeutically effective amount of an antibody that binds to and inhibits PGDH. The antibody may be for example an antibody as described herein.

Some methods of the present disclosure involve a sample containing cells. The sample may be a culture of cells grown *in vitro*. For example, the culture may comprise a suspension of cells or cells cultured in a culture plate or dish.

Methods according to the present disclosure may be performed, or products may be present, *in vitro*, *ex vivo*, or *in vivo*. The term "*in vitro*" is intended to encompass experiments with materials, biological substances, cells and/or tissues in laboratory conditions or in culture whereas the term "*in vivo*" is intended to encompass experiments and procedures with intact multi-cellular organisms. "*Ex vivo*" refers to something present or taking place outside an organism, e.g. outside the human or animal body, which may be on tissue (e.g. whole organs) or cells taken from the organism.

The features disclosed in the foregoing description, or in the following claims, or in the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for obtaining the disclosed results, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

While the invention has been described in conjunction with the exemplary embodiments described above, many equivalent modifications and variations will be apparent to those skilled in the art when given this disclosure. Accordingly, the exemplary embodiments of the invention set forth above are considered to be illustrative and not limiting. Various changes to the described embodiments may be made without departing from the spirit and scope of the invention.

For the avoidance of any doubt, any theoretical explanations provided herein are provided for the purposes of improving the understanding of a reader. The inventors do not wish to be bound by any of these theoretical explanations.

Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise” and “include”, and variations such as “comprises”, “comprising”, and “including” 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.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment. The term “about” in relation to a numerical value is optional and means for example +/- 10%.

Sequences

SEQ ID NO	Description	Sequence
1	ATL_0006026 VH	QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTMTVSS
2	ATL_0006027 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVR QAPGQGLEWMGGIPIFGTANYAQKFQGRVTITADKSTST AYMELSSLRSEDTAVYYCARGVSSGWSPDAFDIWGQGT MTVSS
3	ATL_0006058 VH ATL_0007469 VH	QVQLQESGPGLVKPSSETLSLTCTVSGDSITSYFWAWIRQ PAGKRLEWIGRVYASGSTSYNPSLKSRTMSVDTSKKQF SLKLTSVTAADTAVYYCARDLFFGSGSHFDPWGQGMLVT VSS

4	ATL_0006074 VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIR QPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQF SLKLSSVTAADTAVYYCARRRLLWFGGETGFDYWGQG TLVTVSS
5	ATL_0006075 VH	QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWI RQHPGKGLEWIGYIYYSGSTYYPNPSLKSRTISVDTSKNQ FSLKLSSVTAADTAVYYCASGTLGYCSSTSCYSDAFDIW GQGTTVTVSS
6	ATL_0006026 VL ATL_0007450 VL ATL_0007819 VL ATL_0007820 VL ATL_0007821 VL ATL_0007822 VL ATL_0007823 VL ATL_0007824 VL ATL_0007825 VL ATL_0007826 VL ATL_0007827 VL ATL_0007829 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVDPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
7	ATL_0006027 VL	SSELTQDPAVSVALGQTVGIRCQGDLSRSSYANWYQK PGQAPKLVIIYGKNKRPSGIPDRFSGSTSGNTASLSITGAL ADDEADYYCQSRDTSGAQILFGGGTKVTVL
8	ATL_0006058 VL ATL_0007468 VL	EIVLTQSPGTLSSLSPGERATLSCRASQSVTSSYLAWYQQ KPGQPPRRLIYGTSSRATGIPGRFSGSGSGTDFTLSISRL EPEDFAVYYCQYQGSSPPTFGQGTRLEIK
9	ATL_0006074 VL	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQ HHPGKAPKLMIDVSNRPSGVSNRFSGSKSGNTASLTIS GLQAEDEADYYCSSYTSSSLRVFGGGTKLTVL
10	ATL_0006075 VL	QSALTQPASVSGSPGQSITLSCTGTSSDIGVQTYVSWYQ HHPGKAPRLIFSEVGNRPSGVSTRFSASKSGNTASLTISG LQTEDEALYYCSSYINTNPVLFGGGTKLTVL
11	HCDR1_ATL_0006026; HCDR1_ATL_0007925; HCDR1_ATL_0007952; HCDR1_ATL_0007953; HCDR1_ATL_0007955 HCDR1_ATL_0007450 HCDR1_ATL_0007819 HCDR1_ATL_0007820 HCDR1_ATL_0007821	GYTFTSYG

	HCDR1_ATL_0007822 HCDR1_ATL_0007823 HCDR1_ATL_0007824 HCDR1_ATL_0007825 HCDR1_ATL_0007826 HCDR1_ATL_0007827 HCDR1_ATL_0007829 HCDR1_ATL_0007889 HCDR1_ATL_0007890 HCDR1_ATL_0007892 HCDR1_ATL_0007893 HCDR1_ATL_0007895 HCDR1_ATL_0007896 HCDR1_ATL_0007899 HCDR1_ATL_0007900 HCDR1_ATL_0007901 HCDR1_ATL_0007902 HCDR1_ATL_0007917 HCDR1_ATL_0007918 HCDR1_ATL_0007919 HCDR1_ATL_0007920 HCDR1_ATL_0007921 HCDR1_ATL_0007922 HCDR1_ATL_0007923 HCDR1_ATL_0007924	
12	HCDR1_ATL_0006027	GGTFSSYA
13	HCDR1_ATL_0006058 HCDR1_ATL_0007467 HCDR1_ATL_0007468 HCDR1_ATL_0007469 HCDR1_ATL_0007472 HCDR1_ATL_0007473	GDSITSYF
14	HCDR1_ATL_0006074	GGSFSGYY
15	HCDR1_ATL_0006075	GGSISSGGYY
16	HCDR2_ATL_0006026; HCDR2_ATL_0007925 HCDR2_ATL_0007450 HCDR2_ATL_0007819 HCDR2_ATL_0007824 HCDR2_ATL_0007825 HCDR2_ATL_0007826	ISAYNGNT

	HCDR2_ATL_0007827 HCDR2_ATL_0007829 HCDR2_ATL_0007889 HCDR2_ATL_0007890 HCDR2_ATL_0007892 HCDR2_ATL_0007893 HCDR2_ATL_0007895 HCDR2_ATL_0007896 HCDR2_ATL_0007899 HCDR2_ATL_0007900 HCDR2_ATL_0007901 HCDR2_ATL_0007902 HCDR2_ATL_0007919 HCDR2_ATL_0007920 HCDR2_ATL_0007923	
17	HCDR2_ATL_0006027	IPIFGTA
18	HCDR2_ATL_0006058 HCDR2_ATL_0007933 HCDR2_ATL_0007956 HCDR2_ATL_0007467 HCDR2_ATL_0007468 HCDR2_ATL_0007469 HCDR2_ATL_0007470 HCDR2_ATL_0007471 HCDR2_ATL_0007472 HCDR2_ATL_0007473 HCDR2_ATL_0007926 HCDR2_ATL_0007927 HCDR2_ATL_0007928 HCDR2_ATL_0007929 HCDR2_ATL_0007930 HCDR2_ATL_0007931 HCDR2_ATL_0007932	VYASGST
19	HCDR2_ATL_0006074	INHSGST
20	HCDR2_ATL_0006075	IYYSGST
21	HCDR3_ATL_0006026; HCDR3_ATL_0007925 HCDR3_ATL_0007450 HCDR3_ATL_0007819 HCDR3_ATL_0007820 HCDR3_ATL_0007821	ARDLGPYYDSSGYYGFDI

	HCDR3_ATL_0007822 HCDR3_ATL_0007823 HCDR3_ATL_0007824 HCDR3_ATL_0007825 HCDR3_ATL_0007826 HCDR3_ATL_0007827 HCDR3_ATL_0007889 HCDR3_ATL_0007890 HCDR3_ATL_0007892 HCDR3_ATL_0007893 HCDR3_ATL_0007895 HCDR3_ATL_0007896 HCDR3_ATL_0007899 HCDR3_ATL_0007900 HCDR3_ATL_0007901 HCDR3_ATL_0007902 HCDR3_ATL_0007918 HCDR3_ATL_0007919 HCDR3_ATL_0007921 HCDR3_ATL_0007924	
22	HCDR3_ATL_0006027	ARGVSSGWSPDAFDI
23	HCDR3_ATL_0006058 HCDR3_ATL_0007933 HCDR3_ATL_0007956 HCDR3_ATL_0007467 HCDR3_ATL_0007468 HCDR3_ATL_0007469 HCDR3_ATL_0007470 HCDR3_ATL_0007471 HCDR3_ATL_0007472 HCDR3_ATL_0007473 HCDR3_ATL_0007926 HCDR3_ATL_0007927 HCDR3_ATL_0007928 HCDR3_ATL_0007929 HCDR3_ATL_0007930 HCDR3_ATL_0007931 HCDR3_ATL_0007932	ARDLFFGSGSHFDP
24	HCDR3_ATL_0006074	ARRRLLLWFGGETGFDY
25	HCDR3_ATL_0006075	ASGTLGYCSSTSCYSDAFDI
26	LCDR1_ATL_0006026	SSNIGAGYD

	LCDR1_ATL_0007925 LCDR1_ATL_0007952 LCDR1_ATL_0007953 LCDR1_ATL_0007955 LCDR1_ATL_0007450 LCDR1_ATL_0007819 LCDR1_ATL_0007820 LCDR1_ATL_0007821 LCDR1_ATL_0007822 LCDR1_ATL_0007823 LCDR1_ATL_0007824 LCDR1_ATL_0007825 LCDR1_ATL_0007826 LCDR1_ATL_0007827 LCDR1_ATL_0007829 LCDR1_ATL_0007889 LCDR1_ATL_0007890 LCDR1_ATL_0007892 LCDR1_ATL_0007893 LCDR1_ATL_0007895 LCDR1_ATL_0007896 LCDR1_ATL_0007899 LCDR1_ATL_0007900 LCDR1_ATL_0007901 LCDR1_ATL_0007902 LCDR1_ATL_0007917 LCDR1_ATL_0007918 LCDR1_ATL_0007919 LCDR1_ATL_0007920 LCDR1_ATL_0007921 LCDR1_ATL_0007922 LCDR1_ATL_0007923 LCDR1_ATL_0007924	
27	LCDR1_ATL_0006027	SLRSSY
28	LCDR1_ATL_0006058 LCDR1_ATL_0007933 LCDR1_ATL_0007956 LCDR1_ATL_0007467 LCDR1_ATL_0007468 LCDR1_ATL_0007469 LCDR1_ATL_0007470 LCDR1_ATL_0007471	QSVTSSY

	LCDR1_ATL_0007472 LCDR1_ATL_0007473 LCDR1_ATL_0007926 LCDR1_ATL_0007927 LCDR1_ATL_0007928 LCDR1_ATL_0007929 LCDR1_ATL_0007930 LCDR1_ATL_0007931 LCDR1_ATL_0007932	
29	LCDR1_ATL_0006074	SSDVGGYNY
30	LCDR1_ATL_0006075	SSDIGVQTY
31	LCDR2_ATL_0006026 LCDR2_ATL_0007450 LCDR2_ATL_0007819 LCDR2_ATL_0007820 LCDR2_ATL_0007821 LCDR2_ATL_0007822 LCDR2_ATL_0007823 LCDR2_ATL_0007824 LCDR2_ATL_0007825 LCDR2_ATL_0007826 LCDR2_ATL_0007827 LCDR2_ATL_0007829 LCDR2_ATL_0007889 LCDR2_ATL_0007890 LCDR2_ATL_0007892 LCDR2_ATL_0007893 LCDR2_ATL_0007895 LCDR2_ATL_0007896 LCDR2_ATL_0007901 LCDR2_ATL_0007902 LCDR2_ATL_0007920	GNS
32	LCDR2_ATL_0006027	GKN
33	LCDR2_ATL_0006058 LCDR2_ATL_0007933 LCDR2_ATL_0007956 LCDR2_ATL_0007467 LCDR2_ATL_0007468 LCDR2_ATL_0007469 LCDR2_ATL_0007470 LCDR2_ATL_0007471	GTS

	LCDR2_ATL_0007472 LCDR2_ATL_0007473 LCDR2_ATL_0007926 LCDR2_ATL_0007927 LCDR2_ATL_0007928 LCDR2_ATL_0007929 LCDR2_ATL_0007930 LCDR2_ATL_0007931 LCDR2_ATL_0007932	
34	LCDR2_ATL_0006074	DVS
35	LCDR2_ATL_0006075	EVG
36	LCDR3_ATL_0006026 LCDR3_ATL_0007450 LCDR3_ATL_0007819 LCDR3_ATL_0007820 LCDR3_ATL_0007821 LCDR3_ATL_0007822 LCDR3_ATL_0007823 LCDR3_ATL_0007824 LCDR3_ATL_0007825 LCDR3_ATL_0007826 LCDR3_ATL_0007827 LCDR3_ATL_0007829 LCDR3_ATL_0007889 LCDR3_ATL_0007890 LCDR3_ATL_0007892 LCDR3_ATL_0007893 LCDR3_ATL_0007895 LCDR3_ATL_0007896 LCDR3_ATL_0007899 LCDR3_ATL_0007900 LCDR3_ATL_0007918	QSYDNSLSVA
37	LCDR3_ATL_0006027	QSRDTSGAQIL
38	LCDR3_ATL_0006058 LCDR3_ATL_0007933 LCDR3_ATL_0007956 LCDR3_ATL_0007467 LCDR3_ATL_0007468 LCDR3_ATL_0007469 LCDR3_ATL_0007470 LCDR3_ATL_0007471	QQYGSSPPT

	LCDR3_ATL_0007472 LCDR3_ATL_0007473 LCDR3_ATL_0007926 LCDR3_ATL_0007927 LCDR3_ATL_0007928 LCDR3_ATL_0007929 LCDR3_ATL_0007930 LCDR3_ATL_0007931 LCDR3_ATL_0007932	
39	LCDR3_ATL_0006074	SSYTSSSLRV
40	LCDR3_ATL_0006075	SSYINTNTPVL
41	HFWR1_ATL_0006026	QVQLQQSGAEVKKPGASVKVSCKAS
42	HFWR2_ATL_0006026 HFWR2_ATL_0007925 HFWR2_ATL_0007952 HFWR2_ATL_0007953 HFWR2_ATL_0007955 HFWR2_ATL_0007450 HFWR2_ATL_0007820 HFWR2_ATL_0007821 HFWR2_ATL_0007822 HFWR2_ATL_0007823 HFWR2_ATL_0007824 HFWR2_ATL_0007825 HFWR2_ATL_0007826 HFWR2_ATL_0007827 HFWR2_ATL_0007829 HFWR2_ATL_0007889 HFWR2_ATL_0007890 HFWR2_ATL_0007892 HFWR2_ATL_0007893 HFWR2_ATL_0007895 HFWR2_ATL_0007896 HFWR2_ATL_0007899 HFWR2_ATL_0007900 HFWR2_ATL_0007901 HFWR2_ATL_0007902 HFWR2_ATL_0007917 HFWR2_ATL_0007918 HFWR2_ATL_0007919 HFWR2_ATL_0007920	ISWVRQAPGQGLEWMGW

	HFWR2_ATL_0007921 HFWR2_ATL_0007922 HFWR2_ATL_0007923 HFWR2_ATL_0007924	
43	HFWR3_ATL_0006026 HFWR3_ATL_0007450 HFWR3_ATL_0007819 HFWR3_ATL_0007820 HFWR3_ATL_0007821 HFWR3_ATL_0007822 HFWR3_ATL_0007823 HFWR3_ATL_0007829 HFWR3_ATL_0007889 HFWR3_ATL_0007890 HFWR3_ATL_0007892 HFWR3_ATL_0007893 HFWR3_ATL_0007895 HFWR3_ATL_0007896 HFWR3_ATL_0007899 HFWR3_ATL_0007900 HFWR3_ATL_0007901 HFWR3_ATL_0007902 HFWR3_ATL_0007922	NYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
44	HFWR4_ATL_0006026	WGQGTMTVSS
45	LFWR1_ATL_0006026 LFWR1_ATL_0007450 LFWR1_ATL_0007819 LFWR1_ATL_0007820 LFWR1_ATL_0007821 LFWR1_ATL_0007822 LFWR1_ATL_0007823 LFWR1_ATL_0007824 LFWR1_ATL_0007825 LFWR1_ATL_0007826 LFWR1_ATL_0007827 LFWR1_ATL_0007829 LFWR1_ATL_0007892 LFWR1_ATL_0007893 LFWR1_ATL_0007899 LFWR1_ATL_0007900 LFWR1_ATL_0007901	QAVLTQPSSVSGAPGQRTISCTGS

	LFWR1_ATL_0007902 LFWR1_ATL_0007917	
46	LFWR2_ATL_0006026 LFWR2_ATL_0007925 LFWR2_ATL_0007952 LFWR2_ATL_0007953 LFWR2_ATL_0007955 LFWR2_ATL_0007450 LFWR2_ATL_0007819 LFWR2_ATL_0007820 LFWR2_ATL_0007821 LFWR2_ATL_0007822 LFWR2_ATL_0007823 LFWR2_ATL_0007824 LFWR2_ATL_0007825 LFWR2_ATL_0007826 LFWR2_ATL_0007827 LFWR2_ATL_0007829 LFWR2_ATL_0007889 LFWR2_ATL_0007890 LFWR2_ATL_0007892 LFWR2_ATL_0007893 LFWR2_ATL_0007896 LFWR2_ATL_0007899 LFWR2_ATL_0007900 LFWR2_ATL_0007901 LFWR2_ATL_0007902 LFWR2_ATL_0007920	VHWYQQLPGTAPKPLIY
47	LFWR3_ATL_0006026 LFWR3_ATL_0007450 LFWR3_ATL_0007819 LFWR3_ATL_0007820 LFWR3_ATL_0007821 LFWR3_ATL_0007822 LFWR3_ATL_0007823 LFWR3_ATL_0007824 LFWR3_ATL_0007825 LFWR3_ATL_0007826 LFWR3_ATL_0007827 LFWR3_ATL_0007829 LFWR3_ATL_0007889 LFWR3_ATL_0007890	NRPSGVPDRFSGSKSGTSASLVITGLQAEDEADYYC

