CLAIMS

1. An antibody or an antigen-binding fragment thereof that selectively binds to an epitope within the core region of transglutaminase type 2 (TG2) and that inhibits human TG2 cross-linking lysine and glutamine with Nε(γ-glutamyl)lysine isopeptide bonds, wherein the antibody or antigen-binding fragment thereof comprises the following complementarity determining region (CDR) sequences or CDR and flanking region sequences, or CDR or CDR and flanking region sequences having at least 90% identity with the following:

(a) a LCDR1 sequence, or LCDR1 and flanking region sequence, selected from the group consisting of KASQDINSYLT, TCKASQDINSYLIWF and TCKASQDINSYLIWY;

(b) a LCDR2 sequence, or LCDR2 and flanking region sequence, selected from the group consisting of RTNRLFD, TLIYRTNRLFDGVP, LLIYRTNRLFDGVP, SLIYRTNRLFDGVP, LTNRLMD, LVNRLVD, LLIYRTNRLFDGVPSRFSGSGSGTDFF, SLIYRTNRLFDGVPSRFSGSGSGTDFF, SLIYLTNRLMDGVPSRFSGSGSGTDFF, TLIYLTNRLMDGVPSRFSGSGSGQEFL, SLIYLVNRLVDGVPSRFSGSGSGTDFF, ILIYLVNRLVDGVPSRFSGSGSGQDYA, TLIYLTNRLMDGVP, SLIYLTNRLMDGVP, SLIYLVNRLVDGVP, LVNRLVD and ILIYLVNRLVDGVP;

(c) a LCDR3 sequence, or LCDR3 and flanking region sequence, selected from the group consisting of LQYDDFPYT, YCLQYDDFPYTFG, LQYVDFPYT, LQYVDFPYT and YCLQYVDFPYTFG;

(d) an HCDR1 sequence, or HCDR1 and flanking region sequence, selected from the group consisting of SSAMS, FTLSSSAMSWVR, FTFSSSAMSWVR, THAMS, CAASGFTFSSSAMSWVR, CAASGIIFSSSAMSWVR, IIFSSSAMSWVR, CAASGFTFSTHAMSWVR, FTFSTHAMSWVR, CAASGFTLSTHAMSWVR and FTLSTHAMSWVR;

(e) an HCDR2 sequence, or HCDR2 and flanking region sequence, selected from the group consisting of TISVGGGKTYYPDSVKG, VATISVGGGKTYYPDSVKGRFTISR, WVSTISVGGGKTYYPDSVKGRFTISR, TISSGGRSTYYPDSVKG, TISSGGRSTYYPDSVKG, WVSTISVGGGKTYYPDSVKGRFTISRDNSKNTL, WVSTISVGGGKTYYPDSVKGRFTISRDN, WVSTISSGGRSTYYPDSVKGRFTISRDNSKNTL, WVSTISSGGRSTYYPDSVKGRFTISRDN, WVSTISSGGRSTYYPDSVKGRFTISR, WVATISSGGRSTYYPDSVKGRFTVSRDSSKNTL, WVATISSGGRSTYYPDSVKGRFTVSRDS, WVATISSGGRSTYYPDSVKGRFTVSR, WVATISSGGRSTYYPDSVKGRFTISRDNSKNTL, WVATISSGGRSTYYPDSVKGRFTISRDN and WVATISSGGRSTYYPDSVKGRFTISR; and

(f) an HCDR3 sequence, or HCDR3 and flanking region sequence, selected from the group consisting of LISLY, YCAKLISLYWG, LISPY, LISTY, YCAKLISPYWG, YCAKLISTYWG and FCARLISTYWG.

2. The antibody or antigen-binding fragment thereof of Claim 1, wherein the core region consists of amino acids 143 to 473 of human TG2.

3. The antibody or antigen-binding fragment thereof of Claim 1 or 2, wherein the antibody or antigen-binding fragment thereof selectively binds in whole or in part to a region comprising:

i) amino acids 304 to 326 of human TG2; or

ii) amino acids 351 to 365 of human TG2; or

iii) amino acids 450 to 467 of human TG2.

