

acid sequence of SEQ ID NO:37. In some embodiments of any of the embodiments disclosed herein, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:40 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to the light chain constant region, resulting in a light chain comprising SEQ ID NO:41.

[0014] In further aspects, provided herein is a monoclonal antibody that competes with any of TIG1, TIG2 or TIG3 for binding to human TIGIT, wherein antibody TIG1 is characterized by a mature light chain variable region of SEQ ID NO:14 and mature heavy chain variable region of SEQ ID NO:10, antibody TIG2 is characterized by a mature light chain variable region of SEQ ID NO:22 and a mature heavy chain variable region of SEQ ID NO:18, and antibody TIG3 is characterized by a mature light chain variable region of SEQ ID NO:30 and a mature heavy chain variable region of SEQ ID NO:26, for specific binding to CD155. In some embodiments, the antibody binds to the same epitope on human TIGIT as any of TIG1, TIG2 or TIG3. In some embodiments of any of the embodiments disclosed herein, the antibody inhibits binding of CD155 to human TIGIT. In some embodiments, the antibody comprises three light chain CDRs and three heavy chain CDRs corresponding to three light chain and three heavy chain CDRs of any one of TIG1, TIG2 or TIG3. In some embodiments, the antibody comprises three heavy chain CDRs and three light chain CDRs of any one of TIG1, TIG2 or TIG3. In some embodiments, the antibody comprises three heavy chain CDRs as defined by Kabat and three light chain CDRs as defined by Kabat of any one of TIG1 (SEQ ID NOS: 15-17 light chain and 11-13 heavy chain), TIG2 (SEQ ID NOS. 23-25 light chain, 19-21 heavy chain) or TIG3 (SEQ ID NOS: 31-33 light chain and 27-29 heavy chain). In some embodiments of any of the embodiments disclosed herein, the antibody is chimeric, humanized, or veneered. In some embodiments, the antibody is a human antibody. In some embodiments of any of the embodiments disclosed herein, the antibody has human IgG1 kappa isotype. In some embodiments of any of the embodiments disclosed herein, the antibody is an intact antibody. In some embodiments of any of the embodiments disclosed herein, the antibody is a single-chain antibody, Fab or F(ab')₂ fragment. In some embodiments of any of the embodiments disclosed herein, the antibody comprises a mature heavy chain variable region with at least 90% sequence identity to SEQ ID NO:35 and a mature light chain variable region with at least 90% sequence identity to SEQ ID NO:37. In some embodiments, the mature heavy chain variable region has at least 95 or 99% sequence identity to SEQ ID NO:35 and the mature light chain variable region has at least 95 or 99%

sequence identity to SEQ ID NO:37. In some embodiments, the mature heavy chain variable region has the amino acid sequence of SEQ ID NO:35 and the mature light chain variable region has the amino acid sequence of SEQ ID NO:37. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:40 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting in a light chain comprising SEQ ID NO:41. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:60 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting in a light chain comprising SEQ ID NO:64. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:61 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting in a light chain comprising SEQ ID NO:64. In some embodiments of any of the embodiments disclosed herein, the antibody comprises a mature heavy chain variable region with at least 90% sequence identity to SEQ ID NO:43 and a mature light chain variable region with at least 90% sequence identity to SEQ ID NO:45. In some embodiments, the mature heavy chain variable region has at least 95 or 99% sequence identity to SEQ ID NO:43 and the mature light chain variable region has at least 95 or 99% sequence identity to SEQ ID NO:45. In some embodiments, the mature heavy chain variable region has the amino acid sequence of SEQ ID NO:43 and the mature light chain variable region has the amino acid sequence of SEQ ID NO:45. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:48 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting in a light chain comprising SEQ ID NO:49. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:62 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting in a light chain comprising SEQ ID NO:65. In some embodiments, the mature heavy chain variable region is linked to a heavy chain constant region, resulting in a heavy chain comprising SEQ ID NO:63 provided that the C-terminal lysine may or may not be present, and the mature light chain variable region is linked to a light chain constant region, resulting

in a light chain comprising SEQ ID NO:65. In yet other aspects, provided herein is a monoclonal antibody that binds to an epitope comprising residues 35 and 37 of SEQ NO:1 and/or residues 49 and 51 of SEQ ID NO:1. In some embodiments, the antibody binds to an epitope comprising residues 35, 37, 49 and 51 of SEQ ID NO:1. In some embodiments, the antibody binds to a peptide consisting of residues 35-51 of SEQ ID NO:1 and no more than five flanking amino acids from SEQ ID NO:1 on either side. In some embodiments, the antibody binds to a peptide consisting of residues 35-51 of SEQ ID NO:1. In some embodiments, the epitope consists of 3 to 20 contiguous residues of SEQ ID NO:1. In some embodiments of any of the embodiments disclosed herein, the antibody has one or more of the following properties: (a) inhibiting binding of TIGIT to CD155, optionally with an IC50 of 15-100 ng/ml, (b) increases intrinsic T-cell activation in the presence of antigen presenting cells expressing CD155 as measured by IL-2 production, optionally 1.5-3 fold, (c) increases antigen-specific T-cell activation as measured by IL-12 production, optionally 1.5-3 fold, (d) increases natural killer cell activation as measured by production of any of IL-2, IL-6, TNF α or IFN γ , optionally by 1.5-3 fold, (e) increases T-cell production of at least one pro-inflammatory cytokine, optionally by 1.5-3 fold, and (f) reduces T-cell production of a least one anti-inflammatory cytokine, optionally by 1.5-3 fold.

