ANTI-CD3 ANTIBODIES AND METHODS OF USE

FIELD OF THE INVENTION

The present invention relates to anti-cluster of differentiation 3 (CD3) antibodies and methods of using the same.

BACKGROUND

Cell proliferative disorders, such as cancer, are characterized by the uncontrolled growth of cell subpopulations. They are the leading cause of death in the developed world and the second leading cause of death in developing countries, with over 12 million new cancer cases diagnosed and 7 million cancer deaths occurring each year. The National Cancer Institute estimates that greater than half a million Americans will die of cancer in 2013, accounting for nearly one out of every four deaths in the country. As the elderly population has grown, the incidence of cancer has concurrently risen, as the probability of developing cancer is more than two-fold higher after the age of seventy. Cancer care thus represents a significant and ever-increasing societal burden.

Longstanding approaches to cancer treatment include chemotherapy, radiation therapy, and surgery to remove solid tumors. Recently, bispecific antibody-based immunotherapies have been developed. Such bispecific antibodies are capable of simultaneously binding cell surface antigens on cytotoxic cells and tumor cells, with the intent that the bound cytotoxic cell will destroy the bound tumor cell. Existing bispecific antibodies currently undergoing clinical trials for treating cancer are limited by their short half-lives and/or variable efficacy. Thus, there is an unmet need in the field for the development of effective bispecific antibodies for use in cancer treatment.

SUMMARY

The present disclosure relates to anti-cluster of differentiation 3 (CD3) antibodies and methods of using the same.

In a first aspect, there is provided an anti-cluster of differentiation 3 (CD3) antibody which is a bispecific antibody, wherein the bispecific antibody comprises an anti-CD3 arm comprising a first binding domain comprising the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and an anti-HER2 arm comprising a second binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 169, (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 170, (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 171, (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 172, (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 173, and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 174.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6. In some embodiments, the binding domain comprises (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 184; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 185; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 184. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 185. In some embodiments, the binding domain comprises (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID

NO: 186; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 187; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 186. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 187.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) an HVR-H3 comprising the amino acid sequence of $X_1X_2YSX_3X_4X_5FDY$, wherein X_1 is selected from the group consisting of D, T, and S; X_2 is selected from the group consisting of G, A, and S; X_3 is R or N; X_4 is Y or A; and X_5 is Y or A (SEQ ID NO: 181); (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) an HVR-L3 comprising the amino acid sequence of $X_1X_2SX_3X_4LRT$, wherein X_1 is K or T; X_2 is Q or A; X_3 is F or A; and X_4 is I or A (SEQ ID NO: 182). In some embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 12. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 188; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 189; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 189.

In other embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 13; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 12. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 190; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 191; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 190. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 191.

In other embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid

embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 206. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 207.

Disclosed is an anti-CD3 antibody comprising a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 188 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 189; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 190 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 191; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 192 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 193; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 194 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 195; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 196 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 197; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 198 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 199; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 200 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 201; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 202 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 203; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 204 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 205; or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 206 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 207.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23; (b) an HVR-H2 comprising the amino acid sequence of LINPYKGVX_1TY$X_2X_3X_4X_5$KX_6, wherein X_1 is S or T; X_2 is N or A; X_3 is Q or D; X_4 is K or S; X_5 is F or V; and X_6 is D or G (SEQ ID NO: 183); (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 25; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 24; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 25; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 208; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 209; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 208. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 209.

In other embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 29; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 25; (d)

an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 210; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 211; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 210. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 211.

In other embodiments, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 30; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 25; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 212; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 213; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 212. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 213.

Disclosed is an anti-CD3 antibody comprising a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 208 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 209; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 210 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 211; or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 212 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 213.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 31; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 32; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 33; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 34; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 35; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 36. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 214; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 215; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 214. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 215. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 216; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 217; or (c) a VH

domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 216. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 217.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 214 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 215, or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 216 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 217.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 37; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 38; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 39; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 40; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 41; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 218; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 219; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 218. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 219. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 220; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 221; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 220. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 221.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 218 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 219, or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 220 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 221.