	LFWR3_ATL_0007893 LFWR3_ATL_0007899 LFWR3_ATL_0007900 LFWR3_ATL_0007901 LFWR3_ATL_0007902 LFWR3_ATL_0007921	
48	LFWR4_ATL_0006026 LFWR4_ATL_0007450 LFWR4_ATL_0007819 LFWR4_ATL_0007820 LFWR4_ATL_0007821 LFWR4_ATL_0007822 LFWR4_ATL_0007823 LFWR4_ATL_0007824 LFWR4_ATL_0007825 LFWR4_ATL_0007826 LFWR4_ATL_0007827 LFWR4_ATL_0007829 LFWR4_ATL_0007889 LFWR4_ATL_0007890 LFWR4_ATL_0007892 LFWR4_ATL_0007899 LFWR4_ATL_0007900 LFWR4_ATL_0007901 LFWR4_ATL_0007902 LFWR4_ATL_0007922	FGGGTKVTVL
49	HFWR1_ATL_0006027	QVQLVQSGAEVKKPGSSVKVCKAS
50	HFWR2_ATL_0006027	ISWVRQAPGQGLEWMGG
51	HFWR3_ATL_0006027	NYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC
52	HFWR4_ATL_0006027	WGQGTMTVSS
53	LFWR1_ATL_0006027	SSELTQDPAVSVALGQTVGIRCGD
54	LFWR2_ATL_0006027	ANWYQQKPGQAPKLVII
55	LFWR3_ATL_0006027	KRPSGIPDRFSGSTSGNTASLSITGALADDEADYYC
56	LFWR4_ATL_0006027	FGGGTKVTVL
57	HFWR1_ATL_0006058 HFWR1_ATL_0007933 HFWR1_ATL_0007956 HFWR1_ATL_0007467 HFWR1_ATL_0007468 HFWR1_ATL_0007469	QVQLQESGPGLVKPSETLSLTCTVS

	HFWR1_ATL_0007470 HFWR1_ATL_0007471 HFWR1_ATL_0007472 HFWR1_ATL_0007473 HFWR1_ATL_0007926 HFWR1_ATL_0007927 HFWR1_ATL_0007928 HFWR1_ATL_0007929 HFWR1_ATL_0007930 HFWR1_ATL_0007931 HFWR1_ATL_0007932	
58	HFWR2_ATL_0006058 HFWR2_ATL_0007469 HFWR2_ATL_0007927	WAWIRQPAGKRLEWIGR
59	HFWR3_ATL_0006058 HFWR3_ATL_0007469	SYNPSLKSrvTMSVDTSKKQFSLKLTsvTAADTAVYYC
60	HFWR4_ATL_0006058 HFWR4_ATL_0007933 HFWR4_ATL_0007469 HFWR4_ATL_0007927	WGQGMLVTVSS
61	LFWR1_ATL_0006058 LFWR1_ATL_0007933 LFWR1_ATL_0007956 LFWR1_ATL_0007467 LFWR1_ATL_0007468 LFWR1_ATL_0007469 LFWR1_ATL_0007470 LFWR1_ATL_0007471 LFWR1_ATL_0007472 LFWR1_ATL_0007473 LFWR1_ATL_0007926 LFWR1_ATL_0007927 LFWR1_ATL_0007928 LFWR1_ATL_0007929 LFWR1_ATL_0007930 LFWR1_ATL_0007931 LFWR1_ATL_0007932	EIVLTQSPGTLsLSPGERATLSCRAS
62	LFWR2_ATL_0006058 LFWR2_ATL_0007468	LAWYQQKPGQPPRRLIY
63	LFWR3_ATL_0006058 LFWR3_ATL_0007468	SRATGIPGRFSGSGSGTDFTLsISRLEPEDFAVYYC

64	LFWR4_ATL_0006058	FGQGTRLEIK
	LFWR4_ATL_0007933	
	LFWR4_ATL_0007956	
	LFWR4_ATL_0007467	
	LFWR4_ATL_0007468	
	LFWR4_ATL_0007469	
	LFWR4_ATL_0007470	
	LFWR4_ATL_0007471	
	LFWR4_ATL_0007472	
	LFWR4_ATL_0007473	
	LFWR4_ATL_0007926	
	LFWR4_ATL_0007927	
	LFWR4_ATL_0007928	
	LFWR4_ATL_0007929	
	LFWR4_ATL_0007930	
	LFWR4_ATL_0007931	
	LFWR4_ATL_0007932	
65	HFWR1_ATL_0006074	QVQLQQWGAGLLKPSETLSLTCVY
66	HFWR2_ATL_0006074	WSWIRQPPGKGLEWIGE
67	HFWR3_ATL_0006074	NYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYC
	HFWR3_ATL_0007472	
68	HFWR4_ATL_0006074	WGQGTLTVSS
69	LFWR1_ATL_0006074	QSALTQPASVSGSPGQSITISCTGT
70	LFWR2_ATL_0006074	VSWYQHHPGKAPKLMIY
71	LFWR3_ATL_0006074	NRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYC
72	LFWR4_ATL_0006074	FGGGTKLTVL
	LFWR4_ATL_0007893	
	LFWR4_ATL_0007895	
	LFWR4_ATL_0007896	
	LFWR4_ATL_0007917	
	LFWR4_ATL_0007918	
	LFWR4_ATL_0007919	
	LFWR4_ATL_0007920	
	LFWR4_ATL_0007921	
	LFWR4_ATL_0007923	
	LFWR4_ATL_0007924	
73	HFWR1_ATL_0006075	QVQLQESGPGGLVKPSQTLSTCTVS
74	HFWR2_ATL_0006075	WSWIRQHHPGKGLEWIGY
75	HFWR3_ATL_0006075	YYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYC
76	HFWR4_ATL_0006075	WGQGTTTVTVSS

77	LFWR1_ATL_0006075	QSALTQPASVSGSPGQSITLSCTGT
78	LFWR2_ATL_0006075	VSWYQHHPGKAPRLIFS
79	LFWR3_ATL_0006075	NRPSGVSTRFSASKSGNTASLTISGLQTEDEALYYC
80	LFWR4_ATL_0006075	FGGGTKLTVL
81	Recombinant Human 15-PGDH (C-term Avi-His6)	MAHVMNGKVALVTGAAQGIGRAFAEALLLKGAQKVALVDW NLEAGVQCKAALDEQFEPQKTLFIQCDVADQQQLRDTFR KVVDHFGRLDILVNNAGVNNNEKNWEKTLQINLVSVISGTY LGLDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASK HGIVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEK EENMGQYIEYKDHIDMIKYYGILDPPLIANGITLIEDDAL NGAIMKITTSKGIHFQDYDTTPFQAKTQSLSGGGGSTPPT PSTPPTGLNDIFEAQKIEWHEHHHHHHH
82	Uniprot ID P15428 PGDH_HUMAN 15- hydroxyprostaglandin dehydrogenase [NAD(+)] OS=Homo sapiens	MHVNGKVALVTGAAQGIGRAFAEALLLKGAQKVALVDWNL EAGVQCKAALDEQFEPQKTLFIQCDVADQQQLRDTFRKV VDHFGRLDILVNNAGVNNNEKNWEKTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEKEE NMGQYIEYKDHIDMIKYYGILDPPLIANGITLIEDDALNG AIMKITTSKGIHFQDYDTTPFQAKTQ
83	rhPGDH - Recombinant Human 15-PGDH (C-term His6)	MHVNGKVALVTGAAQGIGRAFAEALLLKGAQKVALVDWNL EAGVQCKAALDEQFEPQKTLFIQCDVADQQQLRDTFRKV VDHFGRLDILVNNAGVNNNEKNWEKTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEKEE NMGQYIEYKDHIDMIKYYGILDPPLIANGITLIEDDALNG AIMKITTSKGIHFQDYDTTPFQAKTQHSHHHHHH
84	Uniprot ID Q8MJY8 PGDH_MACFA 15- hydroxyprostaglandin dehydrogenase [NAD(+)] OS= Macaca fascicularis	MHVNGKVALVTGAAQGIGRAFAEALLLKGAQKVALVDWNL EAGVQCKAALDEKFEQKTLFIQCDVADQQQLRDTFRKV VDHFGRLDILVNNAGVNNNEKNWEKTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEKEE NMGQYIEYKDHIDMIKYYGILDPPLIANGITLIEDDALNG AIMKITTSKGIHFQDYDATPFQAKSQ
85	Recombinant Mouse 15-PGDH (C-term His6) (Sino Biological, 50531-M08E)	MHVNGKVALVTGAAQGIGKAFEAALLLHGAKVALVDWNL EAGVKCKAALDEQFEPQKTLFVQCDVADQKQLRDTFRKV VDHFGRLDILVNNAGVNNNEKNWEQTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IIGFTRSAAMAANLMKSGVRLNVICPGFVDTPILESIEKEE NMGQYIEYKDQIKAMMKFYGVLPSTIANGLINLIEDDALN GAIMKITASKGIHFQDYDISPLLVKAPLTSHHHHHHHHHHH

86	Uniprot ID Q8VCC1 PGDH_MOUSE 15- hydroxyprostaglandin dehydrogenase [NAD(+)] OS=Mus musculus	MHVNGKVALVTGAAQGIGKAF AEALLLHGAKVALVDWNL EAGVKCKAALDEQFEPQKTLFVQCDVADQKQLRDTFRKV VDHFGRLDILVNNAGVNN EKNWEQTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IIGFTRSAAMAANLMKSGVRLNVICPGFVDTPILESIEKEE NMGQYIEYKDQIKAMMKFYGVLPSTIANGLINLIEDDALN GAIMKITASKGIHFQDYDISPLLVKAPLTS
87	Human heavy chain constant sequence for IgG1 LALA	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMH EALHNHYTQKSLSLSPGK
88	Human lambda light chain constant sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQ WKSHRYSQCQVTHEGSTVEKTVAPTECS
89	Human kappa light chain constant sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNFFYPREAKVQ WKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
90	ATL_0007925 VH ATL_0007919 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTETST STAYMELRSLRSDETAVYYCARDLGPYYDDSSGYYYGFD IWGQGTTVTVSS
91	ATL_0007952 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNTNYAQKLQGRVTMTTDTST TSTAYMELRSLRSDETAVYYCARDLGPYYDDASGYYYGF DIWGQGTTVTVSS
92	ATL_0007953 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNANYAQKLQGRVTMTTETS TSTAYMELRSLRSDETAVYYCARDLGPYYDDASGYYYGF DIWGQGTTVTVSS
93	ATL_0007955 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNANSNYAQKLQGRVTMTTDTST STAYMELRSLRSEDAVYYCARDLGPYYDDASGYYYGFD IWGQGTTVTVSS

94	ATL_0007925 VL ATL_0007952 VL ATL_0007953 VL ATL_0007955 VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNNNRPSGVPDFRSGSGSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKLTVL
95	HFWR1_ATL_0007925 HFWR1_ATL_0007952 HFWR1_ATL_0007953 HFWR1_ATL_0007955 HFWR1_ATL_0007450 HFWR1_ATL_0007819 HFWR1_ATL_0007820 HFWR1_ATL_0007821 HFWR1_ATL_0007822 HFWR1_ATL_0007823 HFWR1_ATL_0007824 HFWR1_ATL_0007825 HFWR1_ATL_0007826 HFWR1_ATL_0007827 HFWR1_ATL_0007829 HFWR1_ATL_0007889 HFWR1_ATL_0007890 HFWR1_ATL_0007892 HFWR1_ATL_0007893 HFWR1_ATL_0007895 HFWR1_ATL_0007896 HFWR1_ATL_0007899 HFWR1_ATL_0007900 HFWR1_ATL_0007901 HFWR1_ATL_0007902 HFWR1_ATL_0007917 HFWR1_ATL_0007918 HFWR1_ATL_0007919 HFWR1_ATL_0007920 HFWR1_ATL_0007921 HFWR1_ATL_0007922 HFWR1_ATL_0007923 HFWR1_ATL_0007924	QVQLVQSGAEVKKPGASVKVSCKAS
96	HCDR2_ATL_0007952 HCDR2_ATL_0007917 HCDR2_ATL_0007918 HCDR2_ATL_0007921 HCDR2_ATL_0007922	ISAYQGNT

	HCDR2_ATL_0007924	
97	HCDR2_ATL_0007953	ISAYQGNA
98	HCDR2_ATL_0007955	ISAYNANS
99	HFWR3_ATL_0007925 HFWR3_ATL_0007953 HFWR3_ATL_0007919	NYAQKLQGRVTMTTETSTSTAYMELRSLRSDAVYYC
100	HFWR3_ATL_0007952 HFWR3_ATL_0007917 HFWR3_ATL_0007920 HFWR3_ATL_0007921	NYAQKLQGRVTMTTDTSTSTAYMELRSLRSDAVYYC
101	HFWR3_ATL_0007955	NYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDAVYYC
102	HCDR3_ATL_0007952 HCDR3_ATL_0007953 HCDR3_ATL_0007955 HCDR3_ATL_0007829	ARDLGPIYYDASGYYYGFDI
103	HFWR4_ATL_0007925 HFWR4_ATL_0007952 HFWR4_ATL_0007953 HFWR4_ATL_0007955 HFWR4_ATL_0007450 HFWR4_ATL_0007819 HFWR4_ATL_0007820 HFWR4_ATL_0007821 HFWR4_ATL_0007822 HFWR4_ATL_0007823 HFWR4_ATL_0007824 HFWR4_ATL_0007825 HFWR4_ATL_0007826 HFWR4_ATL_0007827 HFWR4_ATL_0007829 HFWR4_ATL_0007889 HFWR4_ATL_0007890 HFWR4_ATL_0007892 HFWR4_ATL_0007893 HFWR4_ATL_0007895 HFWR4_ATL_0007896 HFWR4_ATL_0007899 HFWR4_ATL_0007900 HFWR4_ATL_0007901 HFWR4_ATL_0007902 HFWR4_ATL_0007917	WGQGTTVTVSS

	HFWR4_ATL_0007918 HFWR4_ATL_0007919 HFWR4_ATL_0007920 HFWR4_ATL_0007921 HFWR4_ATL_0007922 HFWR4_ATL_0007923 HFWR4_ATL_0007924	
104	LFWR1_ATL_0007925 LFWR1_ATL_0007952 LFWR1_ATL_0007953 LFWR1_ATL_0007955 LFWR1_ATL_0007896 LFWR1_ATL_0007920 LFWR1_ATL_0007921 LFWR1_ATL_0007922	QSVLTQPPSVSGAPGQRTISCTGS
105	LCDR2_ATL_0007925 LCDR2_ATL_0007952 LCDR2_ATL_0007953 LCDR2_ATL_0007955 LCDR2_ATL_0007900 LCDR2_ATL_0007919 LCDR2_ATL_0007923	GNN
106	LFWR3_ATL_0007925 LFWR3_ATL_0007952 LFWR3_ATL_0007953 LFWR3_ATL_0007955 LFWR3_ATL_0007892 LFWR3_ATL_0007895 LFWR3_ATL_0007896 LFWR3_ATL_0007917 LFWR3_ATL_0007918 LFWR3_ATL_0007919 LFWR3_ATL_0007920 LFWR3_ATL_0007922 LFWR3_ATL_0007923 LFWR3_ATL_0007924	NRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC
107	LCDR3_ATL_0007925 LCDR3_ATL_0007952 LCDR3_ATL_0007953 LCDR3_ATL_0007955 LCDR3_ATL_0007902	QSYDNNLSVA

	LCDR3_ATL_0007917 LCDR3_ATL_0007922 LCDR3_ATL_0007923 LCDR3_ATL_0007924	
108	LFWR4_ATL_0007925 LFWR4_ATL_0007952 LFWR4_ATL_0007953 LFWR4_ATL_0007955	FGGGTKLTVL
109	ATL_0007933 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRVTISVETSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGMVLV TVSS
110	ATL_0007956 VH ATL_0007926 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRVTISVETSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGLVT VSS
111	ATL_0007933 VL ATL_0007956 VL ATL_0007467 VL ATL_0007469 VL ATL_0007470 VL ATL_0007471 VL ATL_0007472 VL ATL_0007473 VL ATL_0007928 VL ATL_0007929 VL ATL_0007930 VL ATL_0007931 VL ATL_0007932 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVTSSYLAWYQQ KPGQAPRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLE PEDFAVYYCQQYGSSPPTFGQGTRLEIK
112	HCDR1_ATL_0007933 HCDR1_ATL_0007956 HCDR1_ATL_0007470 HCDR1_ATL_0007926 HCDR1_ATL_0007927 HCDR1_ATL_0007928 HCDR1_ATL_0007929 HCDR1_ATL_0007930 HCDR1_ATL_0007931 HCDR1_ATL_0007932	GESITSYF
113	HFWR2_ATL_0007933 HFWR2_ATL_0007956	WSWIRQPAGKGLEWIGR

	HFWR2_ATL_0007467 HFWR2_ATL_0007468 HFWR2_ATL_0007470 HFWR2_ATL_0007471 HFWR2_ATL_0007472 HFWR2_ATL_0007473 HFWR2_ATL_0007926 HFWR2_ATL_0007930 HFWR2_ATL_0007931 HFWR2_ATL_0007932	
114	HFWR3_ATL_0007933 HFWR3_ATL_0007956 HFWR3_ATL_0007926 HFWR3_ATL_0007928 HFWR3_ATL_0007929	NYNPSLKS RV TISVETS KNQFSLKLSSVTAADTAVYYC
115	HFWR4_ATL_0007956 HFWR4_ATL_0007467 HFWR4_ATL_0007468 HFWR4_ATL_0007470 HFWR4_ATL_0007471 HFWR4_ATL_0007472 HFWR4_ATL_0007473 HFWR4_ATL_0007926 HFWR4_ATL_0007928 HFWR4_ATL_0007929 HFWR4_ATL_0007930 HFWR4_ATL_0007931 HFWR4_ATL_0007932	WGQGTLVTVSS
116	LFWR2_ATL_0007933 LFWR2_ATL_0007956 LFWR2_ATL_0007467 LFWR2_ATL_0007469 LFWR2_ATL_0007470 LFWR2_ATL_0007471 LFWR2_ATL_0007472 LFWR2_ATL_0007473 LFWR2_ATL_0007928 LFWR2_ATL_0007929 LFWR2_ATL_0007930 LFWR2_ATL_0007931 LFWR2_ATL_0007932	LAWYQQKPGQAPRLLIY

117	LFWR3_ATL_0007933 LFWR3_ATL_0007956 LFWR3_ATL_0007467 LFWR3_ATL_0007469 LFWR3_ATL_0007470 LFWR3_ATL_0007471 LFWR3_ATL_0007472 LFWR3_ATL_0007473 LFWR3_ATL_0007926 LFWR3_ATL_0007927 LFWR3_ATL_0007928 LFWR3_ATL_0007929 LFWR3_ATL_0007930 LFWR3_ATL_0007931 LFWR3_ATL_0007932	SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
118	ATL_0007450 VH ATL_0007889 VH ATL_0007902 VH ATL_0007901 VH ATL_0007900 VH ATL_0007899 VH ATL_0007896 VH ATL_0007895 VH ATL_0007893 VH ATL_0007892 VH ATL_0007890 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTVTVSS
119	ATL_0007819 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWAGWISAYNGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTVTVSS
120	ATL_0007820 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYAGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTVTVSS
121	ATL_0007821 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNANTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTVTVSS
122	ATL_0007822 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGATNYAQKLQGRVTMTTDTST

		STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
123	ATL_0007823 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNANYAQKLQGRVTMTDTS TSTAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD DIWGQGTTTVSS
124	ATL_0007824 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTITDST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
125	ATL_0007825 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTETST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
126	ATL_0007826 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTDST STAYAELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
127	ATL_0007827 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTDST STAYMELRSLRSED TAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
128	ATL_0007829 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTDST STAYMELRSLRSDDTAVYYCARDLGPYYDASGYYYGFD IWGQGTTTVSS
129	ATL_0007917 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNTNYAQKLQGRVTMTDTS TSTAYMELRSLRSE TAVYYCARDLGPYYESSGYYYGFD DIWGQGTTTVSS
130	ATL_0007918 VH ATL_0007924 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNTNYAQKLQGRVTMTTETST STAYMELRSLRSDDTAVYYCARDLGPYYDSSGYYYGFD IWGQGTTTVSS
131	ATL_0007920 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTDST STAYMELRSLRSE TAVYYCARDLGPYYESSGYYYGFD IWGQGTTTVSS
132	ATL_0007921 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNTNYAQKLQGRVTMTDTS

		TSTAYMELRSLRSDTAVYYCARDLGPYYYDSSGYYYGF DIWGQGTTVTVSS
133	ATL_0007922 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYQGNTNYAQKLQGRVTMTTDS TSTAYMELRSLRSDDTAVYYCARDLGPYYYESSGYYYGF DIWGQGTTVTVSS
134	ATL_0007923 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTETST STAYMELRSLRSDDTAVYYCARDLGPYYYESSGYYYGFD IWGQGTTVTVSS
135	ATL_0007889 VL	QSVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
136	ATL_0007890 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
137	ATL_0007892 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
138	ATL_0007893 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKLTVL
139	ATL_0007895 VL	QSVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNSLSVAFGGGTKLTVL
140	ATL_0007896 VL	QSVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNSLSVAFGGGTKLTVL
141	ATL_0007899 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGQSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
142	ATL_0007900 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNSLSVAFGGGTKVTVL
143	ATL_0007901 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDQSLSVAFGGGTKVTVL
144	ATL_0007902 VL	QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDNNLSVAFGGGTKVTVL

145	ATL_0007917 VL	QAVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGQNNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKLTVL
146	ATL_0007918 VL	QAVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGQNNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKLTVL
147	ATL_0007919 VL	QSVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGNNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDQSLSVAFGGGKLTVL
148	ATL_0007920 VL	QSVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKPLIYGNSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDQNLVAFGGGKLTVL
149	ATL_0007921 VL	QSVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGQSNRPSGVPDRFSGSKSGTSASLVITG LQAEDEADYYCQSYDQSLSVAFGGGKLTVL
150	ATL_0007922 VL	QSVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGQSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKVTVL
151	ATL_0007923 VL	QAVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGNNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKLTVL
152	ATL_0007924 VL	QSVLTQPPSSVSGAPGQRTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGQSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDNNLSVAFGGGKLTVL
153	HFWR2_ATL_0007819	ISWVRQAPGQGLEWAGW
154	HCDR2_ATL_0007820	ISAYAGNT
155	HCDR2_ATL_0007821	ISAYNANT
156	HCDR2_ATL_0007822	ISAYNGAT
157	HCDR2_ATL_0007823	ISAYNGNA
158	HFWR3_ATL_0007824	NYAQKLQGRVTITTDSTSTAYMELRSLRSDDTAVYYC
159	HFWR3_ATL_0007825 HFWR3_ATL_0007918 HFWR3_ATL_0007923 HFWR3_ATL_0007924	NYAQKLQGRVTMTTETSTSTAYMELRSLRSDDTAVYYC
160	HFWR3_ATL_0007826	NYAQKLQGRVTMTTDTSTSTAYAE LRSLRSDDTAVYYC
161	HFWR3_ATL_0007827	NYAQKLQGRVTMTTDTSTSTAYMELRSLRSED TAVYYC
162	HCDR3_ATL_0007917 HCDR3_ATL_0007920 HCDR3_ATL_0007922 HCDR3_ATL_0007923	ARDLGPYYYESSGYYYGFDI

163	LFWR1_ATL_0007889 LFWR1_ATL_0007895 LFWR1_ATL_0007919 LFWR1_ATL_0007924	QSVLTQPSSVSGAPGQRTISCTGS
164	LFWR1_ATL_0007890 LFWR1_ATL_0007918 LFWR1_ATL_0007923	QAVLTQPPSVSGAPGQRTISCTGS
165	LFWR2_ATL_0007895 LFWR2_ATL_0007917 LFWR2_ATL_0007918 LFWR2_ATL_0007919 LFWR2_ATL_0007921 LFWR2_ATL_0007922 LFWR2_ATL_0007923 LFWR2_ATL_0007924	VHWYQQLPGTAPKLLIY
166	LCDR2_ATL_0007917 LCDR2_ATL_0007918	GQN
167	LCDR2_ATL_0007899 LCDR2_ATL_0007921 LCDR2_ATL_0007922 LCDR2_ATL_0007924	GQS
168	LCDR3_ATL_0007901 LCDR3_ATL_0007919 LCDR3_ATL_0007921	QSYDQSLSVA
169	LCDR3_ATL_0007920	QSYDQNLVA
170	Recombinant Macaca fascicularis 15-PGDH (C- term His 6)	MHVNGKVALVTGAAQGIGRAFAEALLKGAKVALVDWNL EAGVQCKAALDEKFEPQKTLFIQCDVADQQQLRDTFRKV VDHFGRLDILVNNAGVNNEKNWEKTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASKHG IVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEKEE NMGQYIEYKDHKDMIKYYGILDPPLIANGITLIEDDALNG AIMKITTSKGIHFQDYDATPFQAKSQLEHHHHHHH
171	Rattus norvegicus 15- PGDH 15-PGDH (UniProt O08699)	MHVNGKVALVTGAAQGIGKAFTEALLHGAKVALVDWNL ETGVKCKAALDEQFEPQKTLFIQCDVADQKQLRDTFRKV VDHFGRLDILVNNAGVNNEKNWEQTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINISSIAGLMPVAQQPVYCASKHGII GFTRSAAMAANLMKSGVRLNVICPGFVKTPILESIEKEEN MGQYIEYTDQIKAMMKFYGILDPSAIANGLINLIEDDALNG AIMKITASKGIHFQDYDLFSPFSKAP
172	Recombinant Rattus norvegicus 15-PGDH (C- term His6)	MHVNGKVALVTGAAQGIGKAFTEALLHGAKVALVDWNL ETGVKCKAALDEQFEPQKTLFIQCDVADQKQLRDTFRKV VDHFGRLDILVNNAGVNNEKNWEQTLQINLVSVISGTYLG LDYMSKQNGGEGGIIINISSIAGLMPVAQQPVYCASKHGII GFTRSAAMAANLMKSGVRLNVICPGFVKTPILESIEKEEN MGQYIEYTDQIKAMMKFYGILDPSAIANGLINLIEDDALNG AIMKITASKGIHFQDYDLFSPFSKAPLEHHHHHHH
173	Recombinant Human 15- PGDH (C-term His6)	MAHVMVNGKVALVTGAAQGIGRAFAEALLKGAKVALVDW NLEAGVQCKAALDEQFEPQKTLFIQCDVADQQQLRDTFR KVVDHFGRLDILVNNAGVNNEKNWEKTLQINLVSVISGTY LGLDYMSKQNGGEGGIIINMSSLAGLMPVAQQPVYCASK HGIVGFTRSAALAANLMNSGVRLNAICPGFVNTAILESIEK

		EENMGQYIEYKDHIDMIKYYGILDPLIANGLITLIEDDAL NGAIMKITTSKGIHFQDYGSKENLYFQGAGHHHHH
174	IGHV1-18*01 Homo Sapiens	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVR QAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCAR
175	IGLV1-40*01 Homo Sapiens	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQ PAGKGLEWIGRIYTSGSTNYPNPSLKSRTMSVDTSKNQF SLKLSSVTAADTAVYYCAR
176	IGHV4-4*07 Homo Sapiens	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQ QLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITG LQAEDEADYYCQSYDSSLG
177	IGKV3-20*01 Homo Sapiens	EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQ KPGQAPRLIYGASSRATGIPDRFSGSGSGTDFLTISRLE PEDFAVYYCQQYGSSP
178	ATL_0007471 VH	QVQLQESGPGLVKPSSETLSLTCTVSGDAITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTMSVDTSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
179	ATL_0007472 VH	QVQLQESGPGLVKPSSETLSLTCTVSGDSITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTISVDTSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
180	ATL_0007467 VH ATL_0007468 VH	QVQLQESGPGLVKPSSETLSLTCTVSGDSITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTMSVDTSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
181	ATL_0007473 VH	QVQLQESGPGLVKPSSETLSLTCTVSGDSITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTMSVETSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
182	ATL_0007928 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWAWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTISVETSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
183	ATL_0007927 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWAWIRQ PAGKRLWIGRVYASGSTSYNPSLKSRTISVETSKKQFS LKLTSVTAADTAVYYCARDLFFGSGSHFDPWGQGM LVT VSS
184	ATL_0007931 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTISVETSKKQFS LKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
185	ATL_0007932 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTISVETSKNQF SLKLTSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
186	ATL_0007470 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTNYPNPSLKSRTMSVDTSKNQF SLKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGT LVT VSS
187	ATL_0007930 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKGLEWIGRVYASGSTSYNPSLKSRTISVETSKNQFS

		LKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGTLVTVSS
188	ATL_0007929 VH	QVQLQESGPGLVKPSSETLSLTCTVSGESITSYFWSWIRQ PAGKRLEWIGRVYASGSTNYNPSLKSRTISVETSKNQFS LKLSSVTAADTAVYYCARDLFFGSGSHFDPWGQGTLVTVSS
189	ATL_0007927 VL	EIVLTQSPGTLSPGERATLSCRASQSVTSSYLAWYQQ KPGQAPRRLIYGTSSRATGIPDRFSGSGSGTDFTLTISRL EPEDFAVYYCQQYGSSPPTFGQGTREIK
190	ATL_0007926 VL	EIVLTQSPGTLSPGERATLSCRASQSVTSSYLAWYQQ KPGQPPRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRL PEDFAVYYCQQYGSSPPTFGQGTREIK
191	HCDR1_ATL_0007471	GDAITSYF
192	HFWR2_ATL_0007928	WAWIRQPAGKGLEWIGR
193	HFWR2_ATL_0007929	WSWIRQPAGKRLEWIGR
194	HFWR3_ATL_0007931	NYNPSLKSRTISVETSKKQFSLKLSSVTAADTAVYYC
195	HFWR3_ATL_0007932	NYNPSLKSRTISVETSKNQFSLKLTSVTAADTAVYYC
196	HFWR3_ATL_0007467 HFWR3_ATL_0007468 HFWR3_ATL_0007470 HFWR3_ATL_0007471	NYNPSLKSRTMSVDTSKNQFSLKLSSVTAADTAVYYC
197	HFWR3_ATL_0007473	NYNPSLKSRTMSVETSKNQFSLKLSSVTAADTAVYYC
198	HFWR3_ATL_0007927	SYNPSLKSRTISVETSKKQFSLKLTSVTAADTAVYYC
199	HFWR3_ATL_0007930	SYNPSLKSRTISVETSKNQFSLKLSSVTAADTAVYYC
200	LFWR2_ATL_0007927	LAWYQQKPGQAPRRLIY
201	LFWR2_ATL_0007926	LAWYQQKPGQPPRLLIY

Table 1. Sequences disclosed in this specification.

Examples

5 The present examples demonstrate the identification of new antibodies with therapeutic potential derived from PD patients that are considered resilient and/or cognitively healthy (Examples 1 and 2), that show excellent kinetic properties (Example 3) and stability (Example 4). *In silico* investigation of the antibody structure and binding to target was performed (Example 5), showing at least two different binding modes for antibodies that inhibit PGDH. *In vitro* functional studies are described in Example 6, showing the ability of antibodies of the disclosure to suppress the pro-inflammatory cytokine IL6, the abundance of phospho-

αSyn129 (a post-translational modification characteristic for the pathogenic αSynuclein species), and restore mitochondrial function in a model of alpha synucleinopathies ("PD in a dish", a model of inflammation induced by alpha synuclein in a dopaminergic neurons, astrocytes and microglia triculture). *In vivo* functional studies are described in Examples 7 and 8, showing the ability of antibodies of the disclosure to reduce levels of neuroinflammation *in vivo* in mice exposed to LPS (Example 7), and to improve gait and postural stability in aged mice (Example 8). Variants of the antibodies used in Examples 1-8 are described and characterised in Example 9.

Materials and methods

10 *Patient Cohorts*

Two cohorts of patients were used in these examples. The PREDICT-PD cohort (predictpd.com) comprises patients with RBD, classified as resilient if they had a formal diagnosis of RBD but were cognitively healthy (MoCA score >25; Nasreddine et al., 2005), and had a UPDRS (Unified Parkinson's Disease Rating Scale, a rating tool used to gauge the severity and progression of Parkinson's disease in patients; Poewe 2009) part III minus tremor score < 7. The East London Project (ELPD) cohort is a PD cohort comprising patients classified as progressors if they had a formal diagnosis of PD, a MoCA score <26 and UPDRS part III minus tremor score >6 (Zirra et al., 2022). Age matched controls from the PREDICT-PD cohort were also used.

Molecular Indexing of Proteins by Self-Assembly (MIPSA)

Detailed methods for performing MIPSA are provided in Credle et al., 2021. Briefly, barcodes are introduced near the 5' end of transcribed mRNA sequences, upstream of the ribosome binding site (RBS). Reverse transcription (RT) of the 5' end of *in vitro* transcribed RNA (IVT-RNA) creates a cDNA barcode, which is linked to a haloalkane-labeled RT primer. An N-terminal HaloTag fusion protein is encoded downstream of the RBS, such that *in vitro* translation results in the intra-complex ("cis"), covalent coupling of the cDNA barcode to the HaloTag and its downstream open reading frame (ORF) encoded protein product.

Immunoprecipitation experiments were performed to identify antigen reactivities in the patient serum samples. Briefly, serum samples diluted 1:100 were incubated with the MIPSA library of *in vitro* translated proteins. The mixture was then added to protein A and protein G beads (ratio 1.1). After washing the beads, they were used as input for PCR to amplify barcode sequences. A second PCR step added Illumina adapters and indexes. Sequencing was performed on an Illumina NextSeq 500 with a single end read of up to 75 cycles. Reads were assigned to ORFs using an 'ORF dictionary' generated from sequencing the unselected MIPSA library. Hits were identified by comparing read counts to the beads only control. Multiple barcodes per antigen help to increase hit confidence.

Recombinant 15-PGDH production

Recombinant human 15-PGDH encoding residues 3-266 and additional C-terminal Avi- and hexahistidine tag (rhPGDH-Avi-His), a commonly used peptide sequence to allow for site specific biotinylation of proteins with that tag via the use of BirA enzyme, was expressed in *E. coli* and purified using immobilized Ni²⁺-affinity chromatography. Purified rhPGDH-Avi-His protein was frozen in 20 mM Tris-HCl pH 7.0, 150 mM NaCl, 0.5 mM DTT and 10% v/v glycerol. Purified rhPGDH-Avi-His was biotinylated using either BirA biotin-protein ligase standard reaction kit (Avidity, LLC) or EZ-Link™ NHS-PEG4 Biotinylation Kit (Thermo

Scientific™, 21455) following the manufacturer's instructions. The biotinylated products (Avi-linked biotinylated-rhPGDH-Avi-His; ALB-rhPGDH and NH₂-linked biotinylated- rhPGDH-Avi-His; NLB-rhPGDH-Avi-His respectively) were buffer exchanged into 20 mM Tris-HCl pH 7.0, 150 mM NaCl, 0.5 mM DTT and 10% v/v glycerol. Commercial sources of 15-PGDH were reconstituted in phosphate buffered saline, recombinant human 15-PGDH: rhPGDH-His R&D Systems (5660-DH-010) and rhPGDH-His Sino Biological (11205-H08E) and recombinant mouse 15-PGDH: rmPGDH-His Sino Biological (50531-M08E). Biotinylated rmPGDH-His Sino Biological was produced using EZ-Link™ NHS-PEG4 Biotinylation Kit (Thermo Scientific™, 21455) following the manufacturer's instructions. The biotinylated rmPGDH-His Sino Biological was buffer exchanged into 20 mM Tris-HCl pH 7.0, 150 mM NaCl, 0.5 mM DTT and 10% v/v glycerol.

Table 2 lists the recombinant antigens used in the examples.

Antigen name	Short name	UniProt Accession number	Supplier	Catalogue number
Recombinant Human 15-PGDH (C-term Avi-His6) (SEQ ID NO: 81)	rhPGDH-Avi-His	P15428	In-house	N/A
Recombinant Human 15-PGDH (C-term His6) (SEQ ID NO: 83)	rhPGDH-His	P15428	R&D Systems	5660-DH-010
Recombinant Human 15-PGDH (C-term His6) (SEQ ID NO: 83)	rhPGDH-His	P15428	Sino Biological	11205-H08E
Recombinant Mouse 15-PGDH (C-term His6) (SEQ ID NO: 85)	rmPGDH-His	Q8VCC1	Sino Biological	50531-M08E
Recombinant Human 15-PGDH (C-term His6) (SEQ ID NO: 173)	rhPGDH-His	P15428	In house	N/A
Recombinant Cyno 15-PGDH (C-term His-6) (SEQ ID NO: 170)	rcPGDH-His	Q8MJY8	In house	N/A
Recombinant Rat 15-PGDH (C-term His-6) (SEQ ID NO: 172)	rrPGDH-His	O08699	In house	N/A

Table 2. Summary of antigen constructs used in the examples.

Screening patient (subjects from Parkinson's cohorts) serum and plasma for 15-PGDH reactivity by ELISA

Recombinant human 15-PGDH (rhPGDH-Avi-His)R&D Systems, 5660-DH-010) as well as negative control antigen Lysozyme (MP Biomedicals, 195303) were directly absorbed to ELISA plates at 1 µg/ml (50 µl per well) and incubated overnight at 4°C. The plates were washed with phosphate-buffered saline (PBS). Anti-human-15-PGDH (Goat IgG) (BioTechne cat# AF5660) was added as a positive control. Plates were blocked with 200 µl/well of blocking solution (1% Bovine Serum Albumin (BSA) w/v in PBS) for 1 hour at room temperature. Following this, the blocking solution was removed and the serum and plasma samples to be assessed were diluted 1/100 in blocking solution (1% BSA w/v in PBS) and applied to the plates. Plates were incubated at room temperature for 1 hour. The plates were washed with PBS+0.1% Tween. Goat anti-human F(ab')₂-horseradish peroxidase (HRP) antibody (Jackson ImmunoResearch, 109-035-097; Lot: 148466; 1:10,000 dilution) was then added to each well at 50 µl/well and incubated for 1 hour at room temperature. The plates were washed with PBS+0.1% Tween and 3,3', 5,5'-tetramethylbenzidine (TMB) solution (Life Technology, 002023) was added to each well to detect antibody binding. Plates were incubated for 5 minutes at room temperature prior to the addition of stopping solution (0.5 M sulphuric acid). Absorbance read on Molecular Devices FilterMaxF5 plate reader at 450 nm.

Serum inhibition of 15-PGDH activity screening

To screen 15-PGDH-reactive serum samples for 15-PGDH inhibition, a modified commercial enzyme activity assay (Abcam ab273327) was used. The assay is illustrated on Fig. 3A. In the assay, 15-PGDH oxidizes a substrate forming intermediates and NADH. The oxidation of NADH reduces a probe generating
5 fluorescence at Ex/Em=535/587 nm. The activity of 15-PGDH is proportional to the fluorescent signal.