4. The antibody or antigen-binding fragment thereof of any preceding claim, wherein the antibody or antigen-binding fragment thereof comprises the following amino acid

sequences, or amino acid sequences having at least 90% identity with the following amino acid sequences:

(a) KASQDINSYLT (LCDR1);
LVNRLVD (LCDR2);
LQYDDFPYT (LCDR3);
THAMS (HCDR1);
TISSGGRSTYYPDSVKG (HCDR2); and
LISTY (HCDR3); or

(b) KASQDINSYLT (LCDR1);
LTNRLMD (LCDR2);
LQYVDFPYT (LCDR3);
SSAMS (HCDR1);
TISSGGRSTYYPDSVKG (HCDR2); and
LISPY (HCDR3); or

(c) KASQDINSYLT (LCDR1);
RTNRLFD (LCDR2);
LQYDDFPYT (LCDR3);
SSAMS (HCDR1);
TISVGGGKTYYPDSVKG (HCDR2); and
LISLY (HCDR3).

5. The antibody or antigen-binding fragment thereof of any preceding claim, wherein the antibody or antigen-binding fragment thereof has at least one light chain variable region comprising the amino acid sequence DIKMTQSPSSMYASLGERVTITCKASQDINSYLTWFQQKPGKSPKTLIYRTNRLFD GVPSRFSGSGSGQDFFLTISSLEYEDMGIYYCLQYDDFPYTFGGGTKLEIK, or DIQMTQTPSSMYASLGERVTITCKASQDINSYLTWFQQKPGKSPKTLIYRTNRLFD GVPSRFSGSGSGQDFFLTISSLEYEDMGIYYCLQYDDFPYTFGGGTKLEIK, or

EIVLTQSPSSMYASLGERVTITCKASQDINSYLTWFQQKPGKSPKTLIYRTNRLFDG VPSRFSGSGSGQDFFLTISSLEYEDMGIYYCLQYDDFPYTFGGGTKLEIK (AB-1_VK), or

DIQMTQSPSSMYASLGERVTITCKASQDINSYLTWFQQKPGKSPKTLIYRTNRLFD GVPSRFSGSGSGQDFFLTISSLEYEDMGIYYCLQYDDFPYTFGGGTKLEIK (AB-1_VK1), or

EIVLTQSPSSLSASVGDRVTITCKASQDINSYLTWYQQKPGKAPKLLIYRTNRLFDG VPSRFSGSGSGTDFFFTISSLQPEDFGTYYCLQYDDFPYTFGGGTKLEIK (hAB-1_RKE), or

DIQMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKSLIYRTNRLFD GVPSRFSGSGSGTDFFLTISSLQPEDFATYYCLQYDDFPYTFGQGTKVEIK (hAB-1_RKJ), or

AIKMTQSPSSMYASLGERVIITCKASQDINSYLTWFQQKPGKSPKTLIYLTNRLMD GVPSRFSGSGSGQEFLLTISGLEHEDMGIYYCLQYVDFPYTFGGGTKLEIK (BB-7 VK), or

DITMTQSPSSIYASLGERVTITCKASQDINSYLTWFQQKPGKSPKIL1YLVNRLVDG VPSRFSGSGSGQDYALTISSLEYEDMGIYYCLQYDDFPYTFGGGTKLEIK (DC-1 VK), or

QIVLTQSPAIMSASPGEKVTMTCSASSSVDYMYWYQQKPGSSPRLLIYDTSNLASG VPVRFSGSGSGTSYSLTISRMGAEDAATYYCQQWNSSPLTFGAGTKLELK (DD-9 VK), or

QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMYWYQQKPGSSPRLLIYDTSNLASG VPVRFSGSGSGTSYSLTISRMEAEDAATFYCQQWSSSPLTFGAGTKLELK (DH-2 VK), or

DIQMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKSLIYLTNRLMD GVPSRFSGSGSGTDFFLTISSLQPEDFATYYCLQYVDFPYTFGQGTKVEIK, or

DIKMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKTLIYLTNRLMD GVPSRFSGSGSGQEFLLTISSLQPEDFATYYCLQYVDFPYTFGQGTKVEIK, or

DIQMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKSLIYLVNRLVD GVPSRFSGSGSGTDFFLTISSLQPEDFATYYCLQYDDFPYTFGQGTKVEIK, or

DITMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKILIYLVNRLVDG VPSRFSGSGSGQDYALTISSLQPEDFATYYCLQYDDFPYTFGQGTKVEIK; and at least one heavy chain variable region comprising the amino acid sequence EVQLVESGGGLVKPGGSLKLSCAASGFTLSSSAMSWVRQTPDRRLEWVATISVGG GKTYYPDSVKGRFTISRDNAKNTLYLQMNSLRSEDTAMYYCAKLISLYWGQGTT LTVSS, or EVQLEESGGGLVKPGGSLKLSCAASGFTLSSSAMSWVRQTPDRRLEWVATISVGG GKTYYPDSVKGRFTISRDNAKNTLYLQMNSLRSEDTAMYYCAKLISLYWGQGTT LTVSS, or EVQLQESGGGLVKPGGSLKLSCAASGFTLSSSAMSWVRQTPDRRLEWVATISVGG GKTYYPDSVKGRFTISRDNAKNTLYLQMNSLRSEDTAMYYCAKLISLYWGQGTT LTVSS (AB1_VH), or EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMSWVRQAPGKGLEWVSTISVGG GKTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLISLYWGQGTLV TVSS (hAB-1_RHA), or AVQLVESGGGLVKPGGSLKLSCAASGIIFSSSAMSWVRQTPEKRLEWVATISSGGR STYYPDSVKGRFTVSRDSAKNTLYLQMDSLRSEDTAIYYCAKLISPYWGQGTTLT VSS (BB-7VH), or EVQLVESGGGLVKPGGSLKLSCAASGFTLSTHAMSWVRQTPEKRLEWVATISSGG RSTYYPDSVKGRFTISRDNVKNTLYLQLSSLRSEDTAVYFCARLISTYWGQGTTLT VSS (DC-1VH), or QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQSSGKGLEWLAHIYWD DDKRYNPSLKSRITISKDSSSNQVFLKITSVDTADTATYYCARSWTTAPFAFWGQG TLVTVSA (DD-9 VH), or QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQPSGKGLEWLAHIYWD DDKRYNPSLKSRLTISKDTSSNQVFLKITSVDTADTATYYCARSGTTAPFAYWGQ GTLVTVSA (DH-2 VH), or EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMSWVRQAPGKGLEWVSTISSGG RSTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLISPYWGQGTLV TVSS, or

EVQLLESGGGLVQPGGSLRLSCAASGIIFSSSAMSWVRQAPGKGLEWVATISSGGR STYYPDSVKGRFTVSRDSSKNTLYLQMNSLRAEDTAVYYCAKLISPYWGQGTLVT VSS, or
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTHAMSWVRQAPGKGLEWVSTISSGG RSTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLISTYWGQGTLV TVSS, or
EVQLLESGGGLVQPGGSLRLSCAASGFTLSTHAMSWVRQAPGKGLEWVATISSGG RSTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARLISTYWGQGTLV TVSS, or an amino acid sequence having at least 90% identity with one or more of the amino acid sequences specified above.

6. The antibody or antigen-binding fragment thereof of any preceding claim, wherein the antibody or fragment thereof has:

(a) a light chain variable region comprising the sequence DITMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKILIYLVNRLVDG VPSRFSGSGSGQDYALTISSLQPEDFATYYCLQYDDFPYTFGQGTKVEIK, and a heavy chain variable region comprising the sequence
EVQLLESGGGLVQPGGSLRLSCAASGFTLSTHAMSWVRQAPGKGLEWVATISSGG RSTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARLISTYWGQGTLV TVSS,
or amino acid sequences having at least 90% identity therewith; or

(b) a light chain variable region comprising the sequence DIKMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKTLIYLTNRLMD GVPS RFSGSGSGQEFLLTISSLQPEDFATYYCLQYVDFPYTFGQGTKVEIK, and a heavy chain variable region comprising the sequence
EVQLLESGGGLVQPGGSLRLSCAASGIIFSSSAMSWVRQAPGKGLEWVATISSGGR STYYPDSVKGRFTVSRDSSKNTLYLQMNSLRAEDTAVYYCAKLISPYWGQGTLVT VSS,
or amino acid sequences having at least 90% identity therewith; or