Disclosed is anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 43; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 44; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 45; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 46; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 47; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 48. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 222; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of

SEQ ID NO: 223; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 222. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 223. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 224; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 225; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 224. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 225. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 226; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 227; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 226. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 227.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 222 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 223; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 224 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 225; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 226 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 227.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 49; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 50; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 51; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 52; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 53; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 54. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 228; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 229; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 228. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 229. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 230; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 231; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 230. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 231.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID

NO: 228 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 229, or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 230 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 231.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 55; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 56; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 57; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 58; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 59; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 60. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 232; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 233; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 232. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 233.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 232 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 233.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 61; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 62; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 64; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 65; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 234; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 235; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 234. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 235.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 234 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 235.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 67; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 68; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 69; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 70; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence

having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 236; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 237; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 236. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 237.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 236 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 237.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 73; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 74; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 75; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 76; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 77; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 78. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 238; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 239; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 238. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 239.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 238 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 239.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 79; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 80; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 81; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 82; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 83; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 84. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 240; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 241; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 240. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 241.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 240 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 241.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino

acid sequence of SEQ ID NO: 85; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 86; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 87; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 88; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 89; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 90. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 242; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 243; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 242. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 243.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 242 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 243.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 91; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 92; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 93; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 94; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 95; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 96. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 244; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 245; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 244. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 245.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 244 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 245.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 97; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 98; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 99; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 100; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 101; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 102. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 246; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 247; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 246. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 247.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 246 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 247.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 103; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 104; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 105; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 106; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 107; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 108. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 248; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 249; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 248. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 249.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 248 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 249.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 109; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 110; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 111; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 112; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 113; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 114. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 250; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 251; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 250. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 251.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 250 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 251.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 115; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 116; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 117; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 118; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 119; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 120. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence

having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 252; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 253; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 252. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 253.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 252 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 253.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 121; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 122; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 123; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 124; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 125; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 254; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 255; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 254. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 255.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 254 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 255.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 127; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 128; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 129; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 130; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 131; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 132. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 256; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 257; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 256. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 257.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 256 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 257.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino

acid sequence of SEQ ID NO: 133; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 134; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 135; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 136; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 137; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 258; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 259; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 258. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 259.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 258 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 259.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 139; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 140; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 141; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 142; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 143; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 144. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 260; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 261; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 260. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 261.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 260 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 261.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 145; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 146; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 147; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 148; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 149; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 150. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 262; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 263; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 262. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 263.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 262 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 263.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 151; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 152; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 153; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 154; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 155; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 156. In some embodiments, the binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 264; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 265; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 264. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 265.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 264 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 265.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody binds to an epitope on CD3 comprising amino acid residue Glu6 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope further comprises one or more additional amino acid residues selected from the group consisting of Gln1, Asp2, and Met7 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope comprises amino acid residues Gln1, Asp2, and Glu6 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope comprises amino acid residues Gln1, Asp2, Glu6, and Met7 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope does not comprise amino acid residue Glu5 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope does not comprise amino acid residues Gly3 and Glu5 of CD3. Disclosed is an anti-CD3 antibody, wherein the epitope consists of amino acid residues Gln1, Asp2, Glu6, and Met7 of CD3.

Disclosed is an anti-CD3 antibody that binds such an epitope and that is a multispecific antibody. In some embodiments, the multispecific antibody is a bispecific antibody. In some embodiments, the bispecific antibody comprises a second binding domain that binds to a second biological molecule, wherein the second biological molecule is a cell surface antigen. In some embodiments, the cell surface antigen is a tumor antigen. In some embodiments, the tumor antigen is selected from the group consisting of CD20; FcRH5 (Fc Receptor-like 5); HER2; LYPD1; Ly6G6D (lymphocyte antigen 6 complex, locus G61); Ly6-D, MEGT1); PMEL17 (silver homolog; SILV; D12S53E; PMEL17; (SI); (SIL); ME20; gp100); Ly6E (lymphocyte antigen 6 complex, locus E; Ly67, RIG-E, SCA-2, TSA-1); CD19; CD33; CD22 (B-cell receptor CD22-B isoform); CD79a (CD79A, CD79a, immunoglobulin-associated alpha; BMPR1B (bone morphogenetic protein receptor-type IB); CD79b (CD79B, CD79β, 1 Gb (immunoglobulin-associated beta), B29); EDAR (Ectodysplasin A Receptor); GFRA1 (GDNF-Ra1);