Serum samples were thawed on ice and centrifuged at 4°C to remove debris and aggregates. Supernatant was drawn off for screening. A reaction mix was prepared from activity kit components (buffer, probe, substrate, and developer) according to the manufacturer's instructions. Serum was diluted in kit assay buffer to a range of concentrations was pre-incubated with recombinant rhPGDH-Avi-His on ice.
10 Immediately prior to fluorescence reading, reaction mix was added to each serum sample. Final concentrations of kit components were according to the manufacturer's instructions. Final top concentration of serum was 1/30 neat serum, with seven three-fold serial dilution points prepared. Final concentration of recombinant enzyme was 8 nM. The change in fluorescence at 587 nm was monitored for 40 minutes in a white 96-well plate at 37°C (BMG Clariostar). An age-matched non-reactive serum sample (SU477) was
15 used as control or the known 15-PGDH small molecule inhibitor SW033291 were used as controls.

Monoclonal antibody inhibition of 15-PGDH activity screening

To screen monoclonal antibodies for enzyme inhibition, a modification of the above protocol was used. Purified antibody rather than serum was pre-incubated with recombinant PGDH. In most assays the final top concentration of antibody was 7.8e-7 M, with six five-fold serial dilutions prepared.

20 In some versions of the assay the reaction mix (except fluorescent reporter) using commercial components was substituted with TBS pH 7.5, 0.01% Tween-20, 150 µM NAD⁺ (ThermoFisher #124530050), 25 µM PGE2 (Tocris/Biotechne #2296).

Data were analysed by plotting the change in fluorescence/time against the concentration of antibody. Owing to variability in activity observed between runs, likely due to enzyme instability, and because non-specific inhibition by any antibody at high concentrations was sometimes apparent, data were normalised
25 to the activity in the presence of an equal quantity of control (non-PGDH-reactive) monoclonal isotype-matched antibody (anti-fluorescein ATL_5338). Where sufficient data were available a 4-parameter [inhibitor] vs response model was fitted to compute IC50 values (Graphpad Prism).

Multiple independent assays (different days, different sites) were conducted with at least two observations
30 of concentration-dependent reduction in enzyme activity, and at least 15% reduction at one or more concentrations, relative to isotype control required to be assessed as an inhibitor of 15-PGDH. All of antibodies ATL_0006026, ATL_0006058, ATL_0006074, ATL_0006075 and ATL_0006027 were found to inhibit PGDH.

Discovery of 15-PGDH reactive antibodies from patient plasma by mass spectrometry

35 Mass spectrometry-based identification of antibodies from plasma was performed according to methods known in the art (REmAb® from Rapid Novor, Inc). Briefly, purification of IgG was performed using 5 mL of serum. Plasma was incubated with 6 mL protein G resin and washed with phosphate buffered saline (PBS). IgG was eluted with a 0.1 M glycine buffer pH 2.7 and neutralized with 1 M Tris-HCl pH 8.0.

Nanodrop was used to determine the concentration of total IgG. Streptavidin Sepharose High Performance (Sigma, GE17-5113-01) was used for depleting the non-specific binding IgG fraction. The collected flowthrough was subjected to a first purification with biotinylated 15-PGDH (ALB-rhPGDH) coupled to the streptavidin beads and incubated at 4°C for 1 hour. The flowthrough from this first enrichment was then used as a substrate for a second purification using the same biotinylated antigen captured on streptavidin beads. The two antigen bound samples were washed with PBS and eluted with glycine buffer. The samples were subjected to various enzymatic digestions prepared using different enzymes (Pepsin, Trypsin, Chymotrypsin, Asp-N, Lys-C, and non-specific). The digestions for each sample were processed with disulfide reduction, alkylation, and then enzyme digestion. Different antibody chains were separated by chromatography and electrophoresis prior to digestion, mass spectrometry analysis, and data analysis. Digestions were analysed by LC-MS/MS using a mass spectrometer following both bottom-up and middle-down strategies. Peptides were characterized from LC-MS/MS data using *de novo* peptide sequencing and then assembled into chains followed by heavy and light candidate sequences pairing into antibody sequences. A bulk BCR sequencing database search was performed, when available, and sequences were scored based on overall coverage and other metrics.

Phage library generation

Phage libraries of scFv molecules displayed on M13 phage were generated by cloning the VH repertoires from five of the subjects identified in the serum ELISA analysis as reactive to 15-PGDH (SU_0001238, SU_0001264, SU_0001242, SU_0001271 & SU_0001286) into a sub-library of phagemid vectors containing a library of VL sequences from healthy donors. Phage display libraries, ranging from size 1.9×10^7 to 8.2×10^8 clones, were generated and phages were produced for phage display selections.

Phage selections

Phages were prepared by culturing a volume equivalent to optical density OD₆₀₀=0.1 of phagemid-carrying TG1 stocks into 50mL of 2TYAG (2TY media supplemented with 100 µg/ml ampicillin and 2% glucose) at 37°C with aeration to optical density OD₆₀₀=0.6. Rescue was performed by addition of M13K07 helper phage (Invitrogen, cat. 18311-019) for 1 hour, followed by harvesting bacteria by centrifugation (3500xg, 10 mins) and changing media to 2TYAK (TY media supplemented with 100 µg/ml ampicillin and 50 µg/ml kanamycin). The cultures were then incubated overnight at 18°C with aeration to rescue phage particles and then separated from bacteria the next day by (4500xg, 15 mins, 4°C). Finally, phages were PEG-precipitated and 0.22 µm filtered.

In order to isolate scFv binding to 15-PGDH antigen, three rounds of panning selections were performed on 15-PGDH antigen (rhPGDH-Avi-His). 192 clones were analysed by Sanger sequencing and unique sequences shortlisted for phage ELISA.

To ensure 15-PGDH epitopes were maximally accessible to the phage-displayed scFv an alternative selection strategy was applied using selections against 15-PGDH in solution to find more binding scFv. Three rounds of soluble selections were performed on the phages against biotinylated 15-PGDH (NLB-rhPGDH-Avi-His), using 200 nM NLB-rhPGDH-Avi-His for round 1, 50 nM NLB-rhPGDH-Avi-His for round 2 and 10 nM NLB-rhPGDH-Avi-His for round 3 respectively. Blocked phage in 6% milk PBS was added to NLB-rhPGDH-Avi-His and then used to resuspend either Streptavidin (M-270, Invitrogen cat. 65305) or

Neutravidin Dynabeads pre-blocked in 3% milk PBS. After incubation and washing, the phages were eluted from the beads with trypsin (100 mg, Sigma, cat. T1426). Selected phages were rescued as above.

Phage ELISA

Binding ELISAs were performed on phage clones identified after 3 rounds of selections to identify clones that were specific to 15-PGDH binding. ELISA detection of binders was determined to either non-biotinylated antigen (rhPGDH-Avi-His) directly immobilised on the plate or to neutravidin captured biotinylated antigen (ALB-rhPGDH-Avi-His or NLB-rhPGDH-Avi-His). Lysozyme (MP Biomedicals, 195303) or NeutrAvidin (Life Technologies, 31000) alone were used as negative controls for each respective ELISA method. For both methods, antigen coated plates and rescued phage were blocked with 3% milk with PBS for 1 hour (room temperature) and then phages were added to the plates and incubated for 1 hour (room temperature). The plates were washed with PBS+0.1% Tween-20 and then incubated with Anti-M13 HRP (SinoBiological, 11973-MM05T-H) for 1 hour at room temperature to detect phage binding. The plates were washed with PBS+0.1% Tween-20 and TMB solution (Life Technology, 002023) added. Plates were incubated for 5 minutes at room temperature prior to the addition of stopping solution (0.5 M sulphuric acid). Absorbance was read on Molecular Devices FilterMaxF5 plate reader at 450 nm. Hits were sequenced by Sanger sequencing to identify the binding single chain, representing the heavy and light chain.

Monoclonal antibody binding to 15-PGDH: Single point and multi-point ELISAs

Selected scFv from the phage that bound specifically to 15-PGDH were reformatted and produced as human IgG. IgG binding to 15-PGDH was tested by single point ELISA against either directly immobilized non-biotinylated rhPGDH-Avi-His (plated 15-PGDH) or to Neutravidin captured biotinylated ALB-rhPGDH-Avi-His (NA captured 15-PGDH), as the antibodies were selected against one or both of the forms of PGDH. This tests whether antibodies bind in an ELISA to the form of PGDH they were selected against. Lysozyme (MP Biomedicals #195303) or NeutrAvidin (Life Technologies, 31000) alone were used as negative controls for each respective ELISA. None of the candidate antibodies bound neutravidin only (control). Antigen coated plates were washed with PBS and blocked with 200 µl/well of 3% milk in 1x PBS for 1 hour at room temperature. IgG being tested as well as an isotype control antibody were added and incubated for 1 hour at room temperature. For single point ELISAs a single concentration of 0.1 mg/mL IgG was tested in triplicate and for multi-point ELISAs Ig were added at top concentration of 0.1 mg/ml with a 10-point 5-fold titration series. Plates were washed with PBS+0.1% Tween-20 and Anti-human F(ab')₂-HRP (Jackson ImmunoResearch, 109-035-097) was added and incubated for 1 hour at room temperature to detect antibody binding. Anti-His HRP (Invitrogen, MA1-21315-HRP) was used as an antigen coating positive control. The plate was washed with PBS+0.1% Tween-20 and TMB solution (Life Technology, 002023) added. Plates were incubated for 10 minutes at room temperature prior to the addition of stopping solution (0.5 M sulphuric acid). Absorbance was read on Molecular Devices FilterMaxF5 plate reader at 450 nm.

Kinetics characterisation of antibodies binding to 15-PGDH by BLI

Antibodies identified to bind to 15-PGDH by ELISA had their kinetics measured by biolayer interferometry (BLI) on an Octet Red96e (Sartorius). Streptavidin biosensors (Sartorius 18-5019) were used to capture biotinylated human or mouse 15-PGDH (NLB-rhPGDH-Avi-His and rmPGDH-His (Sino Biological, 50531-M08E) respectively). Kinetics was measured by monitoring the change in signal in real time using the Octet

Red96e data acquisition software 12.0 (Sartorius) with the system set to 25°C with biosensors shaking at 1000 rpm. The 15-PGDH loaded biosensors were dipped into 1x Kinetics buffer (Sartorius, 18-1105) to achieve a stable baseline (60 seconds), before being dipped into a concentration series of antibody (7-point 2-fold dilution series from 100 nM top concentration) for 600 seconds to measure association, and then returning to 1x Kinetics buffer for 600 seconds to measure dissociation. A reference biosensor loaded with 15-PGDH dipped into 1x Kinetics buffer without antibody was used. Data analysis was performed using the Octet Data Analysis HT 12.0 software (Sartorius). Raw data for each biosensor had the reference biosensors subtracted before aligning the data on the y-axis to the average of the last 5 s of the baseline, inter-step correction to the end of the dissociation step, and applying Savitzky-Golay filtering. Processed data was then fit with a 1:1 binding model using a global fit linked to the antibody in the sample.

Kinetics characterisation of antibodies binding to 15-PGDH by SPR

Antibodies identified to bind to 15-PGDH by ELISA had their kinetics measured by surface plasmon resonance (SPR) on a Carterra LSA instrument. A capture surface was prepared by coating a polycarboxylate sensor chip (HC200M, Carterra) with goat polyclonal anti-human IgG Fc antibody. Four concentrations of the test antibodies were then captured on the surface at two separate locations, with binding confirmed by SPR measurement. The chip was equilibrated to PBS + 0.1% Tween. Human 15-PGDH (NLB-rhPGDH-Avi-His) was injected at a range of concentrations up to 590 nM in PBS + 0.1% Tween. Binding kinetics was measured by monitoring the change in signal in real time using the Carterra control software with the system set to 25°C. Analyte was injected for 300 seconds to measure association, followed by buffer only injection for 1200 s to measure dissociation. Data were referenced and aligned to the capture surface and the buffer-only analyte signal. Processed data was then fit with a 1:1 Langmuir binding model.

Thermal shift assay

Protein thermal shift measurements were performed on an Uncle (Unchained labs). Antibodies were diluted to 1mg/ml or 5mg/ml in 20 mM Histidine Acetate, 150 mM NaCl, pH 5.5 buffer and run through a temperature ramp of 25-95°C increasing at a rate of 0.5°C/minute. Samples were run in triplicate, loading 8.8µl in 3 different wells of a uni (Unchained Labs). Laser settings were set to achieve an initial fluorescence in the 300-350 nm range of 10000 – 50000 counts. Melting temperature (Tm1/Tm2) and aggregation temperature (Tagg/Tonset) were analysed using Uncle Analysis software v6 (Unchained Labs). Tm measurement was calculated using the 350/330nm ratio, while Tonset and Tagg were obtained from SLS read at 266nm and 473nm.

Size exclusion chromatography (SEC-HPLC)

Antibody samples were loaded onto an Agilent ZORBAX GF-250 (9.4 mm x 250 mm 4-micron, with Agilent ZORBAX DIOL preparative guard column 9.4 mm x 15 mm 6-micron) column, at 25 µg injection load. Sample solution components were separated by size, in 20 mM Sodium phosphate, 300 mM Sodium sulfate, 100 mM Arginine, pH 6.6 ± 0.2. The column compartment temperature was set at 25°C, the injection flow rate was 0.75 mL/minute, run time was 25 minutes, and the absorbance wavelength was 280 nm. A Thermo Fisher Vanquish Flex LC system was used, with Thermo Fisher Chromeleon 7 chromatography data system for chromatogram processing and peak integration.

SDS-PAGE

2µg of antibody sample was prepared by diluting in water and 2x Laemmli Sample Buffer (Bio-Rad). Sample was analysed at both reduced and non-reduced conditions; reduced samples had the addition of 50mM DTT (dithiothreitol, Sigma-Aldrich). All samples were heated to 95°C for 5 mins and loaded into wells of Bolt 4-12% Bis-Tris Plus Protein gels (Thermo Scientific) alongside 5µl of a molecular weight marker was loaded on each gel, Precision Plus Protein Dual Colour Standards (Bio-Rad, 1610737) and run in Bolt MES SDS Running Buffer (Thermo Scientific). Samples were run at a constant 200 Volts for 23 minutes followed by staining with InstantBlue Coomassie Stain for a minimum of 1 hour, gels were destained with water washes and an image taken by scanning using the GelDoc Go Imaging system (Bio-Rad).

10 *Recombinant mAb expression*

Recombinant antibodies were expressed transiently from ExpiCHO-S cells using manufacturers protocols for Expifectamine transfections (Thermo). Transfections were cultured for 7 or 12 days with feeds, followed by harvesting by mixed with diatomaceous earth (Sartorius) followed by filtration through a 0.22 µm PES membrane. Harvested supernatant was purified using protein A capture resin and elution in low pH buffer. Elution fractions were buffer exchanged into 20mM Histidine acetate, 150mM sodium chloride pH5.5 buffer and stored at -80C.

Alpha-synuclein fibrils-induced PD model

Induced pluripotent stem cell (iPSC)-derived dopaminergic neurons (Fujifilm; Catalog #: R1148), astrocytes (Fujifilm; Catalog #: R1092), and microglia (Fujifilm; Catalog #: R1131) were utilized to establish a triculture system to recapitulate physiological conditions of the central nervous system. These cells were cultured under standard conditions until they reached the appropriate confluence for experimentation. On day 4 post-establishment of the triculture system, cells were treated with either α-synuclein (αSyn) fibrils at a concentration of 6 µg/ml or phosphate-buffered saline (PBS) as a control. These conditions were maintained for 5 days to allow for the uptake and potential effects of the αSyn fibrils on the cells. Following the incubation period with αSyn fibrils or PBS, cells within the tri-culture system were exposed to 15-PGDH antibody, (ATL-6026 or ATL-6058), or isotype control antibody (ATL-5338). Each antibody was used at a concentration of 70 nM. The cultures were incubated with these antibodies for an additional 48 hours. On day 11 of the culture, supernatant and whole protein extracts were collected. For protein extraction from the cells, a RIPA cell lysis buffer was used. The buffer composition included 50 mM Tris (pH 8.0), 150 mM NaCl, 5 mM EDTA, 1% NP-40, 0.5% sodium deoxycholate, and 1% SDS. Quantification of Interleukin-6 (IL6) and 15-PGDH in the collected samples was performed using an enzyme-linked immunosorbent assay (ELISA) service provided by RayBiotech, Inc. (Peachtree Corners, GA, USA). All ELISA assays were conducted according to the manufacturer's protocols. On day 11 of the culture, cells were fixed with 4% paraformaldehyde in PBS for 10 min and then washed with PBS. Immunostaining was performed after permeabilization in PBS with 0.1% Saponin and blocking for 30 min in 10% donkey serum in PBS with 0.1% Saponin. Immunostaining was performed with specific primary antibodies: rabbit alpha-synuclein Antibody, pS129 (1:100; LSbio, LS-C380861-50), chicken MAP2 antibody (1:400; Thermofisher, PA1-10005). Primary antibodies were diluted in 10% donkey serum in PBS with 0.1% Saponin and incubated overnight at 4 °C. After three PBS washes, cells were incubated with secondary antibodies in 10% donkey serum in

PBS with 0.1% Saponin (Alexa Fluor-488 (1:300; Thermofisher, A78948), Alexa Fluor-647 (1:300; abcam, ab150075) for 1 h at room temperature, and cells were counterstained with DAPI nuclear stain. Cells were then washed with PBS three times and were visualized. Images were acquired with the ECHO Revolve microscope.

- 5 The experimental design for this study is shown in **Figure 15**.

Mitochondrial Membrane Potential Assay

JC-1 probe (Invitrogen, T3168) was used to measure changes in mitochondrial membrane potential of cells after exposure to 8 μ g/mL α Syn fibrils PFFs and treatment with PGDH antibodies. Cells were incubated with 2.0 μ g/mL of JC-1 probe at 37 °C for 30 minutes, subsequently washed twice with PBS, and then replaced
10 in fresh media solution. Cells were imaged on the ECHO revolve microscope at 10x magnification using the 488nm excitation filter and 530 nm emission filter to capture JC-1 monomers and 543nm excitation filter and 590nm emission filter for capturing JC-1 aggregates. Fluorescence intensity was measured using Image J software and the red/green ratio was plotted for each image in GraphPad Prism.

In vivo LPS challenge mouse model of inflammation

15 The mice used in this experiment were male C57BL/6 ordered from Charles River Laboratories (St. Constant, Quebec, Canada). Two groups of 8 mice were treated at -6 days, -3 days and -4 hours with either ATL6026 or Isotype control mAb (ATL5338) at 60 mg/kg. A further group of 8 mice were treated at -7 days until -4 hours twice daily with 10mg/kg SW033291 (MedChem Express, Cat. No.: HY-16968). LPS (Sigma Aldrich, Cat. No.: L2630) was administered at 0 hours, 0.25 mg/kg via i.p. to all mice. Serial blood was
20 sampled at 4 hours for all mice in life via saphenous collection. Blood was collected at 24 hours terminal via cardiac puncture. Mice were transcardially perfused with 50mL ice-cold PBS (20mM pH 7.4) and brain samples were then collected. Levels of cytokines (IL-6, TNF- α and IL-1 β) in samples were measured using a Meso Scale Discovery System (MSD) customized V-plex panel.