[0015] In another aspect, provided herein are pharmaceutical composition comprising any of the antibodies described herein and pharmaceutically acceptable carrier.

[0016] In further aspects, provided herein are methods for treating or effecting prophylaxis of cancer comprising administering to a subject having or at risk of cancer an effective regime or a therapeutically effective amount of any of the antibodies disclosed herein. In some embodiments, the cancer is acute myeloid leukemia or adult T-cell leukemia. In some embodiments of any of the embodiments disclosed herein, the subject is administered tumor infiltrating T-cells which are activated by the antibody. In some embodiments of any of the embodiments disclosed herein, the subject is administered a vaccine inducing an immune response against the cancer, which is enhanced by the antibody. In some embodiments, the vaccine comprises an antigen or a fragment thereof expressed on the surface of cancer cells. In some embodiments of any of the embodiments disclosed herein, the subject is administered natural killer cells whose cytotoxicity against the cancer is enhanced by the antibody. In some embodiments of any of the embodiments disclosed herein, the subject is further administered a second antibody against an antigen expressed on the surface of cells of

cancer, whereby an effector mediated cytotoxicity of the second antibody against the cancer is enhanced by the antibody. In some embodiments of any of the embodiments disclosed herein, the subject is further administered a second antibody against an antigen expressed on the surface of an immune cell. In some embodiments, the immune cell is a T-cell or a natural

[0088] For example, when an amino acid differs between a non-human variable region framework residue and a selected human variable region framework residue, the human framework amino acid can be substituted by the equivalent framework amino acid from the non-human antibody when it is reasonably expected that the amino acid:

- (1) noncovalently binds antigen directly,
- (2) is adjacent to a CDR region,
- (3) otherwise interacts with a CDR region (*e.g.* is within about 6 Å of a CDR region).

[0089] Other candidates for substitution are acceptor human framework amino acids that are unusual for a human immunoglobulin at that position. These amino acids can be substituted with amino acids from the equivalent position of the non-human donor antibody or from the equivalent positions of more typical human immunoglobulins. Other candidates for substitution are acceptor human framework amino acids that are unusual for a human immunoglobulin at that position.

[0090] A preferred humanized antibody has a mature heavy chain variable region at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or less than 100% identical to SEQ ID NO:35 and a mature light chain variable region at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or less than 100% identical to SEQ ID NO:37. Preferably any variation occurs at variable region framework residues other than those identified as likely important to binding (*see* paragraph [0073]). Preferably any variation is a conservative amino acid substitution. A preferred antibody comprises a mature heavy chain variable region with the sequence of SEQ ID NO:35 and a mature light chain variable region with the sequence of SEQ ID NO:37. For expression of a full length antibody, the mature heavy chain variable region is preferably linked to a heavy chain constant region, resulting in a heavy chain consisting of or comprising SEQ ID NO:40 provided the C-terminal lysine may or may not be present and the mature light chain variable region is preferably linked to a light chain constant region, resulting in a light chain consisting of or comprising SEQ ID NO:41.

[0091] Another preferred humanized antibody has a mature heavy chain variable region at

least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or less than 100% identical to SEQ ID NO:43 and a mature light chain variable region at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or less than 100% identical to SEQ ID NO:45. Preferably any variation occurs at variable region framework residues other than those identified as likely important to binding (*see* paragraph [0073] and the Examples). Preferably any variation is a conservative amino acid substitution. A preferred antibody comprises a mature heavy chain variable region having the sequence of SEQ ID NO:43 and a mature light chain variable region having the sequence of SEQ ID NO:45. For expression of a full length antibody, the mature heavy chain variable region is preferably linked to a heavy chain constant region, resulting in a heavy chain consisting of or comprising SEQ ID NO:48 provided the C-terminal lysine may or may not be present and the mature light chain variable region is preferably linked to a light chain constant region, resulting in a light chain consisting of or comprising SEQ ID NO:49.

D. Chimeric and Veneered Antibodies

[0092] The invention further provides chimeric and veneered forms of non-human antibodies, particularly the TIG1, TIG2, and TIG3 antibodies of the examples.

[0093] A chimeric antibody is an antibody in which the mature variable regions of light and heavy chains of a non-human antibody (*e.g.*, a mouse) are combined with human light and heavy chain constant regions. Such antibodies substantially or entirely retain the binding specificity of the non-human antibody, and are about two-thirds human sequence.

[0094] A veneered antibody is a type of humanized antibody that retains some and usually all of the CDRs and some of the non-human variable region framework residues of a non-human antibody but replaces other variable region framework residues that may contribute to B- or T-cell epitopes, for example exposed residues (Padlan, *Mol. Immunol.* 28:489, 1991) with residues from the corresponding positions of a human antibody sequence. The result is an antibody in which the CDRs are entirely or substantially from a non-human antibody and the variable region frameworks of the non-human antibody are made more human-like by the substitutions. Veneered forms of the TIG1, TIG2, or TIG3 antibody are included in the invention.