HVR-H2 comprising the amino acid sequence of SEQ ID NO: 176; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 177; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 178; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 179; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 180. In some embodiments, the second binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 272; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 273; or (c) a VH domain as in (a) and a VL domain as in (b). In some embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 272. In some embodiments, the VL domain comprises the amino acid sequence of SEQ ID NO: 273.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises a second binding domain comprising: (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 266 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 267; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 268 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 269; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 270 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 271; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 272 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 273; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 593 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 594; (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 595 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 596; or (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 619 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 620.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises an anti-CD3 arm comprising a first binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and an anti-CD20 arm comprising a second binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 157; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 158; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 159; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 160; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 161; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 162.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises an anti-CD3 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 184 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 185, and an anti-CD20 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 266 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 267.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises an anti-CD3 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 184 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 185, and an anti-CD20 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 266 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 267, wherein the anti-CD3 antibody comprises an N297G substitution mutation.

Disclosed is an anti-CD3 antibody, wherein the anti-CD3 antibody comprises an anti-CD3 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 184 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 185, and an anti-CD20 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 266 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 267, wherein (a) the anti-CD3 arm comprises T366S, L368A, Y407V, and N297G substitution mutations and (b) the anti-CD20 arm comprises T366W and N297G substitution mutations.

In some embodiments, any one of the preceding anti-CD3 antibodies can comprise one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 ($CH1_1$) domain, a first CH2 ($CH2_1$) domain, a first CH3 ($CH3_1$) domain, a second CH1 ($CH1_2$) domain, second CH2 ($CH2_2$) domain, and a second CH3 ($CH3_2$) domain. In some embodiments, at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain. In some embodiments, the $CH3_1$ and $CH3_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH3_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH3_2$ domain. In some embodiments, the $CH3_1$ and $CH3_2$ domains meet at an interface between said protuberance and cavity. In some embodiments, the $CH2_1$ and $CH2_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH2_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH2_2$ domain. In some embodiments, the $CH2_1$ and $CH2_2$ domains meet at an interface between said protuberance and cavity.

In some embodiments, the half-life of any one of the preceding anti-CD3 antibodies may be about 7 days.

In some embodiments, the invention features an immunoconjugate comprising any one of the preceding anti-CD3 antibodies conjugated to a cytotoxic agent. Also provided is a composition comprising any one of the preceding anti-CD3 antibodies. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent. Disclosed is an isolated nucleic acid that encodes any of the anti-CD3 antibodies disclosed herein, comprising a vector (e.g., an expression vector) for expressing the antibody.

In a second aspect, there is provided an isolated nucleic acid encoding the bispecific antibody as described herein.

In a third aspect, there is provided a vector comprising the isolated nucleic acid as described herein.

In a fourth aspect, there is provided a host cell comprising the vector as described herein.

Disclosed are host cells comprising the preceding nucleic acids and/or vectors. In some embodiments, the host cell is a mammalian cell (e.g., a Chinese hamster ovary (CHO) cell). In other embodiments, the host cell is a prokaryotic cell (e.g., an *E. coli* cell). A

method of producing any one of the preceding anti-CD3 antibodies is also provided, the method comprising culturing the host cell that produces the anti-CD3 antibody and recovering the anti-CD3 antibody from the host cell or the culture medium.