In vivo assessment of gait and postural stability in aged mice

25 Mice were 22-month-old C57BL/6J (Jackson Laboratories, USA). Altogether 56 mice were enrolled in the study and divided into 4 groups with 14 animals in each group. Two groups of mice were dosed with ATL6026 or Isotype control (ATL5338) at 60 mg/kg via intraperitoneal (i.p.) injection 1x/week for the duration of the study. Two further groups were dosed with small molecule SW033291 (MedChem Express, Cat. No.: HY-16968) at 10 mg/kg or Vehicle 1x/day for the duration of the study. At the end of week 4 pre-
30 defined points, including limb joints and tail, were marked on the animal's body to aid the data capture by a high-speed camera (300 fps) and data analysis was performed by converting the movements into data points. Different gait patterns and movements that were analysed were: a) General gait pattern parameters; b) Body posture and balance, c) Fine motor skills. As gait parameters have several (and complex) inter-correlations different gait features, which are manifested in sets of highly correlating parameters, these
35 features were also analysed and identified using Principal Component Analysis (PCA). An overall gait score combines the above kinematic parameters into one single score.

Variant Antibody Production

Recombinant antibodies were expressed transiently from CHO-S cells. Following harvest and clarification, supernatant was purified using protein A capture and elution in low pH buffer. Elution fractions were buffer exchanged into 20mM Histidine acetate, 150mM sodium chloride pH5.5 formulation buffer and stored at – 80C.

CE-SDS

Non reducing Capillary Electrophoresis-SDS was performed on some of the variants to determine monomeric purity. Samples were mixed with SDS-containing buffer and electrokinetically injected into a cartridge capillary. Peaks were measured at 220 nm.

SEC-HPLC of variant antibodies

Size exclusion chromatography (SEC-HPLC) was performed to assess purity of antibody batches on a Thermo Fisher Vanquish Flex UHPLC system. Samples were loaded onto a TOSOH Bioscience TSKgel G3000SWxl 7.8 mm ID x 30 cm L column, at 25 µg injection load of pre filtered samples. The autosampler temperature was set at 4°C, the column compartment temperature was set at 25°C. Sample solution components were separated by size in mobile phase 20 mM Sodium phosphate 100 mM Arginine 300 mM Sodium sulfate pH 6.6 with a flow rate of 0.5 mL/min for 40 minutes. Chromeleon 7.3.1 software was used for analyzing the chromatograms at measurement wavelength of 280 nm (4 nm bandwidth), using drop perpendicular peak integration unless specified. Monomer purity was recorded as the relative of total area under the largest peak.

Biolayer interferometry (BLI) characterisation of variant antibodies

For the initial binding screen, anti-human Fc biosensors were equilibrated to assay buffer and immersed in a 5 µg/mL solution of test antibody. Sensors loaded with antibody were immersed in concentration series of up to 400 nM purified recombinant human 15-PGDH, and kinetic association data were acquired. The sensors were returned to assay buffer and kinetic dissociation data were acquired. Data were referenced against buffer-only analyte and isotype-control-loaded (ATL_5338) sensor data.

For the final binding screen, the assay was modified to support kinetic characterisation. Test antibody loaded anti-human-Fc biosensors were immersed in a dilution series of recombinant human 15-PGDH (SEQ ID NO: 173 or SEQ ID NO: 83), cynomolgous monkey 15-PGDH (SEQ ID NO: 170), recombinant mouse 15-PGDH (SEQ ID NO: 85) and recombinant rat 15-PGDH (SEQ ID NO: 172) orthologue analytes at a top concentration of 40 nM (ATL_6026 variants) or 20 nM (ATL_6058 variants). Data were referenced as before and fitted to 1:1 kinetic binding model, which was used to calculate a KD value for each variant.

All BLI measurements were carried out using a Sartorius Octet Red 96e instrument at 25°C. The assay buffer was 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% v/v P20.

Inhibition screening of variant antibodies by fluorescence based enzymatic activity assay

A BMGLabtech CLARIOstar was used to measure fluorescence intensity with emission set to 460 nm (10 nm bandwidth), and excitation set to 355 nm (10 nm bandwidth) from low volume opaque white plates. The samples were mixed with 15-PGDH in the plate wells, with NAD⁺ and PGE₂ injected during the program run. The assay buffer was 0.1 M Tris-HCl, pH 8.0, 0.01% Tween-20 with NAD⁺ and PGE₂ stock solutions

prepared in 0.5 M Tris-HCl, pH 8.0. 15-PGDH enzyme stock solution was prepared in 5 mM Tris-HCl, pH 8.0, 150 mM NaCl, 0.01% Tween-20.

The assay was based on the principle of conversion of non-fluorescent NAD⁺ to fluorescent NADH catalyzed by 15-PGDH in the presence of substrate PGE₂. Inhibition of 15-PGDH was monitored by measuring the reduction in fluorescence signal.

For screening, a four-point 10-fold dilution series was used to compare inhibition to the parent by comparing the slope of the increasing fluorescence signal. The isotype control or a non-binding antibody was used as a negative control, while a no-PGDH mix or small molecule inhibitor SW033291 (MedChem Express, Cat. No.: HY-16968) was used as the positive control (data not shown). Maximum inhibition was calculated from the linear model of taking Δ RFU of the 0 nM concentration of the sample as 100% activity (0% inhibition), and Δ RFU of zero as 0% activity (100% inhibition).

Thermostability assessment of variant antibodies using SYPRO thermal shift assay

The Unchained Labs UNcle platform was used to generate the thermal melting profile of mAbs in the presence of SYPRO Orange (Thermo Fisher #S6651). The mAbs were prepared at < 5 mg/mL in 20 mM Histidine acetate, pH 5.5, 150 mM sodium chloride, then mixed in a one-to-one ratio with SYPRO Orange diluted 40-fold with the mAb formulation buffer. 8.8 μ L of this mix was loaded into a UNI cuvette chamber in triplicate for each mAb. The T_m using SYPRO program was used with the thermal ramp set from 25°C to 95°C at 0.5°C/minute. The results were analyzed with Uncle Analysis V 6.0.

EXAMPLE 1 – Target discovery using high-throughput proteome profiling of Parkinson's Disease patient serum

The present inventors set out to identify protective autoantibodies associated with Parkinson's Disease (PD) and/or protection to PD. To do this, commercially available serum samples of 12 (PD) patients (obtained from Tissue Solutions) were analysed using Molecular Indexing of Proteins by Self-Assembly (MIPSA) as described in Credle et al., 2021. MIPSA produces libraries of soluble full-length proteins, each uniquely identifiable via covalent conjugation to a DNA barcode, flanked by universal PCR primer binding sequences. The resulting library of uniquely indexed full-length proteins was subsequently displayed on bacteriophages and immune precipitated using the serum samples, followed by high-throughput DNA sequencing analysis. This method allowed for the unbiased profiling of autoantibodies in the serum of the PD patients.

This analysis revealed one subject, subject 0000478 (SU478), that had strong reactivity against 15-PGDH (Figure 1). Serum of this patient was subsequently tested in a 15-PGDH inhibition assay and found to not only bind but also inhibit PGDH enzymatic activity compared with serum from an age-matched PD subject (SU485) and non-reactive control (SU477) (Figure 2). Notably, this particular patient showed high levels of disease resilience, as evidenced by the late onset of the disease, i.e. after the age of 90, without any signs of cognitive decline, suggesting that the autoantibody is associated with PD resilience. A panel of 8 monoclonal antibodies specific for human 15-PGDH were identified in this subject, and after functional screening a single antibody, labelled ATL_6058, was selected for further investigation.

A broader serum screening serum was subsequently carried out to test whether PD subjects from other cohorts also demonstrate 15-PGDH reactivity. 84 PD serum/plasma samples from two cohorts, the East London PD Project (ELPD) and PREDICT-PD, and including 26 healthy controls, without prodromal PD were screened for binding to 15-PGDH. The PD patients included resilient patients (RBD without PD), as well as progressors (RBD and PD). The results of this screen are shown in **Figure 3**. **Figure 3B** shows 6 of the subjects showed autoreactivity to 15-PGDH by measuring binding to 15-PGDH in an ELISA (a z-score of 1.5 or higher indicates binding). Four of these subjects were PD patients or at risk of developing PD due to their RBD and two were healthy controls. Notably, of the four PD patients, two were resilient patients (SU1238 and SU1242) (see **Table 3**). Resilience in this instance was defined as a patient having RBD without progressing to disease. RBD is a prodromal symptom associated with progression to PD. Median years for progressing to PD after RBD diagnosis is 7 years, therefore a patient having RBD for 7 years without progressing to PD can be considered resilient. In addition, 90% of people diagnosed with RBD will progress to PD within 10 years. Therefore, a patient who is 12 years post RBD diagnosis without progressing to PD can be considered resilient.

In addition, two subjects (SU478 and SU1286) showed PD symptoms but did not exhibit cognitive impairment (see **Table 3**). These results suggest that the occurrence of antibodies with PGDH reactivity is associated with PD and/or protection to PD.

Subject	Notes
SU1271	Healthy; No prodromal PD
SU478	PD diagnosed at 91 years old; no cognitive impairment
SU1238	Resilient – REM sleep Behaviour Disorder (RBD) 7 years no progression to PD
SU1242	Resilient - RBD 12 years no progression to PD
SU1264	Healthy; No prodromal PD
SU1286	PD 6.8 years + RBD; no cognitive impairment

Table 3. Clinical presentation of PD patients (SU478, 1286), patients at risk of PD (1238, 1242) and healthy controls (SU1271; 1264)

To test whether the subjects identified to bind 15-PGDH were also able to inhibit 15-PGDH enzymatic activity an inhibition assay was carried out and **Figure 4** shows the results of this assay. **Figure 4** shows that serum samples from 5 out of 6 subjects that bind 15-PGDH (SU1238, SU1242, SU1264 and SU478) are also able to inhibit 15-PGDH compared with a control non-reactive age-matched control sample (SU477), to varying extents, with the strongest inhibition seen in serum samples from SU478. These data are therefore consistent with the kinetic data shown in **Figure 1B**.

Notably, the probability of 3/4 resilient/cognitively healthy PD patients producing autoantibodies against 15-PGDH by chance is extremely low. It is therefore likely that autoreactivity against PGDH was highly selected for and advantageous to the individual. This highlights the relevance of this target in PD.

Together, the above data show the discovery of anti-PGDH autoreactivity in PD patients, in particular in resilient and cognitively healthy PD patients, indicating that this may have a protective function in PD pathophysiology.

EXAMPLE 2 – Discovery of anti-PGDH antibodies in PD patients

Next, the inventors sought to identify the antibodies responsible for the strong 15-PGDH reactivity in the serum of PD Patients SU478; SU1238; SU1242; and SU1286 (which was found to bind but not inhibit 15-PGDH), and healthy control SU1271. All PD patients had a Montreal Cognitive Assessment (MoCA), which is a test to determine impairment of cognitive function, examination score of ≥ 26 (Nasreddine et al., 2005). The maximum score according to this examination is 30 and a score of ≥ 26 is classed as normal. If an MMSE was used instead, all PD patients had a score of ≥ 25 (Folstein et al., 1975). The maximum score is 30 and a score of ≥ 25 is classed as normal.

Monoclonal antibodies (mAbs) were identified from patient serum samples either through proteomics using mass spectrometry (SU478) or phage display (SU1238; SU1242; SU1286, and SU1271).

Mass spectrometry was used to identify the amino acid composition of the antibodies directly from the expressed proteins as isolated from serum. Serum proteomics resulted in a panel of mAbs specific for human PGDH. Further functional screening resulted in the identification of ATL6058 as an antibody that binds PGDH with high affinity ($EC_{50} = 2.81E-10M$) (see Table 4 and Figure 8) and inhibits PGDH at low concentrations compared with an isotype control antibody (Figure 5).

Antibodies from PD patients SU1238; SU1242; SU1286, and SU1271 were identified through phage display and selection, followed by Neutravidin-captured PGDH ELISA (antibodies identified from patients SU1238 and SU1286) or a directly immobilised PGDH ELISA (antibodies identified from patients SU1271 and SU1242). The binding antibodies were subsequently tested for their ability to inhibit 15-PGDH and antibodies ATL6026 and ATL6027 were identified as 15-PGDH inhibitors.

The results from the directly immobilised PGDH ELISA are shown in Figure 6. Figures 6A-B show that antibodies ATL6026 and ATL6027 show similar binding to the positive control

The results from the neutravidin-captured PGDH ELISA are shown in Figure 7 for the antibodies identified by soluble selection with neutravidin-captured PGDH ELISA (Figure 7A and D, antibodies 6074 and 6075, where antibody 6075 was found to inhibit PGDH), the antibodies identified by mass spectrometry (Figure 7B and C, antibody 6058 which was found to inhibit PGDH).

Figure 8 shows the results of a multipoint ELISA showing all tested antibodies have good binding affinity for PGDH, as evidenced by the low EC_{50} values.

Figure 9 shows representative data from PGDH inhibition assays for ATL6026 (Figure 9A), ATL6027 (Figure 9B), ATL6074 (Figure 9C), ATL6075 (Figure 9D), identified via phage display.

Table 4 lists the inhibitory antibodies identified through phage display.

Subject	15-PGDH inhibitory antibodies discovered	EC50, M	Selection strategy

SU_0001238	ATL_0006075	2.68E-10	Soluble selection, Neutravidin - captured ELISA
SU_0001271	ATL_0006027	9.50E-09	Soluble selection, direct coated ELISA
SU_0001286	ATL_0006074	1.71E-10	Soluble selection, Neutravidin - captured ELISA
SU_0001242	ATL_0006026	8.60E-09	Soluble selection, direct coated ELISA

Table 4. 15-PGDH inhibitory antibodies discovered using phage display and the outlined selection strategy.

As mentioned above, an additional antibody, ATL_0006058, was identified by mass spectrometry in a cognitively healthy PD patient (SU478) who was found to be strongly seroreactive for PGDH, and the antibody (native VH-VL pair) was also found to inhibit PGDH with high affinity (EC50= 2.81E-10M).

In summary, 5 antibodies (ATL_6058; ATL_6075; ATL_6074; ATL_6027; ATL_6026) that bind and inhibit PGDH with high affinity were identified. These antibodies were further characterised as shown in the examples below.

EXAMPLE 3 – Kinetics and cross-reactivity

Next, binding affinity and cross-reactivity of the 5 antibodies identified in Example 2 was determined by biolayer interferometry (BLI). The results of this are shown on Fig. 10, and summarised in Table 5 below. The data show that all the human monoclonal antibodies tested are cross reactive with mouse PGDH and bind PGDH with high affinity. ATL6074 has highest on-rate but relatively faster off-rate, all others have slow off-rates. Thus, none of the antibodies have kinetic properties that would make them less suitable candidates, and all were further studied for stability (see below).

Antibody	rhPGDH KD, M	rhPGDH ka, 1/Ms	rhPGDH kd, 1/s
ATL_0006026	2.56E-10	8.82E+04	2.25E-05
ATL_0006058	<1.0E-12	2.90E+05	<1.0E-07
ATL_0006074	5.87E-10	1.07E+06	6.29E-04
ATL_0006075	1.59E-10	8.69E+04	1.38E-05
ATL_0006027	<1.0E-12	2.80E+05	<1.0E-07

Table 5a. Kinetic rate constant for antibodies binding to human 15-PGDH. Fits for some antibodies cannot be accurately calculated due to the very slow dissociation (<1.0E-07 1/s) and so an estimate of equilibrium dissociation constant is provided <1.0E-12 M. rh = recombinant human.

Antibody	rmPGDH KD, M	rmPGDH ka, 1/Ms	rmPGDH kd, 1/s
ATL_0006026	6.27E-10	1.04E+05	6.53E-05
ATL_0006058	2.09E-10	1.02E+05	2.12E-05
ATL_0006074	4.67E-10	1.10E+06	5.13E-04
ATL_0006075	8.02E-10	1.32E+05	1.06E-04
ATL_0006027	<1.0E-12	1.57E+05	<1.0E-07

Table 5b. Kinetic rate constant for antibodies binding to mouse 15-PGDH. Fits for some antibodies cannot be accurately calculated due to the very slow dissociation (<1.0E-07 1/s) and so an estimate of equilibrium dissociation constant is provided <1.0E-12 M _{rm} = recombinant mouse.

In conclusion, these data show that all tested antibodies are cross-reactive and bind with high affinity to both human and mouse PGDH. This has several advantages, including the fact that downstream testing and optimisation of the antibodies does not require humanised mouse models.

Binding affinity of the 5 antibodies was also assessed by SPR. The results are shown in Fig. 11, and summarised in Table 6 below.

Antibody	Mean KD, M	Mean ka, 1/Ms	Mean kd, 1/s	n
ATL_0006026	2.70E-09	5.10E+04	1.40E-04	8
ATL_0006027	3.80E-09	8.40E+04	3.40E-04	2
ATL_0006058	<2.0E-10	2.20E+05	<4.5E-05	8
ATL_0006074	1.70E-09	9.40E+04	1.60E-04	8
ATL_0006075	1.30E-09	3.80E+04	2.90E-04	8

Table 6. Kinetic rate constant for antibodies binding to human. A fit for ATL_0006058 cannot be accurately calculated due to the very low dissociation observed during the assay timecourse and so upper bound estimates of equilibrium constant KD and off rate kd are provided.

These data show that all antibodies tested have a binding affinity below 10 nM in a format in which the antigen is free in solution (in the absence of surface-related avidity effects caused by divalent antibody).

EXAMPLE 4 – Stability study

To ensure that ATL_6026, ATL6027, ATL_6058, ATL_6074 and ATL_6075 are stable antibodies purified from small scale antibody expression batches were tested for their stability.

Figure 12 shows that all antibodies tested show good thermostability (within the ranges expected for IgG), with ATL6058 showing the highest thermostability.

Tables 7A-C below summarise the properties of the antibodies described herein. All antibodies of the disclosure strongly bind and inhibit PGDH. Figure 13 shows the VH and VL sequences of these antibodies, aligned using the IMGT numbering.

Identifier	VL discovery method	Subject resiliency	Subject	Titration ELISA EC50, M
ATL_0006026	Phage display	Resilient - RBD without diagnosed PD	SU_00001242	8.60E-09
ATL_0006058	Mass Spec	Parkinson's	SU_0000478	2.81E-10
ATL_0006074	Phage display	Progressor, long history of PD	SU_0001286	1.71E-10

ATL_0006075	Phage display	Resilient - RBD without diagnosed PD	SU_0001238	2.68E-10
ATL_0006027	Phage display	Healthy; no RBD	SU_0001271	9.50E-09

Table 7A. Summary of properties of antibodies of the disclosure (origin and binding by ELISA).