(c) a light chain variable region comprising the sequence

EIVLTQSPSSLSASVGDRVTITCKASQDINSYLTWYQQKPGKAPKLLIYRTNRLFDG
VPSRFSGSGSGTDFFFTISSLQPEDFGTYYCLQYDDFPYTFGGGTKLEIK, or
DIQMTQSPSSLSASVGDRVTITCKASQDINSYLTWFQQKPGKAPKSLIYRTNRLFDG
VPSRFSGSGSGTDFFLTISSLQPEDFATYYCLQYDDFPYTFGQGTKVEIK,
and a heavy chain variable region comprising the sequence
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMSWVRQAPGKGLEWVSTISVGG
GKTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLISLYWGQGTLV
TVSS,
or amino acid sequences having at least 90% identity therewith.

7. An anti-TG2 antibody or an antigen-binding fragment thereof, which comprises:

(a) a light chain variable region comprising the sequence
DVLMTQNPLSLPVSLGDQASISCRSSQSIEHINGNTYLEWYLQKPGQSPKFLIYKVS
NRFSGVPDRFSGSGSGTDFTLRISRVEAEDLGIYYCFQGSHVPFTFGGGTKLEIK,
and a heavy chain variable region comprising the sequence
EVQLQQSGPELVKPGASVKMSCKASGYRFTSYVMHWVKQKSGQGLEWIGYINPY
NDGAKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARLSSDYWGQGT
TLTVSS; or

(b) a light chain variable region comprising the sequence
DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKV
SNRFSGVPDRFSGSGSGTDFTLKISRVGAEDLGVYYCLQVSHVPFTFGSGTKLEIK,
and a heavy chain variable region comprising the sequence
EVQLQQSGPELVKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGFINPY
NDGTKYNEKFKGKATLTSDKASTTAYMELSSLTSEDSAVYYCARFSSGYWGQGT
TLTVSS; or

(c) a light chain variable region comprising the sequence
DVLMTQNPLSLPVSLGDQASISCRSSRSIEHSNGNTYLEWYLQKPGQSPKFLIYKVS
NRFSGVPDRFSGSGSGTDFTLRISSVEAEDLGVYYCFQGSHVPFTFGGGTKLEIK,
and a heavy chain variable region comprising the sequence
EVQLQQSGPELVKPGASVKMSCRASGYTFTTYVIHWVKQKPGQGLEWIGYINPYN

DGARYNEKFKGKATLTSDKSSTTAYMELSSLTSEDSAVYYCARLSSDYWGQGTTL TVSS; or

(d) a light chain variable region comprising the sequence QIVLTQSPAIMSASPGEKVTMTCSASSSVDYMYWYQQKPGSSPRLLIYDTSNLASG VPVRFSGSGSGTSYSLTISRMGAEDAATYYCQQWNSSPLTFGAGTKLELK, and a heavy chain variable region comprising the sequence QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQSSGKGLEWLAHIYWD DDKRYNPSLKSRITISKDSSSNQVFLKITSVDTADTATYYCARSWTTAPFAFWGQG TLVTVSA; or

(e) a light chain variable region comprising the sequence QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMYWYQQKPGSSPRLLIYDTSNLASG VPVRFSGSGSGTSYSLTISRMEAEDAATFYCQQWSSSPLTFGAGTKLELK, and a heavy chain variable region comprising the sequence QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQPSGKGLEWLAHIYWD DDKRYNPSLKSRLTISKDTSSNQVFLKITSVDTADTATYYCARSGTTAPFAYWGQ GTLVTVSA; or

(f) a light chain variable region comprising the sequence QAVVTQESALTTSPGETVTLTCRSSTGAVAANNYANWIQEKPDHLFTGLIAGTNK RAPGVPARFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNYWVFGGGTKVTVLG, and a heavy chain variable region comprising the sequence EVQLQQSGPELVKPGASVKMSCKASGYRFTDYNMHWVKQNLGKSLEWIGYINPK NGVIYYNQKFKGKATLTVNRSSNTAYMEIRSLTSEDSAVYYCATALTYWGQGTL VTVSA.