In a fifth aspect, there is provided a method of producing the bispecific antibody as described herein, the method comprising culturing the host cell as described herein in a culture medium and recovering the bispecific antibody from the host cell or the culture medium.

In a sixth aspect, there is provided an immunoconjugate comprising the bispecific antibody as described herein and a cytotoxic agent.

In a seventh aspect, there is provided a composition comprising the bispecific antibody as described herein and a pharmaceutically acceptable carrier, excipient, or diluent.

In an eighth aspect, there is provided the bispecific antibody as described herein for use as a medicament.

In some embodiments, any one of the preceding anti-CD3 antibodies can be for use as a medicament. In some embodiments, any one of the preceding anti-CD3 antibodies can be for use in treating or delaying progression of a cell proliferative disorder or an autoimmune disorder in a subject in need thereof. In some embodiments, any one of the preceding anti-CD3 antibodies can be for use in enhancing immune function in a subject having a cell proliferative disorder or an autoimmune disorder.

Disclosed is the use of any one of the preceding anti-CD3 antibodies in the manufacture of a medicament for treating or delaying progression of a cell proliferative disorder or an autoimmune disorder.

In a ninth aspect, there is provided use of the bispecific antibody as described herein in the manufacture of a medicament for treating or delaying progression of a cell proliferative disorder in a subject.

Disclosed is the use of any one of the preceding anti-CD3 antibodies in the manufacture of a medicament for enhancing immune function in a subject having a cell proliferative disorder or an autoimmune disorder.

In a tenth aspect, there is provided use of the bispecific antibody as described herein in the manufacture of a medicament for enhancing immune function in a subject having a cell proliferative disorder.

Disclosed is a method of treating or delaying the progression of a cell proliferative disorder or an autoimmune disorder in a subject in need thereof, the method comprising administering to the subject an effective amount any one of the preceding anti-CD3 antibodies. Disclosed is a method of enhancing immune function in a subject having a cell proliferative disorder or an autoimmune disorder, the method comprising administering to the subject any one of the preceding anti-CD3 antibodies. In some embodiments, the anti-CD3 antibody binds to (a) a CD3 molecule located on an immune effector cell and (b) a second biological molecule located on a target cell other than the immune effector cell. In some embodiments, the anti-CD3 antibody activates the immune effector cell following binding to (a) and (b). In some embodiments, the activated immune effector cell is capable of exerting a cytotoxic effect and/or an apoptotic effect on the target cell. In some embodiments, the anti-CD3 antibody is administered to the subject in a dosage of about 0.01 mg/kg to about 10 mg/kg. In some embodiments, the anti-CD3 antibody is administered to the subject in a dosage of about 0.1 mg/kg to about 10 mg/kg. In some embodiments, the anti-CD3 antibody is administered to the subject in a dosage of about 1 mg/kg. In some embodiments, the anti-CD3 antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the anti-CD3 antibody is administered subcutaneously. In some embodiments, the anti-CD3 antibody is administered intravenously.

In some embodiments, the method further comprises administering to the subject a PD-1 axis binding antagonist or an additional therapeutic agent. In some embodiments, the additional therapeutic agent is administered prior to or subsequent to the administration of the anti-CD3 antibody. In some embodiments, the additional therapeutic agent is administered concurrently with the anti-CD3 antibody. In some embodiments, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist. In some embodiments, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (lambrolizumab), CT-011 (pidilizumab), and AMP-224. In other embodiments, the PD-1 axis binding antagonist is a PD-L1

binding antagonist. In some embodiments, the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736. In other embodiments, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some embodiments, the PD-L2 binding antagonist is an antibody or an immunoadhesin.