Identifier	PGDH Maximum inhibition % Average	PGDH Maximum inhibition % stdev	PGDH inhibition IC50, M	Inhibits
ATL_0006026	68	22	1.2E-08	Yes (n=4)
ATL_0006058	23	13	<1.0E-09	Yes (n=3)
ATL_0006074	82	15	3.0E-09	Yes (n=4)
ATL_0006075	85	4	3.9E-09	Yes (n=2)
ATL_0006027	25	9	1.0E-08	Yes (n=3)

Table 7B. Summary of properties of antibodies of the disclosure (inhibition).

Identifier	Tm1 (°C) (FF Ratio 350nm/330nm)	Tagg(°C) (SLS 266nm)	SEC-HPLC purity	SDS-PAGE purity
ATL_0006026	71	66	>95%	>95%
ATL_0006027	65	74	>95%	>95%
ATL_0006058	75	73	>90%	>90%
ATL_0006074	65	63	N/A	>95%
ATL_0006075	66	65	>95%	>95%

5 Table 7C. Summary of properties of antibodies of the disclosure (thermostability and production).

10 Tables 7A-C show that Tm1 and Tm2 was within a normal range for monoclonal antibodies (mAbs) and Tagg occurs at or very close to Tm1, indicating that aggregation is induced by unfolding more strongly than by protein-protein or protein-buffer interaction. The purity levels indicate that the antibodies are not significantly dissociating into their respective heavy and light chains. The purity analysis also indicates that the antibodies are not forming higher order species indicative of aggregation or co-purifying with host cell proteins that would affect subsequent assays.

EXAMPLE 5 – In silico protein structure predictions

15 For further functional characterisation, antibodies ATL6026 and ATL6058 were prioritised because they are both strong inhibitors of PGDH, but were identified with different methods from different individuals. ATL6026 was shown to have consistent high levels of PGDH inhibition across multiple biological replicates (antibody batches). The VH was identified by serum screening of a PD prodromal patient (resilient patient with 12 years RBD (REM sleep behaviour disorder, a prodromal PD marker), no PD and no cognitive impairment - normal MoCA score, 29/30), and seroreactive for PGDH. The VL was identified through phage display.

20 display.

AlphaFold-Multimer v2.3.2 was used with default parameters for predicting antibody-antigen complex structures. To create input FASTA files for each complex prediction, we combined the antibody VH and VL sequences with two identical PGDH amino acid sequences, forming an antigen representation as a dimer. The PGDH amino acid sequence was derived from an in-house construct utilized in *in vitro* assays. The highest confidence predicted complex structures were selected for subsequent structural analysis. Contacts between residues that form the paratope of the antibody are those with at least one atom found within 4.5 Å of any atom from the target epitope.

The antibody was predicted by AlphaFold2 (AF2) to bind and block the PGDH active site. ATL6026 is predicted to bind directly at the PDGH active site (Figure 14A and Table 8).

ATL6058 also was shown to have consistent PGDH inhibition but with a different inhibition profile (compare Fig. 5 and 9). It was discovered using mass spectrometry from patient serum and therefore has a native VL. It has the highest thermostability of the antibodies tested. It was discovered in a patient with very late onset PD and no cognitive impairment, and this patient's serum was the most inhibitory and most reactive of the samples tested. Based on its predicted protein structure, the antibody was predicted to bind at a different site from ATL6026, at a site suggesting allosteric inhibition (see Figure 14B and Table 9). The predicted paratope residues are shown in Table 10.

Amino acid position in 15-PGDH (Uniprot: P15428)	Amino acid
143	M
144	P
145	V
146	A
147	Q
185	F
206	Y
208	D
209	H
212	D
213	M
215	K
216	Y
217	Y
218	G
246	T
247	T
248	S
163	R
167	L
170	N

171	L
237	A
239	N
258	T
259	T
260	P
261	F
262	Q

Table 8. Predicted 15-PGDH epitope residues (obtained by alphafold2) for ATL6026.

Amino acid position in 15-PGDH (Uniprot: P15428)	Amino acid
221	D
224	L
227	N
231	T
235	D
237	A
238	L
246	T
247	T
248	S
249	K
250	G
251	I
252	H
253	F
255	D

Table 9. Predicted 15-PGDH epitope residues (obtained by alphafold2) for ATL6058.

Antibody	chain type	position	residue
ATL_0006026	VH	29	T
ATL_0006026	VH	36	S
ATL_0006026	VH	37	Y
ATL_0006026	VH	38	G
ATL_0006026	VH	55	W
ATL_0006026	VH	57	S
ATL_0006026	VH	59	Y

ATL_0006026	VH	62	N
ATL_0006026	VH	64	N
ATL_0006026	VH	66	N
ATL_0006026	VH	107	D
ATL_0006026	VH	109	G
ATL_0006026	VH	110	P
ATL_0006026	VH	111	Y
ATL_0006026	VH	111A	Y
ATL_0006026	VH	111B	Y
ATL_0006026	VH	111C	D
ATL_0006026	VH	112D	S
ATL_0006026	VH	112C	S
ATL_0006026	VH	112B	G
ATL_0006026	VH	112A	Y
ATL_0006026	VH	113	Y
ATL_0006026	VL	35	A
ATL_0006026	VL	36	G
ATL_0006026	VL	37	Y
ATL_0006026	VL	109	N
ATL_0006026	VL	113	S
ATL_0006026	VL	114	L
ATL_0006058	VH	29	S
ATL_0006058	VH	35	T
ATL_0006058	VH	36	S
ATL_0006058	VH	37	Y
ATL_0006058	VH	38	F
ATL_0006058	VH	57	Y
ATL_0006058	VH	59	S
ATL_0006058	VH	64	S
ATL_0006058	VH	108	L
ATL_0006058	VH	109	F
ATL_0006058	VH	110	F
ATL_0006058	VH	111	G
ATL_0006058	VH	112A	S
ATL_0006058	VH	114	H
ATL_0006058	VL	36	S
ATL_0006058	VL	38	Y
ATL_0006058	VL	52	R
ATL_0006058	VL	55	Y

Table 10. Predicted paratope residues in the VH and VL of ATL6026 and ATL6058 obtained by alphafold2.

These *in silico* predictions are therefore a further indication that the antibodies are inhibitory. Further experimental characterisation will be carried out to confirm these predictions, e.g. by epitope binding or crystallography.

5

EXAMPLE 6 --- *in vitro* PD model

The pro-inflammatory cytokine IL-6 is elevated in serum and cerebrospinal fluid (CSF) of PD patients, and increased levels of IL-6 are associated with non-motor symptoms and cognitive dysfunction indicating that IL-6 plays a role in a pathophysiology of non-motor symptoms in PD (Wijeyekoon et al., 2020; Fu et al., 2023).

10

IL-6 in the CNS is secreted by astrocytes, microglia, oligodendrocytes, neurons, and endothelial cells. Each of these cell types can contribute to the overall IL-6 levels in response to various stimuli, playing roles in both normal physiology and in pathological conditions. To test whether the anti-15-PGDH antibodies of the present disclosure were able to reduce the levels of inflammation, ATL6026 and ATL6058 were tested in an iPSC-derived tri-culture system. The culture system was established using iPSC-derived dopaminergic neurons, astrocytes, and microglia, to recapitulate physiological conditions of the central nervous system and treated with pre-formed α Syn fibrils to induce PD like inflammation and pathology (Figure 15).

15

In this model, both ATL6026 and ATL6058 significantly engage with their target, resulting in decreased 15-PGDH levels in cell lysates and cell culture supernatants compared with an isotype control antibody (Figures 16A and 16B). ATL6026 also significantly reduced the levels of IL-6 in cell culture supernatants (Figure 16C).

20

The tri-culture system not only recapitulated the inflammatory effects seen in PD but also several aspects of PD pathology including mitochondrial dysfunction and seeding of α Synuclein. Exposure of cells to alpha synuclein fibrils in neuronal cell models has previously been shown to result in mitochondrial dysfunction shown by loss of mitochondrial membrane potential (MMP), decreased ATP production and increased ROS (Thorne and Tumbarello, 2022). To test whether the anti-15-PGDH antibodies of the present disclosure were able to reduce mitochondrial dysfunction, the red/green fluorescence intensity ratio of the tri-culture system with JC-1 dye was measured as an indicator of MMP. The results showed that α Synuclein preformed fibrils (α Syn PFFs) depolarize the mitochondrial membrane, and ATL6026 and ATL6058 rescue this depolarization (Figure 17). These data suggest a role for these anti-15-PGDH antibodies in decreasing α Syn fibril-mediated mitochondrial dysfunction.

25

In addition, immunostaining of the tri-culture system showed that treatment with ATL-6026 decreased the abundance of phospho- α Syn129 in the α Synuclein fibril model, a post-translational modification characteristic for the pathogenic α Synuclein species (Figure 18A and 18B).

30

These *in vitro* data highlight the therapeutic promise of the anti-15-PGDH antibodies of the present disclosure for the treatment of neuroinflammatory disorders and synucleinopathies, such as PD, as demonstrated by their ability to reduce neuroinflammation, mitochondrial dysfunction and the abundance

of phospho- α Syn129. The levels of PGE2 in the supernatant of such cultures will also be tested, and it is expected that addition of ATL6026 will result in an increase in PGE2 in the supernatant.

EXAMPLE 7 – In vivo LPS challenge mouse model of inflammation

- 5 To test whether the anti-15-PGDH antibodies of the present disclosure were able to reduce levels of neuroinflammation *in vivo*, the inventors examined the effect of ATL6026 treatment on inflammatory markers in a C57BL/6 mouse model of neuroinflammation induced by lipopolysaccharide (LPS) via intraperitoneal (i.p.) injection.
- 10 LPS is a component of the outer membrane of gram-negative bacteria and when administered centrally or systemically is commonly used as an inflammatory model (Cavaillon et al., 2017). LPS is used as an inflammatory inducer by activating microglia and triggering the response of cytokines, monocytes, macrophages, and other inflammatory mediators (da Silva et al., 2024). After LPS exposure microglia in the brain become activated, undergo a morphological and functional change to initiate an inflammatory
- 15 cascade. This activation leads to the release of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), exacerbating neuroinflammation.

Wild type mice were pretreated with ATL6026 and their inflammatory cytokine response to LPS was assessed by measuring levels of interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor-alpha

20 (TNF- α) in the plasma and the brain. A small molecule PGDH inhibitor (SW, SW033291) was used as a positive control. Blood samples were obtained from mice at two timepoints (4h, 24h) to ensure the dynamic response was captured.

The results showed that ATL6026 decreased the LPS-induced cytokine response of all three cytokines measured in plasma at 4 hours relative to mice treated with isotype control antibody and decreased IL-6 in the plasma and brain, and TNF- α in the brain up to 24 hours post-LPS challenge (**Figure 19A-C**). For the majority of timepoints/inflammatory cytokines ATL6026 also showed a greater reduction of inflammatory

25 cytokine than the small molecule PGDH inhibitor (SW, SW033291) positive control. Notably in several cases the inflammatory cytokine response measured for the small molecule treated mice was the same or

30 greater than the isotype control group, whereas ATL6026 achieved a reduction in the level of inflammatory cytokine relative to the isotype control group in all cases. These data thus suggest ATL6026 is more effective at reducing levels of neuroinflammation *in vivo* compared to the small molecule inhibitor of PGDH.

The results indicate that the anti-15-PGDH antibodies of the present disclosure (e.g. ATL6026) are able to

35 reduce the inflammatory response in the periphery and the brain, providing further evidence of the potential utility of these antibodies in the treatment of neuroinflammatory disorders such as PD.

EXAMPLE 8 – In vivo assessment of gait and postural stability in aged mice

Aging is major risk factor for Parkinson's disease and affects the disease in several ways. The effects of aging can be seen at many levels and impacts cellular processes that can lead to neurodegeneration

40 (Hindle 2010). Subsequently, this negatively impacts gait and postural stability (Levy 2007). Postural

instability, or difficulty balancing, is possibly the most challenging of the major Parkinson's disease symptoms.

To evaluate the effects of treatment with the anti-15-PGDH antibodies of the present disclosure on gait and postural stability in aged mice, ATL6026 was administered to 22-month-old C57BL/6J mice and animal performance for fine motor kinematic gait was assessed after 4 weeks of dosing. A small molecule PGDH inhibitor (SW, SW033291) was used as a positive control.

Treatment with ATL6026 positively impacted several key aspects of gait such as speed, hind stance time, diagonal interlimb coordination, double support, maximum knee angle, and peak hind leg swing speed, indicating a promising therapeutic effect toward improved movement and postural stability (Figure 20A-F). Notably, a comparison of overall gait score between the treatment groups shows mice treated with ATL6026 had a more profound positive effect in gait and stability vs isotype control (Figure 21A) than was achieved by the small molecule inhibitor of 15-PGDH vs vehicle (Figure 21B).

Together, these data (Examples 6-8) demonstrate the identification of inhibitory 15-PGDH antibodies with therapeutic potential in neuroinflammatory disorders and synucleinopathies, such as PD, as demonstrated by their ability to improve gait and postural stability, as well as reducing neuroinflammation, mitochondrial dysfunction, and the abundance of phospho-αSyn129.

EXAMPLE 9 – Antibody variants

To identify lead antibodies with optimal development characteristics, variants of the VH and VL sequences of ATL_6026 (SEQ ID NO: 1 and 6) and ATL_6058 (SEQ ID NO: 3 and 8) were generated and tested for purity, thermal stability, and binding and inhibition of human 15-PGDH.

In order to generate VH and VL variants, the ATL_6026 and ATL_6058 VH and VL sequences were compared with the closest respective germline VH and VL sequences and found to have a number of amino acid substitutions compared with the nearest germline sequences (Table 11). Reverting sequences to germline typically reduces immunogenicity and improves antibody expression and stability.

In addition, theoretical liability sequence motifs were identified in the ATL_6026 VH and VL sequences and the ATL_6058 VH sequence based on known predicted deamidation (NS, NG, NT), isomerisation (DG, DS, DT, DD), and oxidation (M) sequence motifs (using the methods in Lu et al. 2019; Table 11).

Therefore variants were generated with one or more of these liability sequence motifs mutated to substitute one or more amino acids within a motif with an amino acid with similar charge properties ("liability mutation") in an effort to screen the effect of removing of these motifs on purity, stability, binding and inhibition. Removal of these motifs reduces the theoretical risk of post-translational amino acid modifications (e.g. deamidation, isomerization, and oxidation) which potentially negatively impact long term stability, shelf life and/or manufacturability in development stages.

Antibody	Nearest germline	Difference(s) to nearest germline (Parent_residue,	Potential liability motifs identified (Parent residue(s) IMGT number(s))	Liability mutations in tested variants
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		IMGT number, Germline_residue)		(Parent_residue, IMGT number, variant_residue)
ATL_6026 - heavy chain variable region (SEQ ID NO: 1)	IGHV1-18*01 (SEQ ID NO: 174)	Q5V	M 53, NG 62 63, NT 64 65, M 78, DT 81 82, M 89, DD 97 98, DT 98 99, DS 111.C 112.D, M 123	M53A, N62A/Q, G63A, N64A, T65A/S, M78I/A, D81E, M89A, D97E, D98E, T99A, D111.CE, S112.DA, M123T
ATL_6026 - light chain variable region (SEQ ID NO: 6)	IGLV1-40*01 (SEQ ID NO: 175)	A2S, S8P, P52L, V90A, V124L	NS 57 65, NS 109 113	N57A/Q, S65A/N, N109Q/A, S113A/N
ATL_6058 - heavy chain variable region (SEQ ID NO: 3)	IGHV4-4*07 (SEQ ID NO: 176)	A40S, R49G, S66N, K85N, T92S, M122T	DS 28 29, M 78, DT 81 82, DT 98 99, M122	D28E, S29A, M78I, D81E, M122T
ATL_6058 - light chain variable region (SEQ ID NO: 8)	IGKV3-20*01 (SEQ ID NO: 177)	P49A, R52L, G74D, S90T	N/A	N/A

Table 11. Summary of tested germline variations and liability mutations.

Sequence variant antibodies were expressed from Chinese Hamster Ovary (CHO) cells and purified using Protein A capture and low pH elution. Antibodies were buffer exchanged and stored in 20 mM Histidine acetate buffer pH 5.5, 150 mM Sodium chloride at -80°C.

- 5 Purity of the variant antibody batches was assessed using size exclusion chromatography (SEC-HPLC), thermostability was assessed using a thermal shift assay, binding potency to human 15-PGDH was tested using biolayer interferometry (BLI), and their inhibition of human 15-PGDH was tested using a fluorescence-based assay.

- 10 All of the variants of ATL_6026 and ATL_6058 expressed were identified as having > 95% monomeric purity by SEC-HPLC. Some variants were screened by CE-SDS for monomeric purity (%) in non-reducing conditions. They all showed >95% purity (data not shown).

- 15 Thermal unfolding data for twenty-four variants of ATL_6026 were generated, with all showing $T_{m1} > 58^{\circ}\text{C}$ (T_{m1} being the temperature at which 10% of the mAb in solution is determined to be unfolded). The thermostability of all variants was acceptable, with the lowest T_{m1} observed for a variant antibody being 10°C lower than the parent in this formulation, and the lead candidate ATL_7955 having a slightly lower T_{m1} (by 5° C) than the parent. (Table 12a).

Antibody	T_{m1} (°C)
ATL_0006026	68
ATL_0007450	66
ATL_0007819	66
ATL_0007820	66
ATL_0007821	67
ATL_0007822	68
ATL_0007823	68

ATL_0007824	67
ATL_0007825	66
ATL_0007826	63
ATL_0007827	68
ATL_0007829	67
ATL_0007889	69
ATL_0007890	69
ATL_0007892	65
ATL_0007893	69
ATL_0007896	66
ATL_0007899	64
ATL_0007900	68
ATL_0007901	67
ATL_0007902	67
ATL_0007925	63
ATL_0007952	59
ATL_0007953	58
ATL_0007955	63

Table 12a. Thermostability data for antibody variants of ATL_6026.

Thermal unfolding data for eight variants of ATL_6058 were generated, with all showing $T_{m1} = 64 \pm 1^{\circ}\text{C}$, very similar to the parent (**Table 12b**).

Antibody	T_{m1} ($^{\circ}\text{C}$)
ATL_0006058	64
ATL_0007926	65
ATL_0007927	65
ATL_0007928	64
ATL_0007929	64
ATL_0007930	64
ATL_0007931	64
ATL_0007932	64
ATL_0007933	64

Table 12b. Thermostability data for antibody variants of ATL_6058.

5 Variants were created in multiple rounds, with the results from each round used to inform the design of the next set of variants. All sequence variants were screened by comparing their binding profile to the parent in a biolayer interferometry (BLI) binding assay to human 15-PGDH. Data are summarised in **Table 13**.

Following BLI, sequence variants with parent-like binding response were tested for 15-PGDH inhibition, where variants with a similar fluorescence response to the parent were considered to have mutations with
10 no negative impact on function. A summary of the data is presented in **Table 14**.

Antibody	Response (nm)	Response (nm)	Response (nm)	Passed inhibition
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	round 1 screen	round 1.2 screen	round 2 screen	screen? ($\text{slope}_{\text{sample}} < \text{slope}_{\text{isotype}}$ control/non- binder)
ATL_0006026	0.3952	0.3398	0.2433	Y
ATL_0007450	0.4321	0.3527		Y
ATL_0007819		0.2863		Y
ATL_0007820		0.3446		Y
ATL_0007821		0.3326		Y
ATL_0007822		0.3241		Y
ATL_0007823		0.3257		Y
ATL_0007824		0.3734		Y
ATL_0007825		0.2857		Y
ATL_0007826		0.339		Y
ATL_0007827		0.3302		Y
ATL_0007829		0.328		Y
ATL_0007889			0.2222	Y
ATL_0007890			0.0863	Y
ATL_0007892			0.2457	Y
ATL_0007893			0.1792	Y
ATL_0007895			0.1027	Y
ATL_0007896			0.2404	Y
ATL_0007899			0.2456	Y
ATL_0007900			0.1762	Y
ATL_0007901			0.2046	Y
ATL_0007902			0.2336	Y
ATL_0007917			0.0835	Y
ATL_0007918			0.1196	Y
ATL_0007919			0.0965	Y
ATL_0007920			0.0917	Y
ATL_0007921			0.111	Y
ATL_0007922			0.1269	Y
ATL_0007923			0.1035	Y
ATL_0007924			0.102	Y

ATL_0007925			0.2843	Y
ATL_0006058	0.3807	0.4356	0.408	Y
ATL_0007467	0.408			Y
ATL_0007468	0.4533			Y
ATL_0007469	0.4422			Y
ATL_0007470	0.4003			Y
ATL_0007471	0.3835			Y
ATL_0007472		0.3236		Y
ATL_0007473		0.4623		Y
ATL_0007926			0.2849	Y
ATL_0007927			0.3307	Y
ATL_0007928			0.2865	Y
ATL_0007929			0.3041	Y
ATL_0007930			0.2933	Y
ATL_0007931			0.311	Y
ATL_0007932			0.2982	Y

Table 13. Summary of screen for variant binding to human 15-PGDH and enzymatic inhibition.

5 Variants displaying similar binding and inhibition to the parent were further evaluated based on their sequence risk. Sequence risk was assessed based on the number of residues in the framework different to nearest germline and the number of theoretical liability motifs present, with the objective of minimizing both. ATL_7925 was determined to be the optimum of the ATL_6026 variants generated, ATL_7933 was the optimum of the ATL_6058 variants generated. These became the lead candidates for the final round.

Three backup variants to ATL_7925 were selected by either removing more, or different, theoretical liability motifs in the VH; ATL_7952 being more human-like and ATL_7953 and ATL_7955 having fewer remaining theoretical liability motifs.

- 10 One backup variant to ATL_7933 was selected with the mutation M122T which simultaneously removed a theoretical liability motif (methionine oxidation) and reverted the residue to germline.

The parent, lead and backup variants are summarised in **Table 14** and a sequence alignment of these antibodies according to IMGT numbering is provided as **Figure 22**.

- 15 Kinetic parameters (KD, Kon and Koff) for the lead and backup candidates binding to human 15-PGDH were derived by BLI (sensorgrams shown in **Figure 23**). Their maximum inhibition by enzymatic activity was measured by a fluorescence-based enzymatic activity assay, both of which were similar to the parent antibodies ATL_6026 and ATL_6058, and displayed concentration dependent inhibition of 15-PGDH (**Table 14; Figures 24 and 25**). Following this final round, ATL_7955 was determined to be the lead from the ATL_6026 variants generated, ATL_7933 was the optimum of the ATL_6058 variants generated.

Antibody	K_D (M)	K_{on} ($M^{-1} s^{-1}$)	K_{off} (s^{-1})	Max inhibition (%)	VH substitutions relative to parent (IMGT numbering)	VL substitutions relative to parent (IMGT numbering)
ATL_0006026	1.49e-9	1.01e+5	1.49e-4	63	-	-
ATL_0007955	8.57e-10	1.15e+5	9.87e-5	61	Q5V, G63A, T65S, D97E, T99A, S112.DA, M123T	A2S, S8P, S65N, V90A, S113N, V124L
ATL_0007925	2.251e-9	1.167e+5	2.627e-4	41	Q5V, D81E, D98E, M123T	A2S, S8P, S65N, V90A, S113N, V124L
ATL_0007952	8.95e-10	1.30e+5	1.16e-4	55	Q5V, N62Q, D98E, S112.DA, M123T	A2S, S8P, S65N, V90A, S113N, V124L
ATL_0007953	1.22e-9	1.18e+5	1.44e-4	63	Q5V, N62Q, T65A, D81E, D98E, S112.DA, M123T	A2S, S8P, S65N, V90A, S113N, V124L
ATL_0006058	1.517e-10	3.1e+5	4.703e-5	87	-	-
ATL_0007933	1.605e-9	4.024e+5	6.456e-4	87	D28E, A40S, R49G, S66N, M78I, D81E, K85N, T92S	P49A, R52L, G74D, S90T
ATL_0007956	8.794e-10	3.886e+5	3.417e-4	85	D28E, A40S, R49G, S66N, M78I, D81E, K85N, T92S, M122T	P49A, R52L, G74D, S90T

Table 14. Summary of lead and backup variants of ATL_6026 and ATL_6058 with binding parameters to human 15-PGDH and enzymatic inhibition.

5 Kinetic parameters for antibody binding to 15-PGDH orthologs found in non-human primate (*Macaca fascicularis*) and rodent (*Mus musculus* and *Rattus norvegicus*) species were also derived by BLI. As shown in **Table 15**, the parents and all variants tested had similar binding to non-human primate (*Macaca fascicularis*) and rodent (*Mus musculus* and *Rattus norvegicus*) 15-PDGH, as compared to binding to human 15-PDGH.

Antibody	Macaca fascicularis		
	K_D (M)	K_{on} ($M^{-1} s^{-1}$)	K_{off} (s^{-1})
ATL_0006026	1.44e-9	1.27e+5	1.82e-4
ATL_0007925	2.26e-9	1.34e+5	3.01e-4

ATL_0007952	9.71e-10	1.57e+5	1.52e-4
ATL_0007953	1.11e-9	1.53e+5	1.70e-4
ATL_0007955	7.99e-10	1.41e+5	1.13e-4
ATL_0006058	6.66e-11	3.283e+5	2.186e-5
ATL_0007933	1.422e-9	4.599e+5	6.538e-4
ATL_0007956	1.284e-9	4.713e+5	6.05e-4

Table 15a. Summary of lead and backup variants of ATL_6026 and ATL_6058 with binding parameters to Macaca fascicularis 15-PGDH.

Mus musculus			
Antibody	K _D (M)	K _{on} (M ⁻¹ s ⁻¹)	K _{off} (s ⁻¹)
ATL_0006026	1.31e-10	1.48e+5	1.93e-5
ATL_0007925	1.49e-10	1.68e+5	2.51e-5
ATL_0007952	1.39e-10	1.65e+5	2.30e-5
ATL_0007953	1.51e-10	1.48e+5	2.24e-5
ATL_0007955	1.03e-10	1.38e+5	1.41e-5
ATL_0006058	1.02e-10	7.414e+4	7.581e-6
ATL_0007933	8.86e-10	1.584e+5	1.404e-4
ATL_0007956	9.43e-10	1.463e+5	1.381e-4

Table 15b. Summary of lead and backup variants of ATL_6026 and ATL_6058 with binding parameters to Mus musculus 15-PGDH.

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Rattus norvegicus			
Antibody	K _D (M)	K _{on} (M ⁻¹ s ⁻¹)	K _{off} (s ⁻¹)
ATL_0006026	1.41e-10	1.03e+5	1.45e-5
ATL_0007925	2.44e-10	1.17e+5	2.86e-5
ATL_0007952	1.62e-10	1.19e+5	1.93e-5
ATL_0007953	9.90e-11	1.05e+5	1.04e-5
ATL_0007955	2.45e-10	9.83e+4	2.41e-5
ATL_0006058	2.26e-10	3.616e+5	8.182e-5
ATL_0007933	2.106e-9	5.721e+5	1.205e-3
ATL_0007956	3.179e-9	5.14e+5	1.634e-3

Table 15c. Summary of lead and backup variants of ATL_6026 and ATL_6058 with binding parameters to Rattus norvegicus 15-PGDH.

References

10 A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. The entirety of each of these references is incorporated herein.

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- 15 For standard molecular biology techniques, see Sambrook, J., Russel, D.W. *Molecular Cloning, A Laboratory Manual*. 3 ed. 2001, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory Press.

Claims:

1. An isolated antibody that specifically binds and inhibits 15-PGDH.
2. The isolated antibody according to claim 1, wherein the antibody comprises a heavy chain variable domain with the following CDRs:

5 CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 12 (ATL_6027); SEQ ID NO: 13 (ATL_6058; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 14 (ATL_6074); SEQ ID NO: 15 (ATL_6075); SEQ ID NO: 112 (ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932) or SEQ ID NO: 191 (ATL_7471);

10 CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); SEQ ID NO: 16 (ATL_6026; ATL_7925; ATL_7450; ATL_7819; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7919; ATL_7920; ATL_7923); SEQ ID NO: 17 (ATL_6027); SEQ ID NO: 18 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 19 (ATL_6074); SEQ ID NO: 20 (ATL_6075); SEQ ID NO: 96 (ATL_7952; ATL_7917; ATL_7918; ATL_7921; ATL_7922; ATL_7924); SEQ ID NO: 97 (ATL_7953); SEQ ID NO: 154 (ATL_7820); SEQ ID NO: 155 (ATL_7821); SEQ ID NO: 156 (ATL_7822); or SEQ ID NO: 157 (ATL_7823); and

15 CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955; ATL_7952; ATL_7953; ATL_7829); SEQ ID NO: 21 (ATL_6026; ATL_7925; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7918; ATL_7919; ATL_7921; ATL_7924); SEQ ID NO: 22 (ATL_6027); SEQ ID NO: 23 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 24 (ATL_6074); SEQ ID NO: 25 (ATL_6075); or SEQ ID NO: 162 (ATL_7917; ATL_7920; ATL_7922; ATL_7923);

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or a set of CDRs containing one to six amino acid mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs.

3. The isolated antibody according to any preceding claim, wherein the antibody comprises a heavy chain variable domain with the following CDRs:
- 40

CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953);

CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); SEQ ID NO: 16 (ATL_6026; ATL_7925); SEQ ID NO: 96 (ATL_7952); or SEQ ID NO: 97 (ATL_7953); and

5 CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955; ATL_7952; ATL_7953); or SEQ ID NO: 21 (ATL_6026; ATL_7925);

or a set of CDRs containing one to six, or one to three amino acid mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs, optionally wherein the

10 substitution is at position 62, optionally wherein the substitution is N62A or N62Q, and/or at position 63, optionally wherein the substitution is G63A; and/or at position 64, optionally wherein the substitution is N64A; and/or at position 65, optionally wherein the substitution is T65A or T65S; and/or at position 111C, optionally wherein the substitution is D111CE; and/or at position 112D, optionally wherein the substitution is S122DA;

optionally wherein the heavy chain variable domain (VH) comprises the following framework
15 sequences: HFWR1 of SEQ ID NO: 41 (ATL_6026) or SEQ ID NO: 95 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); HFWR2 of SEQ ID NO: 42 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955); HFWR3 of SEQ ID NO: 43 (ATL_6026); SEQ ID NO: 99 (ATL_7925; ATL_7953); SEQ ID NO: 100 (ATL_7952); or SEQ ID NO: 101 (ATL_7955); and HFWR4 of SEQ
20 ID NO: 44 (ATL_6026); or SEQ ID NO: 103 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); or

framework sequences with one to nine or one to six mutations, optionally wherein the mutations
25 are substitutions, compared with the framework sequences above, optionally wherein the substitution is at position 5, optionally wherein the substitution is Q5V, and/or at position 53, optionally wherein the substitution is M53A; and/or at position 78, optionally wherein the substitution is M78I or M78A; and/or at position 81, optionally wherein the substitution is D81E; and/or at position 89, optionally wherein the substitution is M89A; and/or at position 97, optionally
wherein the substitution is D97E; and/or at position 98, optionally wherein the substitution is D98E; and/or at position 99, optionally wherein the substitution is T99A; and/or at position 123, optionally wherein the substitution is M123T.

30 4. The isolated antibody according to claim 3, wherein the antibody binds to an epitope that comprises one or more or all of residues Met143; Pro144; Val145; Ala146; Gln147; Phe185; Tyr206; Asp208; His209; Asp212; Met213; Lys215; Tyr216; Tyr217; Gly218; Thr246; Thr247; Ser248; Arg163; Leu167; Asn170; Leu171; Ala237; Asn239; Thr258; Thr259; Pro260; Phe261; Gln262 of 15 PGDH, provided as SEQ ID NO: 82.

35 5. The isolated antibody according to any preceding claim, wherein the antibody comprises a heavy chain variable domain with the following CDRs:

CDRH1 comprising an amino acid sequence of SEQ ID NO: 11 (ATL_7955);

CDRH2 comprising an amino acid sequence of SEQ ID NO: 98 (ATL_7955); and

40 CDRH3 comprising an amino acid sequence of SEQ ID NO: 102 (ATL_7955);

optionally wherein the heavy chain variable domain (VH) comprises the following framework sequences:

HFWR1 of SEQ ID NO: 95 (ATL_7955);
HFWR2 of SEQ ID NO: 42 (ATL_7955);
HFWR3 of SEQ ID NO: 101 (ATL_7955); and
HFWR4 of SEQ ID NO: 103 (ATL_7955).

5

6. The isolated antibody according to claim 1 or claim 2, wherein the antibody comprises a heavy chain variable domain with the following CDRs:

CDRH1 comprising an amino acid sequence of SEQ ID NO: 13 (ATL_6058); or SEQ ID NO: 112 (ATL_7933, ATL_7956);

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CDRH2 comprising an amino acid sequence of SEQ ID NO: 18 (ATL_6058; ATL_7933; ATL_7956); and

CDRH3 comprising an amino acid sequence of SEQ ID NO: 23 (ATL_6058; ATL_7933; ATL_7956);

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or a set of CDRs containing one, two, or three amino acid, mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs, optionally wherein the substitution is at position 28, optionally wherein the substitution is D28E; and/or at position 29, optionally wherein the substitution is S29A;

optionally wherein the heavy chain variable domain (VH) comprises the following framework sequences: HFWR1 of SEQ ID NO: 57 (ATL_6058; ATL_7933; ATL_7956); HFWR2 of SEQ ID

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NO: 58 (ATL_6058) or SEQ ID NO: 113 (ATL_7933; ATL_7956); HFWR3 of SEQ ID NO: 59 (ATL_6058) or SEQ ID NO: 114 (ATL_7933; ATL_7956); and HFWR4 of SEQ ID NO: 60 (ATL_6058; ATL_7933) or SEQ ID NO: 115 (ATL_7956); or framework sequences with one to

eight mutations, optionally wherein the mutations are substitutions, compared with the framework

sequences above; optionally wherein the substitution is at position 40, optionally wherein the substitution is A40S; and/or at position 49, optionally wherein the substitution is R49G; and/or at

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position 66, optionally wherein the substitution is S66N; and/or at position 78, optionally wherein the substitution is M78I; and/or at position 81, optionally wherein the substitution is D81E; and/or at position 85, optionally wherein the substitution is K85N; and/or at position 92, optionally

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wherein the substitution is T92S; and/or at position 122, optionally wherein the substitution is M122T.

7. The isolated antibody according to claim 6, wherein the antibody binds to an epitope that comprises one or more (or all of) residues Asp221; Leu224; Asn227; Thr231; Asp235; Ala237; Leu238; Thr246; Thr247; Ser248; Lys249; Gly250; Ile251; His252; Phe253; Asp255 of 15 PGDH, provided as SEQ ID NO: 82.

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8. The isolated antibody according to claim 6 or claim 7, wherein the antibody comprises a heavy chain variable domain with the following CDRs:

CDRH1 comprising an amino acid sequence of SEQ ID NO: 112 (ATL_7933);

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CDRH2 comprising an amino acid sequence of SEQ ID NO: 18 (ATL_7933); and

CDRH3 comprising an amino acid sequence of SEQ ID NO: 23 (ATL_7933);

optionally wherein the heavy chain variable domain (VH) comprises the following framework sequences:

- 5 HFWR1 of SEQ ID NO: 57 (ATL_7933);
HFWR2 of SEQ ID NO: 113 (ATL_7933);
HFWR3 of SEQ ID NO: 114 (ATL_7933); and
HFWR4 of SEQ ID NO: 60 (ATL_7933).

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

- 10 HFWR1 of SEQ ID NO: 41 (ATL_6026); SEQ ID NO: 49 (ATL_6027); SEQ ID NO: 57
(ATL_6058, ATL_7933; ATL_7956; ATL_7470, ATL_7926; ATL_7927; ATL_7928;
ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468;
ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 65 (ATL_6074); SEQ ID NO: 73
(ATL_6075); or SEQ ID NO: 95 (ATL_7925; ATL_7952; ATL_7953; ATL_7955;
15 ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824;
ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892;
ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902;
ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923;
ATL_7924);
20 HFWR2 of SEQ ID NO: 42 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955;
ATL_7450; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825;
ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893;
ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917;
ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ
25 ID NO: 50 (ATL_6027); SEQ ID NO: 58 (ATL_6058; ATL_7469; ATL_7927); SEQ ID NO:
66 (ATL_6074); SEQ ID NO: 74 (ATL_6075); SEQ ID NO: 113 (ATL_7933; ATL_7956;
ATL_7467; ATL_7468; ATL_7470; ATL_7471; ATL_7472; ATL_7473; ATL_7926;
ATL_7930; ATL_7931; ATL_7932); or SEQ ID NO: 153 (ATL_7819); SEQ ID NO: 192
(ATL_7928); or SEQ ID NO: 193 (ATL_7929);
30 HFWR3 of SEQ ID NO: 43 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821;
ATL_7822; ATL_7823; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893;
ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7922); SEQ
ID NO: 51 (ATL_6027); SEQ ID NO: 59 (ATL_6058; ATL_7469); SEQ ID NO: 67
(ATL_6074; ATL_7472); SEQ ID NO: 75 (ATL_6075); SEQ ID NO: 99 (ATL_7925;
35 ATL_7953; ATL_7919); SEQ ID NO: 100 (ATL_7952; ATL_7917; ATL_7920; ATL_7921);
SEQ ID NO: 101 (ATL_7955); SEQ ID NO: 114 (ATL_7933; ATL_7956; ATL_7926;
ATL_7928; ATL_7929); SEQ ID NO: 158 (ATL_7824); SEQ ID NO: 159 (ATL_7825;
ATL_7918; ATL_7923; ATL_7924); SEQ ID NO: 160 (ATL_7826); SEQ ID NO: 161
(ATL_7827); SEQ ID NO: 194 (ATL_7931); SEQ ID NO: 195 (ATL_7932); SEQ ID NO:
40 196 (ATL_7467; ATL_7468; ATL_7470; ATL_7471); SEQ ID NO: 197 (ATL_7473); SEQ
ID NO: 198 (ATL_7927); or SEQ ID NO: 199 (ATL_7930); and

- 5 HFWR4 of SEQ ID NO: 44 (ATL_6026); SEQ ID NO: 52 (ATL_6027); SEQ ID NO: 60 (ATL_6058; ATL_7933; ATL_7469; ATL_7927); SEQ ID NO: 68 (ATL_6064); SEQ ID NO: 76 (ATL_6075); SEQ ID NO: 103 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); or SEQ ID NO: 115 (ATL_7956; ATL_7467; ATL_7468; ATL_7470; ATL_7471; ATL_7472; ATL_7473; ATL_7926; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932),
- 10 or framework sequences with one to five mutations, optionally wherein the mutations are substitutions, compared with the framework sequences above; optionally wherein the substitution is at position 78, optionally wherein the substitution is M78I or M78A; and/or at position 81; optionally wherein the substitution is D81E; and/or at position 97, optionally wherein the substitution is D97E; and/or at position 98, optionally wherein the substitution is D98E; and/or at position 98, optionally wherein the substitution is D98E; and/or at position 99, optionally wherein the substitution is T99A.
- 15
10. The isolated antibody according to any preceding claim, wherein the antibody comprises a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence identity with the amino acid sequence selected from the group consisting of: SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID NO: 5; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 109; SEQ ID NO: 110; SEQ ID NO: 118; SEQ ID NO: 119; SEQ ID NO: 120; SEQ ID NO: 121; SEQ ID NO: 122; SEQ ID NO: 123; SEQ ID NO: 124; SEQ ID NO: 125; SEQ ID NO: 126; SEQ ID NO: 127; SEQ ID NO: 128; SEQ ID NO: 129; SEQ ID NO: 130; SEQ ID NO: 131; SEQ ID NO: 132; SEQ ID NO: 133; SEQ ID NO: 134; SEQ ID NO: 178; SEQ ID NO: 179; SEQ ID NO: 180; SEQ ID NO: 181; SEQ ID NO: 182; SEQ ID NO: 183; SEQ ID NO: 184; SEQ ID NO: 185; SEQ ID NO: 186; SEQ ID NO: 187; and SEQ ID NO: 188; optionally selected from the group consisting of: SEQ ID NO: 1; SEQ ID NO: 3; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 109; SEQ ID NO: 110; optionally selected from the group consisting of: SEQ ID NO: 93 and SEQ ID NO: 109.
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- 25
- 30
11. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL), with the following CDRs:
- 35 CDRL1 comprising an amino acid sequence of SEQ ID NO: 26 (ATL_7955; ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7901; ATL_7902; ATL_7917; ATL_7918; ATL_7919; ATL_7920; ATL_7921; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 27 (ATL_6027); SEQ ID NO: 28 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468;
- 40

- ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 29 (ATL_6074); or SEQ ID NO: 30 (ATL_6075);
- CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955; ATL_7925; ATL_7952; ATL_7953; ATL_7900; ATL_7919; ATL_7923); SEQ ID NO: 31 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7901; ATL_7902; ATL_7920); SEQ ID NO: 32 (ATL_6027); SEQ ID NO: 33 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 34 (ATL_6074); SEQ ID NO: 35 (ATL_6075); SEQ ID NO: 166 (ATL_7917; ATL_7918); or SEQ ID NO: 167 (ATL_7899; ATL_7921; ATL_7922; ATL_7924); and
- CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955; ATL_7925; ATL_7952; ATL_7953; ATL_7902; ATL_7917; ATL_7922; ATL_7923; ATL_7924); SEQ ID NO: 36 (ATL_6026; ATL_7450; ATL_7819; ATL_7820; ATL_7821; ATL_7822; ATL_7823; ATL_7824; ATL_7825; ATL_7826; ATL_7827; ATL_7829; ATL_7889; ATL_7890; ATL_7892; ATL_7893; ATL_7895; ATL_7896; ATL_7899; ATL_7900; ATL_7918); SEQ ID NO: 37 (ATL_6027); SEQ ID NO: 38 (ATL_6058; ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472; ATL_7473); SEQ ID NO: 39 (ATL_6074); SEQ ID NO: 40 (ATL_6075); SEQ ID NO: 168 (ATL_7901; ATL_7919; ATL_7921); or SEQ ID NO: 169 (ATL_7920);
- or a set of CDRs containing one to four amino acid mutations, such as substitutions, compared with the above set of CDRs.
12. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) with the following CDRs:
- CDRL1 comprising an amino acid sequence of SEQ ID NO: 26 (ATL_6026; ATL_7925; ATL_7952; ATL_7953; ATL_7955);
- CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955; ATL_7925; ATL_7952; ATL_7953) or SEQ ID NO: 31 (ATL_6026); and
- CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955; ATL_7925; ATL_7952; ATL_7953) or SEQ ID NO: 36 (ATL_6026);
- or a set of CDRs containing one to four amino acid mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs, optionally wherein the substitution is at position 57, optionally wherein the substitution is N57A or N57Q; and/or at position 65, optionally wherein the substitution is S65N or S65A; and/or at position 109, optionally wherein the substitution is N109A or N109Q; and/or at position 113, optionally wherein the substitution is S113N or S113A;
- optionally wherein the light chain variable domain (VL) comprises the following framework sequences: LFWR1 of SEQ ID NO: 45 (ATL_6026) or SEQ ID NO: 104 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); LFWR2 of SEQ ID NO: 46 (ATL_6026; ATL_7925; ATL_7952;

- ATL_7953; ATL_7955); LFWR3 of SEQ ID NO: 47 (ATL_6026) or SEQ ID NO: 106 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); and LFWR4 of SEQ ID NO: 48 (ATL_6026) or SEQ ID NO: 108 (ATL_7925; ATL_7952; ATL_7953; ATL_7955); or framework sequences with one to five mutations, optionally wherein the mutations are substitutions, compared with the framework sequences above, optionally wherein the substitution is at position 2, optionally wherein the substitution is A2S; and/or at position 8, optionally wherein the substitution is S8P; and/or at position 52, optionally wherein the substitution is P52L; and/or at position 90, optionally wherein the substitution is V90A; and/or at position 124, optionally wherein the substitution is V124L.
13. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) with the following CDRs:
- CDRL1 comprising an amino acid sequence of SEQ ID NO: 26 (ATL_7955);
- CDRL2 comprising an amino acid sequence of SEQ ID NO: 105 (ATL_7955); and
- CDRL3 comprising an amino acid sequence of SEQ ID NO: 107 (ATL_7955);
- optionally wherein the light chain variable domain (VL) comprises the following framework sequences: LFWR1 of SEQ ID NO: 104 (ATL_7955); LFWR2 of SEQ ID NO: 46 (ATL_7955); LFWR3 of SEQ ID NO: 106 (ATL_7955); and LFWR4 of SEQ ID NO: 108 (ATL_7955).
14. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) with the following CDRs:
- CDRL1 comprising an amino acid sequence of SEQ ID NO: 28 (ATL_6058; ATL_7933; ATL_7956);
- CDRL2 comprising an amino acid sequence of SEQ ID NO: 33 (ATL_6058; ATL_7933; ATL_7956); and
- CDRL3 comprising an amino acid sequence of SEQ ID NO: 38 (ATL_6058; ATL_7933; ATL_7956);
- or a set of CDRs containing one, two, or three amino acid mutations, optionally wherein the mutations are substitutions, compared with the above set of CDRs;
- optionally wherein the light chain variable domain (VL) comprises the following framework sequences: LFWR1 of SEQ ID NO: 61 (ATL_6058; ATL_7933; ATL_7956); LFWR2 of SEQ ID NO: 62 (ATL_6058) or SEQ ID NO: 116 (ATL_7933; ATL_7956); LFWR3 of SEQ ID NO: 63 (ATL_6058) or SEQ ID NO: 117 (ATL_7933; ATL_7956); and LFWR4 of SEQ ID NO: 64 (ATL_6058; ATL_7933; ATL_7956); or framework sequences with one to four mutations, optionally wherein the mutations are substitutions, compared with the framework sequences above, optionally wherein the substitution is at position 49, optionally wherein the substitution is P49A; and/or at position 52, optionally wherein the substitution is R52L; and/or at position 74, optionally wherein the substitution is G74D; and/or at position 90, optionally wherein the substitution is S90T.
15. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) with the following CDRs:
- CDRL1 comprising an amino acid sequence of SEQ ID NO: 28 (ATL_7933);

CDRL2 comprising an amino acid sequence of SEQ ID NO: 33 (ATL_7933); and
CDRL3 comprising an amino acid sequence of SEQ ID NO: 38 (ATL_7933); and
wherein the light chain variable domain (VL) comprises the following framework sequences:
LFWR1 of SEQ ID NO: 61 (ATL_7933); LFWR2 of SEQ ID NO: 116 (ATL_7933); LFWR3 of
5 SEQ ID NO: 117 (ATL_7933); and LFWR4 of SEQ ID NO: 64 (ATL_7933).

16. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) with the following framework sequences:

LFWR1 of SEQ ID NO: 45 (ATL_6026; ATL_0007450; ATL_0007819;
10 ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824;
ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007892;
ATL_0007893; ATL_0007899; ATL_0007900; ATL_0007901; ATL_0007902;
ATL_0007917); SEQ ID NO: 53 (ATL_6027); SEQ ID NO: 61 (ATL_6058; ATL_7933;
ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930;
15 ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469; ATL_7472;
ATL_7473); SEQ ID NO: 69 (ATL_6074); SEQ ID NO: 77 (ATL_6075); SEQ ID NO: 104
(ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_0007896; ATL_0007920;
ATL_0007921; ATL_0007922); SEQ ID NO: 163 (ATL_0007889; ATL_0007895;
ATL_0007919; ATL_0007924); or SEQ ID NO: 164 (ATL_0007890; ATL_0007918;
20 ATL_0007923);
LFWR2 of SEQ ID NO: 46 (ATL_6026; ATL_7925; ATL_7952; ATL_7953;
ATL_7955; ATL_0007450; ATL_0007819; ATL_0007820; ATL_0007821; ATL_0007822;
ATL_0007823; ATL_0007824; ATL_0007825; ATL_0007826; ATL_0007827;
ATL_0007829; ATL_0007889; ATL_0007890; ATL_0007892; ATL_0007893;
25 ATL_0007896; ATL_0007899; ATL_0007900; ATL_0007901; ATL_0007902;
ATL_0007920); SEQ ID NO: 54 (ATL_6027); SEQ ID NO: 62 (ATL_6058; ATL_7468);
SEQ ID NO: 70 (ATL_6074); SEQ ID NO: 78 (ATL_6075); SEQ ID NO: 116 (ATL_7933;
ATL_7956; ATL_7467; ATL_7469; ATL_7470; ATL_7471; ATL_7472; ATL_7473;
ATL_7928; ATL_7929; ATL_7930; ATL_7931; ATL_7932); SEQ ID NO: 165
30 (ATL_0007895; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007921;
ATL_0007922; ATL_0007923; ATL_0007924); SEQ ID NO: 200 (ATL_7927); or SEQ ID
NO: 201 (ATL_7926)
;
LFWR3 of SEQ ID NO: 47 (ATL_6026; ATL_0007450; ATL_0007819;
35 ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824;
ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007889;
ATL_0007890; ATL_0007893; ATL_0007899; ATL_0007900; ATL_0007901;
ATL_0007902; ATL_0007921); SEQ ID NO: 55 (ATL_6027); SEQ ID NO: 63 (ATL_6058;
ATL_7468); SEQ ID NO: 71 (ATL_6074); SEQ ID NO: 79 (ATL_6075); SEQ ID NO: 106
40 (ATL_7925; ATL_7952; ATL_7953; ATL_7955; ATL_0007892; ATL_0007895;
ATL_0007896; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007920;
ATL_0007922; ATL_0007923; ATL_0007924); or SEQ ID NO: 117 (ATL_7933;

ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929; ATL_7930;
ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7469; ATL_7472; ATL_7473); and
LFWR4 of SEQ ID NO: 48 (ATL_6026; ATL_0007450; ATL_0007819;
ATL_0007820; ATL_0007821; ATL_0007822; ATL_0007823; ATL_0007824;
ATL_0007825; ATL_0007826; ATL_0007827; ATL_0007829; ATL_0007889;
ATL_0007890; ATL_0007892; ATL_0007899; ATL_0007900; ATL_0007901;
ATL_0007902; ATL_0007922); SEQ ID NO: 56 (ATL_6027); SEQ ID NO: 64 (ATL_6058;
ATL_7933; ATL_7956; ATL_7470; ATL_7926; ATL_7927; ATL_7928; ATL_7929;
ATL_7930; ATL_7931; ATL_7932; ATL_7471; ATL_7467; ATL_7468; ATL_7469;
ATL_7472; ATL_7473); SEQ ID NO: 72 (ATL_6074; ATL_0007893; ATL_0007895;
ATL_0007896; ATL_0007917; ATL_0007918; ATL_0007919; ATL_0007920;
ATL_0007921; ATL_0007923; ATL_0007924); SEQ ID NO: 80 (ATL_6075); or SEQ ID
NO: 108 (ATL_7925; ATL_7952; ATL_7953; ATL_7955);
or framework sequences with one, two, or three mutations, such as substitutions, compared with
the framework sequences above.

17. The isolated antibody according to any preceding claim, wherein the antibody comprises a light
chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least
80%, at least 85%, at least 90%, at least 95% sequence identity, or that has 100% sequence
identity with the amino acid sequence selected from the group consisting of: of SEQ ID NO: 6;
SEQ ID NO: 7; SEQ ID NO: 8; SEQ ID NO: 9; SEQ ID NO: 10; SEQ ID NO: 94; SEQ ID NO: 111;
SEQ ID NO: 135; SEQ ID NO: 136; SEQ ID NO: 137; SEQ ID NO: 138; SEQ ID NO: 139; SEQ ID
NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 143; SEQ ID NO: 144; SEQ ID NO:
145; SEQ ID NO: 146; SEQ ID NO: 147; SEQ ID NO: 148; SEQ ID NO: 149; SEQ ID NO: 150;
SEQ ID NO: 151; SEQ ID NO: 152; SEQ ID NO: 189; and SEQ ID NO: 190; optionally the group
consisting of: SEQ ID NO: 6; SEQ ID NO: 8; SEQ ID NO: 94; and SEQ ID NO: 111; optionally the
group consisting of: SEQ ID NO: 94 and SEQ ID NO: 111.

18. The isolated antibody according to any preceding claim, wherein the antibody comprises:
(a) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least
75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 1
and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least
75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:
6; or
(b) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least
75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 2
and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least
75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:
7; or
(c) a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least
75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO: 3
and a light chain variable domain (VL) comprising a sequence that has at least 70%, at least

19. The isolated antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain (VL) comprising CDRL1, CDRL2, and CDRL3 within a human framework, and/or within a germline framework and/or wherein the antibody comprises a heavy chain variable domain (VH) comprising CDRH1, CDRH2, and CDRH3 within a human framework, and/or within a germline framework.
20. The isolated antibody according to any preceding claim, wherein:
- (a) the antibody binds human PGDH, wherein the antibody binds human PGDH with a K_D of at most $10^{-6}M$, $10^{-7}M$, $10^{-8}M$, $10^{-9}M$, preferably at most $10^{-9}M$, as measured by ELISA, and/or wherein the antibody binds human PGDH with an EC_{50} below 100 nM, below 50 nM, or below 10nM as measured by titration ELISA; and/or
- (b) the antibody inhibits PGDH as determined using a 15-PGDH enzyme activity assay, and/or wherein the antibody inhibits human PGDH with an IC_{50} below 200 nM or below 150 nM.
21. The isolated antibody according to any preceding claim, wherein the antibody:
- a. alters PGE2 levels in an *in vitro* cell culture, and/or wherein the antibody alters one or more of autophagy, activity, oxidative stress, and apoptosis of dopaminergic neurons *in vitro*, and/or wherein the antibody alters microglia inflammatory state *in vitro*; and/or
- b. reduces inflammation, optionally neuroinflammation, in an *in vitro* cell culture, optionally wherein a reduction in inflammation is determined by measuring the levels of one or more pro-inflammatory cytokines, optionally wherein the pro-inflammatory cytokine is IL-6, IL-1 β , and/or TNF α , and/or wherein an *in vitro* cell culture comprises cells exposed to a proinflammatory condition, optionally comprising exposure to α Syn fibrils; and/or
- c. alters 15-PGDH levels in an *in vitro* cell culture; and/or
- d. alters phospho- α Syn129 levels in an *in vitro* cell culture comprising cells exposed to α Syn fibrils; and/or
- e. alters mitochondrial function in an *in vitro* cell culture, optionally wherein an alteration in mitochondrial function is determined by measuring the mitochondrial membrane potential (MMP) comprising cells exposed to α Syn fibrils.
22. The isolated antibody according to any preceding claim, wherein the antibody:
- a. increases the levels of circulating PGE2 *in vivo*; and/or
- b. binds 15-PGDH in the active site or at an allosteric site; and/or
- c. decreases the levels of one or more pro-inflammatory cytokines *in vivo*, optionally wherein the pro-inflammatory cytokine is IL-6, IL-1 β , and/or TNF α , and/or wherein the antibody decreases the levels of one or more pro-inflammatory cytokines in an animal model and/or in a subject exposed to pro-inflammatory conditions, optionally comprising exposure to LPS.
23. The isolated antibody according to any preceding claim, wherein the antibody is a monoclonal antibody, and/or wherein the antibody is an IgG1, or a modified version thereof, optionally a LALA

IgG1, optionally wherein the LALA IgG1 comprises a sequence according to SEQ NO: 87, or wherein the antibody is an isolated VH domain according to any preceding claim.

- 5 24. An isolated nucleic acid comprising a nucleotide sequence encoding an antibody according to any preceding claim.
25. A vector or set of vectors comprising the nucleic acid according to claim 24.
- 10 26. A host cell comprising the vector or set of vectors according to claim 25, or a host cell *in vitro* transformed with a nucleic acid of claim 24.
27. A composition comprising the antibody or fragment thereof according to any of claims 1-23, and at least one additional component, optionally comprising a pharmaceutically acceptable excipient, vehicle or carrier.
- 15 28. An antibody according to any of claims 1-23, or a composition according to claim 27, for use as a therapeutic.
29. An antibody according to any of claims 1-23, or a composition according to claim 27, for use in
- 20 the treatment of a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a synuclein-mediated neurodegenerative disease.
30. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition according to claim 27, or an antibody
- 25 according to any of claims 1-23, optionally wherein the subject has, or is at risk of developing a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a synuclein-mediated neurodegenerative disease,.
31. Use of an antibody according to claims 1-23 in the manufacture of a medicament, optionally a
- 30 medicament for the treatment of a disease associated with inflammation and/or neuroinflammation, optionally wherein the disease is a synucleinopathy or a synuclein-mediated neurodegenerative disease.
32. The antibody, method, or use according to any one of claims 29-31, wherein the disease is
- 35 selected from Parkinson's Disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Alzheimer's Disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS), optionally wherein the disease is Parkinson's Disease.