8. The antibody of any preceding claim, which comprises or consists of an intact antibody.

9. The antigen-binding fragment of any preceding claim, which comprises or consists of an antigen-binding fragment selected from the group consisting of: an Fv fragment, for example a single chain Fv fragment or a disulphide-bonded Fv fragment; an Fab fragment; and an Fab-like fragment, for example an Fab' fragment or an $F(ab)_2$ fragment.

10. The antibody or antigen-binding fragment thereof of any preceding claim, which is an IgG1, IgG2, IgG3 or IgG4.

11. A polynucleotide encoding an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 10.

12. An antibody according to any of Claims 1 to 10, wherein the antibody or antigen-binding fragment thereof does not inhibit TG1, TG3, TG13 and/or TG7 activity.

13. An antibody or antigen-binding fragment thereof that selectively binds to an epitope within the core region of transglutaminase type 2 (TG2) and that inhibits human TG2 cross-linking lysine and glutamine with Nε(γ-glutamyl)lysine isopeptide bonds whose binding to TG2, for example human TG2, is inhibited or reduced when an antibody according to any of Claims 1 to 10 or 12 is bound to TG2, for example human TG2.

14. A compound comprising an antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13 and a further moiety, for example a readily detectable moiety, and/or a directly or indirectly cytotoxic moiety.

15. A pharmaceutical composition/formulation comprising an antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13, or a compound according to Claim 14, in admixture with a pharmaceutically acceptable excipient, adjuvant, diluent or carrier.

16. The pharmaceutical composition/formulation according to Claim 15, wherein the composition/formulation is formulated for intravenous, intramuscular, or subcutaneous delivery to a patient.

17. An antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13, or a compound according to Claim 14, for use in medicine.

18. Use of an antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13, or a compound according to Claim 14, in the manufacture of a medicament for treating and/or diagnosing Celiac disease, abnormal wound healing, scarring, hypertrophic scars, ocular scarring, inflammatory bowel disease, macular degeneration, psoriasis, fibrosis-related diseases (e.g. liver fibrosis, pulmonary fibrosis such as interstitial lung disease and fibrotic lung disease, cardiac fibrosis, myelofibrosis, kidney fibrosis such as glomerulosclerosis and tubulointerstitial fibrosis), atherosclerosis, restenosis, inflammatory diseases, autoimmune diseases, neurodegenerative/neurological diseases (e.g. Huntington's Disease, Alzheimer's disease, Parkinson's disease, polyglutamine disease, spinobulbar muscular atrophy, dentatorubral-pallidoluysian atrophy, spinocerebellar ataxias 1, 2, 3, 6, 7 and 12, rubropallidal atrophy, spinocerebellar palsy), glioblastomas such as glioblastoma in Li-Fraumeni syndrome and sporadic glioblastoma, malignant melanomas, pancreatic ductal adenocarcinomas, myeloid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproliferative syndrome, gynaecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis.

19. An *in vitro* method of reducing or inhibiting TG2 enzyme activity, the method comprising administering an antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13 or a polynucleotide according to Claim 11, or a compound according to Claim 14, to a sample comprising TG2, for example a tissue or cell sample comprising TG2.

20. A method of producing an antibody or antigen-binding fragment thereof according to any of Claims 1 to 10, 12 or 13, or a compound according to Claim 14, the method comprising expressing a polynucleotide according to Claim 11.

21. A method of producing an antibody or antigen-binding fragment thereof that selectively binds a human TG2 and that inhibits human TG2 cross-linking lysine and glutamine with Nε(γ-glutamyl)lysine isopeptide bonds, the method comprising providing a non-human animal that had been administered with a compound comprising:

i) a polypeptide comprising a human TG2 core region/catalytic domain but not comprising a transglutaminase barrel or sandwich domain, or a fragment thereof; and, optionally,

ii) an adjuvant.

22. The method of Claim 21 further comprising the step of selecting an antibody or antigen-binding fragment thereof that selectively binds a transglutaminase protein, for example a TG2 such as human TG2.

23. An antibody or antigen-binding fragment thereof obtainable by the method of any of Claims 20 to 22, wherein the antibody or antigen-binding fragment thereof selectively binds to an epitope within the core region of TG2 and inhibits human TG2 cross-linking lysine and glutamine with Nε(γ-glutamyl)lysine isopeptide bonds.