Disclosed is a method of treating or delaying the progression of a cell proliferative disorder or an autoimmune disorder in a subject in need thereof, the method comprising administering to the subject an anti-CD3 antibody and a PD-1 axis binding antagonist, wherein the anti-CD3 antibody comprises an anti-CD3 arm and an anti-CD20 arm. Disclosed is a method of enhancing immune function in a subject having a cell proliferative disorder or an autoimmune disorder, the method comprising administering to the subject an anti-CD3 antibody and a PD-1 axis binding antagonist, wherein the anti-CD3 antibody comprises an anti-CD3 arm and an anti-CD20 arm (i.e., a CD20 TDB). In some embodiments, (a) the anti-CD3 arm comprises a first binding domain comprising (i) a VH domain comprising an amino acid sequence of SEQ ID NO: 184, and (ii) a VL domain comprising an amino acid sequence of SEQ ID NO: 185; (b) the anti-CD20 arm comprises a second binding domain comprising (i) a VH domain comprising an amino acid sequence of SEQ ID NO: 266, and (ii) a VL domain comprising an amino acid sequence of SEQ ID NO: 267; and/or (c) the PD-1 axis binding antagonist is an anti-PD-L1 antibody.

In some embodiments, the anti-CD3 antibody comprises an anti-CD20 arm comprising a N297G substitution mutation. In some embodiments, the anti-CD3 antibody comprises an anti-CD3 arm comprising T366S, L368A, Y407V, and/or N297G substitution mutation(s) and an anti-CD20 arm comprising T366W and/or N297G substitution mutation(s). In some embodiments, the anti-CD3 antibody comprises an anti-CD3 arm comprising a N297G substitution mutation. In some embodiments, the anti-CD3 antibody comprises an anti-CD20 arm comprising T366S, L368A, Y407V, and/or N297G substitution mutation(s) and an anti-CD3 arm comprising T366W and/or N297G substitution mutation(s).

In some embodiments, the anti-CD3 antibody comprises an anti-HER2 arm comprising a N297G substitution mutation. In some embodiments, the anti-CD3 antibody comprises an anti-CD3 arm comprising T366S, L368A, Y407V, and/or N297G substitution mutation(s) and an anti-HER2 arm comprising N297G, N297A, L234A, L235A, and/or D265A substitution mutation(s). In some embodiments, the anti-CD3 antibody comprises an anti-CD3 arm comprising a N297G substitution mutation. In some embodiments, the anti-CD3 antibody comprises an anti-HER2 arm comprising T366S, L368A, Y407V, and/or N297G substitution mutation(s) and an anti-CD3 arm comprising N297G, N297A, L234A, L235A, and/or D265A substitution mutation(s).

In some embodiments, the method further comprises administering to the subject a glucocorticoid. In some embodiments, the glucocorticoid is selected from the group consisting of dexamethasone, hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, fludrocortisone, and pharmaceutically acceptable esters, salts, and complexes thereof. In some embodiments, the glucocorticoid is dexamethasone. In some embodiments, the glucocorticoid is a pharmaceutically acceptable ester, salt, or complex of dexamethasone.

In some embodiments, the method further comprises administering to the subject rituximab.

In some embodiments, the method further comprises administering to the subject obinutuzumab.

In some embodiments, the method further comprises administering to the subject an antibody-drug conjugate (ADC).

In any of the preceding uses or methods, the cell proliferative disorder can be cancer. In some embodiments, the cancer is selected from the group consisting of breast cancer, colorectal cancer, non-small cell lung cancer, non-Hodgkin's lymphoma (NHL), B cell lymphoma, B cell leukemia, multiple myeloma, renal cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, glioblastoma, germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), Burkitt's lymphoma (BL), B-cell prolymphocytic leukemia, Splenic marginal zone lymphoma, Hairy cell leukemia, Splenic lymphoma/leukemia, unclassifiable, Splenic diffuse red pulp small B-cell lymphoma, Hairy cell leukemia variant, Waldenström macroglobulinemia, Heavy chain diseases, α Heavy chain disease, γ Heavy chain disease, μ Heavy chain disease, Plasma cell myeloma, Solitary plasmacytoma of bone, Extraosseous plasmacytoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Nodal marginal zone lymphoma, Pediatric nodal marginal zone lymphoma, Pediatric follicular lymphoma, Primary cutaneous follicle centre lymphoma, T-cell/histiocyte rich large B-cell lymphoma, Primary DLBCL of the CNS, Primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, Lymphomatoid granulomatosis, Primary mediastinal (thymic) large B-cell lymphoma, Intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, Plasmablastic lymphoma, Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, Primary effusion lymphoma: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In some embodiments, the preferred cancer is germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), or Burkitt's lymphoma (BL)

In any of the preceding uses or methods, the autoimmune disorder can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome, glomerulonephritis, Neuromyelitis Optica (NMO) and IgG neuropathy.

Disclosed is a kit comprising: (a) a composition comprising any one of the preceding anti-CD3 antibodies and (b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a cell proliferative disorder.

In an eleventh aspect, there is provided a kit comprising: (a) the composition as described herein; and (b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a cell proliferative disorder.

In any of the preceding uses or methods, the subject can be a human.

WHAT IS CLAIMED IS:

1. An anti-cluster of differentiation 3 (CD3) antibody which is a bispecific antibody, wherein the bispecific antibody comprises an anti-CD3 arm comprising a first binding domain comprising the following six hypervariable regions (HVRs):

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

an anti-HER2 arm comprising a second binding domain comprising the following six HVRs:
(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 169,
(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 170,
(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 171,
(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 172,
(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 173, and
(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 174.

2. The bispecific antibody of claim 1, wherein the first binding domain comprises: (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 184; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 185; or (c) a VH domain as in (a) and a VL domain as in (b).

3. The bispecific antibody of claim 2, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 184 and/or the VL domain comprises the amino acid sequence of SEQ ID NO: 185.

4. The bispecific antibody of any one of claims 1-3, wherein the second binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 270; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 271; or (c) a VH domain as in (a) and a VL domain as in (b).

5. The bispecific antibody of claim 4, wherein the second binding domain comprises (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 270 and/or (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 271.

6. The bispecific antibody of any one of claims 1-5, wherein the bispecific antibody comprises an anti-CD3 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 184 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 185, and an anti-HER2 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 270 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 271.

7. The bispecific antibody of any one of claims 1-6, wherein the first binding domain binds to a human CD3 polypeptide or a cynomolgus monkey (cyno) CD3 polypeptide.

8. The bispecific antibody of claim 7, wherein (a) the human CD3 polypeptide is a human CD3ε polypeptide; or (b) the cyno CD3 polypeptide is a cyno CD3ε polypeptide.

9. The bispecific antibody of claim 7, wherein (a) the human CD3 polypeptide is a human CD3γ polypeptide; or (b) the cyno CD3 polypeptide is a cyno CD3γ polypeptide.

10. The bispecific antibody of any one of claims 1-9, wherein the bispecific antibody comprises an aglycosylation site mutation.

11. The bispecific antibody of claim 10, wherein the aglycosylation site mutation reduces effector function of the bispecific antibody.

12. The bispecific antibody of claim 10 or 11, wherein the aglycosylation site mutation is a substitution mutation.

13. The bispecific antibody of any one of claims 1-12, wherein the bispecific antibody comprises a substitution mutation in the Fc region that reduces effector function.

14. The bispecific antibody of claim 12 or 13, wherein the substitution mutation is at amino acid residue N297, L234, L235, and/or D265 (EU numbering).

15. The bispecific antibody of claim 14, wherein the substitution mutation is selected from the group consisting of N297G, N297A, L234A, L235A, and D265A.

16. The bispecific antibody of any one of claims 1-15, wherein the bispecific antibody is monoclonal, human, humanized, or chimeric.

17. The bispecific antibody of any one of claims 1-16, which is a full-length antibody.

18. The bispecific antibody of any one of claims 1-17, wherein the bispecific antibody is an IgG antibody.

19. The bispecific antibody of claim any one of claims 1-18, wherein (a) the anti-CD3 arm comprises T366S, L368A, Y407V, and/or N297G substitution mutations; and (b) the anti-HER2 arm comprises N297G, N297A, L234A, L235A, and/or D265A substitution mutations.

20. The bispecific antibody of any one of claims 1-19, wherein the bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 ($CH1_1$) domain, a first CH2 ($CH2_1$) domain, a first CH3 ($CH3_1$) domain, a second CH1 ($CH1_2$) domain, second CH2 ($CH2_2$) domain, and a second CH3 ($CH3_2$) domain.

21. The bispecific antibody of claim 20, wherein at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain, wherein the $CH3_1$ and $CH3_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH3_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH3_2$ domain.

22. The bispecific antibody of any one of claim 20, wherein at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain, wherein the $CH2_1$ and $CH2_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH2_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH2_2$ domain.

23. An isolated nucleic acid encoding the bispecific antibody of any one of claims 1-22.

24. A vector comprising the isolated nucleic acid of claim 23.

25. A host cell comprising the vector of claim 24.

26. A method of producing the bispecific antibody of any one of claims 1-22, the method comprising culturing the host cell of claim 25 in a culture medium and recovering the bispecific antibody from the host cell or the culture medium.

27. An immunoconjugate comprising the bispecific antibody of any one of claims 1-22 and a cytotoxic agent.

28. A composition comprising the bispecific antibody of any one of claims 1-22 and a pharmaceutically acceptable carrier, excipient, or diluent.

29. The composition of claim 28, wherein the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

30. The bispecific antibody of any one of claims 1-29 for use as a medicament.

31. Use of the bispecific antibody of any one of claims 1-22 in the manufacture of a medicament for treating or delaying progression of a cell proliferative disorder in a subject.

32. Use of the bispecific antibody of any one of claims 1-22 in the manufacture of a medicament for enhancing immune function in a subject having a cell proliferative disorder.

33. The use of claim 31 or 32, wherein the cell proliferative disorder is a HER2-positive cancer.

34. The use of claim 33, wherein the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer.

35. The use of any one of claims 31-34, wherein the bispecific antibody binds to (a) a CD3 molecule located on an immune effector cell and (b) a HER2 molecule located on a target cell other than the immune effector cell.

36. The use of claim 35, wherein the bispecific antibody activates the immune effector cell following binding to (a) and (b).

37. The use of any one of claims 31-36, wherein the bispecific antibody is formulated for administration to the subject in a dosage of about 0.01 mg/kg to about 10 mg/kg.

38. The use of claim 37, wherein the bispecific antibody is formulated for administration to the subject in a dosage of about 0.1 mg/kg to about 10 mg/kg.

39. The use of claim 38, wherein the bispecific antibody is formulated for administration to the subject in a dosage of about 1 mg/kg.

40. The use of any one of claims 31-39, wherein the medicament is formulated for administration with a PD-1 axis binding antagonist and/or an additional therapeutic agent.

41. The use of claim 40, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

42. The use of claim 41, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

43. The use of claim 40, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

44. The use of claim 43, wherein the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (lambrolizumab), and AMP-224.

45. The use of claim 40, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

46. The use of claim 45, wherein the PD-L2 binding antagonist is an antibody or an immunoadhesin.

47. The use of any one of claims 31-46, wherein the medicament is formulated for administration with a glucocorticoid or an antibody-drug conjugate (ADC).

48. The use of any one of claims 31-47, wherein the medicament is formulated for administration with one or more additional therapeutic agents that target the HER2 pathway.

49. The use of claim 48, wherein the one or more additional therapeutic agents that target the HER2 pathway are selected from trastuzumab, T-DM1, and pertuzumab.

50. The use of claim 49, wherein the additional therapeutic agent is trastuzumab.

51. The use of any one of claims 31-50, wherein the bispecific antibody is formulated for administration to a subject subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

52. The use of any one of claims 31-51, wherein the subject is a human.

53. A kit comprising:

(a) the composition of claim 28 or 29; and

(b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a cell proliferative disorder.

54. The kit of claim 53, wherein the cell proliferative disorder is a HER2-positive cancer.

55. The kit of claim 54, wherein the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer.