

al. (*American Journal of Pathology*, Vol. 181, No. 6, December 2012), Henry, *et al.* (*Oncotarget*, Vol. 6, No. 37 2015), Zhang, *et al.* (*PLoS ONE* 7(3): e31127.), and Bainbridge, *et al.* (*PLoS ONE* 9(7): e102695.), each herein incorporated by reference in their entirety. In addition, ROR expression may not be expressed, or only demonstrate limited expression, in normal, *i.e.* non-cancerous, tissue as described in Balakrishnan *et al.* (*Clin Cancer Res.* 2017 Jun 15; 23(12): 3061–3071), herein incorporated in its entirety. Thus ROR antigens can be used as a tumor-specific marker in certain tumors. Examples of tumors and cancers with demonstrated ROR expression include, but are not limited to, pancreatic cancer, ovarian cancer, breast cancer, lung cancer, gastric cancer, melanoma, Ewing sarcoma, chronic lymphocytic leukemia, mantle cell lymphoma, and B-ALL, as described in Gohil *et al.* (*Oncoimmunology.* 2017; 6(7): e1326437.), herein incorporated in its entirety. Other cancers include, but are not limited to, hematological cancer, prostate cancer, colon cancer, renal cancer, and uterine cancer. Use of ROR multispecific antibodies, formatted in various antibody platforms, to target tumors is described in Gohil, *et al.*, international application WO 2017/053469, international application WO 2014/167022, U.S. Pub. No. 2017/0198045, international application WO 2016/094873, international application WO 2017/127499, and international application WO 2016/142768, each of which is herein incorporated by reference in its entirety.

[0006] ROR antigen binding molecules thus have therapeutic potential in treatment of cancer. Multispecific ROR binding molecules that bind T cell surface antigens in addition to a ROR antigen have potential to provide T cell redirected killing of ROR-expressing cancer cells.

[0007] There is, therefore, a need for ROR antigen binding molecules, including multispecific ROR antigen binding molecules. There is also a need for ROR antigen binding molecules that have improvements including increased affinity or avidity, reduced off-target binding, and/or reduced unintended immune activation. There is a particular need for a multispecific ROR antigen binding molecule that has improved manufacturability, and is readily purified.

4. SUMMARY

[0008] The present disclosure provides aspects as disclosed in the claims. In a first example aspect, antigen binding molecules are provided. In every example embodiment, the antigen binding molecule includes at least an antigen binding site specific for a ROR antigen; the binding molecules are therefore termed ROR antigen binding molecules.

[0009] Described herein are tyrosine-protein kinase transmembrane receptor (ROR) antigen binding molecules comprising: A) a CDR1, a CDR2, and a CDR3 amino acid sequences of a light chain variable region (VL) from a ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6; and B) comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a heavy chain variable region (VH) from the ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6, wherein the ROR antigen binding site is a first antigen binding site and is specific for (i) ROR1 and ROR2, (ii) ROR1, or (iii) ROR2. In certain aspectsexamples, the ROR antigen binding molecule further comprises a second antigen binding site. In certain aspectsexamples, the second antigen binding site is the same as the first antigen binding site. In certain aspectsexamples, the second antigen binding site is specific for a second antigen different from the ROR antigen of the first antigen binding site. In certain aspectsexamples, the second antigen is a CD3 antigen.

[0010] Described herein are tyrosine-protein kinase transmembrane receptor (ROR) antigen binding molecules comprising: a first and a second polypeptide chain, wherein: (a) the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E, wherein the domains are arranged, from N-terminus to C-terminus, in a A-B-D-E orientation, and wherein domain A has a VL amino acid sequence, domain B has a CH3 amino acid sequence, domain D has a CH2 amino acid sequence, domain E has a constant region domain amino acid sequence; (b) the second polypeptide chain comprises a domain F and a domain G, wherein the domains are arranged, from N-terminus to C-terminus, in a F-G orientation, and wherein domain F has a VH amino acid sequence and domain G has a CH3 amino acid sequence; and (c) the first and the second polypeptides are associated through an interaction between the A and the F domains and an interaction between the B and the G domains to form the ROR antigen binding molecule, wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a ROR antigen.

[0011] In certain aspectsexamples, the ROR antigen is ROR1. In certain aspectsexamples, the ROR antigen is ROR2. In certain aspectsexamples, the ROR antigen is ROR1 and ROR2. In certain aspectsexamples, the ROR antigen is a domain selected from the group consisting of: a ROR1 Frizzles domain, ROR2 Frizzles domain, a ROR1 Ig-like domain, a ROR2 Ig-like domain, a ROR1 Kringle domain, and a ROR2 Kringle domain. In certain aspectsexamples, the ROR antigen comprises a human ROR antigen.

[0012] In certain aspectsexamples, Domain A comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding

site, wherein the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6, and Domain F comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6. In certain

[aspectsexamples](#), the specific ROR antigen binding site is I2A-10, I2A-10 D54E Y55Q, or I2A-27 from Table 6.

[0013] In certain [aspectsexamples](#), Domain A comprises a VL having one or two amino acid mutations as compared with a VL sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VL. In certain [aspectsexamples](#), Domain F comprises a VH having one or two amino acid mutations as compared with a VH sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VH. In certain [aspectsexamples](#), Domain A comprises a VL having the VL sequence of I2A-10 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain A comprises a VL having the VL sequence of I2A-27 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain F comprises a VL having the VL sequence of I2A-10 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain F comprises a VL having the VL sequence of I2A-27 with one or more mutations in one or more CDR regions.

[0014] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0015] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are different and separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the B domain interacts with the G domain, and wherein neither the B domain nor the G domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0016] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise mutations that generate engineered disulfide bridges between the B domain and the G domain. In certain [aspectsexamples](#), the mutations of the B domain and the G domain that generate engineered disulfide bridges are a S354C mutation in one of the B domain and G domain, and a 349C in the other domain.

[0017] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations are a T366W

mutation in one of the B domain and G domain, and a T366S, L368A, and aY407V mutation in the other domain.

[0018] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise charge-pair mutations. In certain [aspectsexamples](#), the charge-pair mutations are a T366K mutation in one of the B domain and G domain, and a L351D mutation in the other domain.

[0019] In certain [aspectsexamples](#), the E domain has a CH3 amino acid sequence.

[0020] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0021] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are different. In certain [aspectsexamples](#), the different sequences separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the E domain interacts with the K domain, and wherein neither the E domain nor the K domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0022] In certain [aspectsexamples](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the E domain and the K domain. In certain [aspectsexamples](#), the mutations that generate engineered disulfide bridges are a S354C mutation in one of the E domain and the K domain, and a 349C in the other domain.

[0023] In certain [aspectsexamples](#), the orthogonal modifications in the E domain and the K domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations are a T366W mutation in one of the E domain or the K domain and a T366S, L368A, and aY407V mutation in the other domain.

[0024] In certain [aspectsexamples](#), the orthogonal modifications in the E domain and the K domain comprise charge-pair mutations. In certain [aspectsexamples](#), the charge-pair mutations are a T366K mutation in one of the E domain or the K domain and a corresponding L351D mutation in the other domain.

[0025] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are endogenous sequences of two different antibody domains, the domains selected to have a specific interaction that promotes the specific association between the first and the third polypeptides. In certain [aspectsexamples](#), the two different amino acid sequences are a CH1 sequence and a CL sequence.

[0026] In certain [aspectsexamples](#), the sequence that forms the junction between the A domain and the B domain is IKRTPREP or IKRTVREP.

[0027] In certain [aspectsexamples](#), the sequence that forms the junction between the F domain and the G domain is SSASPREP.

[0028] In certain [aspectsexamples](#), at least one CH3 amino acid sequence has a C-terminal tripeptide insertion connecting the CH3 amino acid sequence to a hinge amino acid sequence, wherein the tripeptide insertion is selected from the group consisting of PGK, KSC, and GEC.

[0029] In certain [aspectsexamples](#), the sequences are human sequences.

[0030] In certain [aspectsexamples](#), at least one CH3 amino acid sequence is an IgG sequence. In certain [aspectsexamples](#), the IgG sequences are IgG1 sequences.

[0031] In certain [aspectsexamples](#), at least one CH3 amino acid sequence has one or more isoallotype mutations. In certain [aspectsexamples](#), the isoallotype mutations are D356E and L358M.

[0032] In certain [aspectsexamples](#), the CL amino acid sequence is a Ckappa sequence.

[0033] In certain [aspectsexamples](#), the CH2 sequences have one or more engineered mutations that reduce Fc effector function. In certain [aspectsexamples](#), the one or more engineered mutations are at position L234, L235, and P329. In certain [aspectsexamples](#), the one or more engineered mutations are L234A, L235A, and P329G. In certain [aspectsexamples](#), the one or more engineered mutations are L234A, L235A, and P329K.

[0034] Also described herein are tyrosine-protein kinase transmembrane receptor (ROR) antigen binding molecules comprising: a first, second, third, and fourth polypeptide chain, wherein: (a) the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E, wherein the domains are arranged, from N-terminus to C-terminus, in a A-B-D-E orientation, and domain A has a VL amino acid sequence, domain B has a CH3 amino acid sequence, domain D has a CH2 amino acid sequence, and domain E has a constant region domain amino acid sequence; (b) the second polypeptide chain comprises a domain F and a domain G, wherein the domains are arranged, from N-terminus to C-terminus, in a F-G orientation, and wherein domain F has a VH amino acid sequence and domain G has a CH3 amino acid sequence; (c) the third polypeptide chain comprises a domain H, a domain I, a domain J, and a domain K, wherein the domains are arranged, from N-terminus to C-terminus, in a H-I-J-K orientation, and wherein domain H has a variable region domain amino acid sequence, domain I has a constant region domain amino acid sequence, domain J

has a CH2 amino acid sequence, and K has a constant region domain amino acid sequence; (d) the fourth polypeptide chain comprises a domain L and a domain M, wherein the domains are arranged, from N-terminus to C-terminus, in a L-M orientation, and wherein domain L has a variable region domain amino acid sequence and domain M has a constant region domain amino acid sequence; (e) the first and the second polypeptides are associated through an interaction between the A and the F domains and an interaction between the B and the G domains; (f) the third and the fourth polypeptides are associated through an interaction between the H and the L domains and an interaction between the I and the M domains; and (g) the first and the third polypeptides are associated through an interaction between the D and the J domains and an interaction between the E and the K domains to form the ROR antigen binding molecule, wherein the interaction between the A domain and the F domain form a first antigen binding site, the interaction between the H domain and the L domain form a second antigen binding site, and wherein the first antigen binding site, the second antigen binding site, or the first and the second antigen binding site are specific for a ROR antigen.

[0035] In certain [aspectsexamples](#), the first antigen binding site is specific for the ROR antigen. In certain [aspectsexamples](#), the second antigen binding site is specific for the ROR antigen. In certain [aspectsexamples](#), the first and the second antigen binding site is specific for the ROR antigen.

[0036] In certain [aspectsexamples](#), the ROR antigen is ROR1. In certain [aspectsexamples](#), the ROR antigen is ROR2. In certain [aspectsexamples](#), the ROR antigen is ROR1 and ROR2. In certain [aspectsexamples](#), the ROR antigen is a domain selected from the group consisting of: a ROR1 Frizzle domain, ROR2 Frizzle domain, a ROR1 Ig-like domain, a ROR2 Ig-like domain, a ROR1 Kringle domain, and a ROR2 Kringle domain. In certain [aspectsexamples](#), the ROR antigen comprises a human ROR antigen.

[0037] In certain [aspectsexamples](#), Domain A comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6, and Domain F comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6. In certain [aspectsexamples](#), the specific ROR antigen binding site is I2A-10, I2A-10 D54E Y55Q or I2A-27 from Table 6.

[0038] In certain [aspectsexamples](#), Domain A comprises a VL having one or two amino acid mutations as compared with a VL sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VL. In certain [aspectsexamples](#), Domain F

comprises a VH having one or two amino acid mutations as compared with a VH sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VH. In certain [aspectsexamples](#), Domain A comprises a VL having the VL sequence of I2A-10 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain A comprises a VL having the VL sequence of I2A-27 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain F comprises a VL having the VL sequence of I2A-10 with one or more mutations in one or more CDR regions. In certain [aspectsexamples](#), Domain F comprises a VL having the VL sequence of I2A-27 with one or more mutations in one or more CDR regions.

[0039] In certain [aspectsexamples](#), the second antigen binding site comprises: A) within the third polypeptide chain a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and B) within the fourth polypeptide chain a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

[0040] In certain [aspectsexamples](#), the second antigen binding site comprises: A) within the fourth polypeptide chain a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and B) within the third polypeptide chain a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

[0041] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0042] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are different and separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the B domain interacts with the G domain, and wherein neither the B domain nor the G domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0043] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise mutations that generate engineered disulfide bridges between the B domain and the G domain. In certain [aspectsexamples](#), the mutations of the B domain and the G domain that generate

engineered disulfide bridges are a S354C mutation in one of the B domain and G domain, and a 349C in the other domain.

[0044] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations are a T366W mutation in one of the B domain and G domain, and a T366S, L368A, and aY407V mutation in the other domain.

[0045] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise charge-pair mutations. In certain [aspectsexamples](#), the charge-pair mutations are a T366K mutation in one of the B domain and G domain, and a L351D mutation in the other domain.

[0046] In certain [aspectsexamples](#), the E domain has a CH3 amino acid sequence.

[0047] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0048] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are different. In certain [aspectsexamples](#), the different sequences separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the E domain interacts with the K domain, and wherein neither the E domain nor the K domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0049] In certain [aspectsexamples](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the E domain and the K domain. In certain [aspectsexamples](#), the mutations that generate engineered disulfide bridges are a S354C mutation in one of the E domain and the K domain, and a 349C in the other domain.

[0050] In certain [aspectsexamples](#), the orthogonal modifications in the E domain and the K domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations are a T366W mutation in one of the E domain or the K domain and a T366S, L368A, and aY407V mutation in the other domain.

[0051] In certain [aspectsexamples](#), the orthogonal modifications in the E domain and the K domain comprise charge-pair mutations. In certain [aspectsexamples](#), the charge-pair mutations are a T366K mutation in one of the E domain or the K domain and a corresponding L351D mutation in the other domain.

[0052] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are endogenous sequences of two different antibody domains, the domains selected to have a

specific interaction that promotes the specific association between the first and the third polypeptides. In certain [aspectsexamples](#), the two different amino acid sequences are a CH1 sequence and a CL sequence.

[0053] In certain [aspectsexamples](#), domain I has a CL sequence and domain M has a CH1 sequence.

[0054] In certain [aspectsexamples](#), domain H has a VL sequence and domain L has a VH sequence.

[0055] In certain [aspectsexamples](#), domain H has a VL amino acid sequence; domain I has a CL amino acid sequence; domain K has a CH3 amino acid sequence; domain L has a VH amino acid sequence; and domain M has a CH1 amino acid sequence.

[0056] In certain [aspectsexamples](#), the ROR antigen binding molecule further comprises: a fifth polypeptide chain, wherein: (a) the first polypeptide chain further comprises a domain N and a domain O, wherein the domains are arranged, from N-terminus to C-terminus, in a N-O-A-B-D-E orientation, and wherein domain N has a variable region domain amino acid sequence, domain O has a constant region domain amino acid sequence; (b) the ROR antigen binding molecule further comprises a fifth polypeptide chain, comprising: a domain P and a domain Q, wherein the domains are arranged, from N-terminus to C-terminus, in a P-Q orientation, and wherein domain P has a variable region domain amino acid sequence and domain Q has a constant region domain amino acid sequence; and (c) the first and the fifth polypeptides are associated through an interaction between the N and the P domains and an interaction between the O and the Q domains to form the ROR antigen binding molecule.

[0057] In certain [aspectsexamples](#), (a) the amino acid sequences of domain N and domain A are identical, the amino acid sequences of domain H is different from the sequence of domain N and domain A, the amino acid sequences of domain O and domain B are identical, the amino acid sequences of domain I is different from the sequence of domain O and domain B, the amino acid sequences of domain P and domain F are identical, the amino acid sequences of domain L is different from the sequence of domain P and domain F, the amino acid sequences of domain Q and domain G are identical, the amino acid sequences of domain M is different from the sequence of domain Q and domain G; and (b) wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the N domain and the P domain form a third antigen binding site specific for the first antigen. In certain [aspectsexamples](#), the first antigen is the ROR antigen. In certain [aspectsexamples](#), the second antigen is a CD3 antigen.

[0058] In certain [aspectsexamples](#), (a) the amino acid sequences of domain N, domain A, and domain H are different, the amino acid sequences of domain O, domain B, and domain I are different, the amino acid sequences of domain P, domain F, and domain L are different, and the amino acid sequences of domain Q, domain G, and domain M are different; (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the domain N and domain P form a third antigen binding site specific for a third antigen, and (c) the first, the second, or the third antigen is the ROR antigen.

[0059] In certain [aspectsexamples](#), the ROR antigen binding molecule further comprises: a sixth polypeptide chain, wherein: (a) the third polypeptide chain further comprises a domain R and a domain S, wherein the domains are arranged, from N-terminus to C-terminus, in a R-S-H-I-J-K orientation, and wherein domain R has a variable region domain amino acid sequence and domain S has a constant domain amino acid sequence; (b) the ROR antigen binding molecule further comprises a sixth polypeptide chain, comprising: a domain T and a domain U, wherein the domains are arranged, from N-terminus to C-terminus, in a T-U orientation, and wherein domain T has a variable region domain amino acid sequence and domain U has a constant domain amino acid sequence; and (c) the third and the sixth polypeptides are associated through an interaction between the R and the T domains and an interaction between the S and the U domains to form the ROR antigen binding molecule.

[0060] In certain [aspectsexamples](#): (a) the amino acid sequences of domain R and domain A are identical, the amino acid sequences of domain H is different from the sequence of domain R and domain A, the amino acid sequences of domain S and domain B are identical, the amino acid sequences of domain I is different from the sequence of domain S and domain B, the amino acid sequences of domain T and domain F are identical, the amino acid sequences of domain L is different from the sequence of domain T and domain F, the amino acid sequences of domain U and domain G are identical, the amino acid sequences of domain M is different from the sequence of domain U and domain G and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen; and the interaction between the R domain and the T domain form a third antigen binding site specific for the first antigen. In certain [aspectsexamples](#), the first antigen is the ROR antigen. In certain [aspectsexamples](#), the second antigen is a CD3 antigen.

[0061] In certain [aspectsexamples](#), (a) the amino acid sequences of domain R and domain H are identical, the amino acid sequences of domain A is different from the sequence of domain R and domain H, the amino acid sequences of domain S and domain I are identical, the amino acid sequences of domain B is different from the sequence of domain S and domain I, the amino acid sequences of domain T and domain L are identical, the amino acid sequences of domain F is different from the sequence of domain T and domain L, the amino acid sequences of domain U and domain M are identical, the amino acid sequences of domain G is different from the sequence of domain U and domain M, and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a third antigen binding site specific for the second antigen. In certain [aspectsexamples](#), the second antigen is the ROR antigen. In certain [aspectsexamples](#), the first antigen is a CD3 antigen.

[0062] In certain [aspectsexamples](#), (a) the amino acid sequences of domain R, domain A, and domain H are different, the amino acid sequences of domain S, domain B, and domain I are different, the amino acid sequences of domain T, domain F, and domain L are different, and the amino acid sequences of domain U, domain G, and domain M are different; (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a third antigen binding site specific for a third antigen; and (c) the first, the second, or the third antigen is the ROR antigen.

[0063] In certain [aspectsexamples](#), the ROR antigen binding molecule further comprises: a fifth and a sixth polypeptide chain, wherein: (a) the first polypeptide chain further comprises a domain N and a domain O, wherein the domains are arranged, from N-terminus to C-terminus, in a N-O-A-B-D-E orientation; (b) the third polypeptide chain further comprises a domain R and a domain S, wherein the domains are arranged, from N-terminus to C-terminus, in a R-S-H-I-J-K orientation; (c) the ROR antigen binding molecule further comprises a fifth and a sixth polypeptide chain, wherein: the fifth polypeptide chain comprises a domain P and a domain Q, wherein the domains are arranged, from N-terminus to C-terminus, in a P-Q orientation, and the sixth polypeptide chain comprises a domain T and a domain U, wherein the domains are arranged, from N-terminus to C-terminus, in a T-U orientation; and (d) the first and the fifth polypeptides are associated through an interaction between the N and the P domains and

an interaction between the O and the Q domains, and the third and the sixth polypeptides are associated through an interaction between the R and the T domains and an interaction between the S and the U domains to form the ROR antigen binding molecule.

[0064] In certain [aspectsexamples](#), (a) the amino acid sequences of domain N and domain A are identical, the amino acid sequences of domain H and domain R are identical, the amino acid sequences of domain O and domain B are identical, the amino acid sequences of domain I and domain S are identical, the amino acid sequences of domain P and domain F are identical, the amino acid sequences of domain L and domain T are identical, the amino acid sequences of domain Q and domain G are identical, the amino acid sequences of domain M and domain U are identical; and (b) wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the domain N and domain P form a second antigen binding site specific for the first antigen, the interaction between the H domain and the L domain form a third antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a fourth antigen binding site specific for the second antigen.

[0065] In certain [aspectsexamples](#), (a) the amino acid sequences of domain H and domain A are identical, the amino acid sequences of domain N and domain R are identical, the amino acid sequences of domain I and domain B are identical, the amino acid sequences of domain O and domain S are identical, the amino acid sequences of domain L and domain F are identical, the amino acid sequences of domain P and domain T are identical, the amino acid sequences of domain M and domain G are identical, the amino acid sequences of domain Q and domain U are identical; and (b) wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the domain N and domain P form a second antigen binding site specific for a second antigen, the interaction between the H domain and the L domain form a third antigen binding site specific for the first antigen, and the interaction between the R domain and the T domain form a fourth antigen binding site specific for the second antigen.

[0066] In certain [aspectsexamples](#), the sequence that forms the junction between the A domain and the B domain is IKRTPREP or IKRTVREP.

[0067] In certain [aspectsexamples](#), the sequence that forms the junction between the F domain and the G domain is SSASPREP.

[0068] In certain [aspectsexamples](#), at least one CH3 amino acid sequence has a C-terminal tripeptide insertion connecting the CH3 amino acid sequence to a hinge amino acid sequence, wherein the tripeptide insertion is selected from the group consisting of PGK, KSC, and GEC.

[0069] In certain [aspectsexamples](#), the sequences are human sequences.

[0070] In certain [aspectsexamples](#), at least one CH3 amino acid sequence is an IgG sequence. In certain [aspectsexamples](#), the IgG sequences are IgG1 sequences.

[0071] In certain [aspectsexamples](#), at least one CH3 amino acid sequence has one or more isoallotype mutations. In certain [aspectsexamples](#), the isoallotype mutations are D356E and L358M.

[0072] In certain [aspectsexamples](#), the CL amino acid sequence is a Ckappa sequence.

[0073] In certain [aspectsexamples](#), the CH2 sequences have one or more engineered mutations that reduce Fc effector function. In certain [aspectsexamples](#), the one or more engineered mutations are at position L234, L235, and P329. In certain [aspectsexamples](#), the one or more engineered mutations are L234A, L235A, and P329G. In certain [aspectsexamples](#), the one or more engineered mutations are L234A, L235A, and P329K.

[0074] Also described herein are tyrosine-protein kinase transmembrane receptor (ROR) antigen binding molecules comprising: a first antigen binding site specific for a ROR antigen, wherein the first antigen binding site comprises: A) a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6; and B) comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6.

[0075] In certain [aspectsexamples](#), the first antigen binding site comprises a VL having one or two amino acid mutations as compared with a VL sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VL. In certain [aspectsexamples](#), the first antigen binding site comprises a VH having one or two amino acid mutations as compared with a VH sequence of the antibody in Table 6, wherein the one or two amino acid mutations are in one or more CDR regions in the VH.

[0076] In certain [aspectsexamples](#), the first antigen binding site is specific for ROR1. In certain [aspectsexamples](#), the first antigen binding site is specific for ROR2. In certain [aspectsexamples](#), the first antigen binding site is specific for ROR1 and ROR2. In certain [aspectsexamples](#), the ROR antigen is a domain selected from the group consisting of: a ROR1 Frizzles domain, ROR2 Frizzles domain, a

ROR1 Ig-like domain, a ROR2 Ig-like domain, a ROR1 Kringle domain, and a ROR2 Kringle domain. In certain [aspectsexamples](#), the ROR antigen comprises a human ROR antigen.

[0077] In certain [aspectsexamples](#), the ROR antigen binding molecule further comprises a second antigen binding site. In certain [aspectsexamples](#), the second antigen binding site is specific for the ROR antigen. In certain [aspectsexamples](#), the second antigen binding site is specific for a second antigen different from the ROR antigen. In certain [aspectsexamples](#), the second antigen is a CD3 antigen. In certain [aspectsexamples](#), the antigen binding site is specific for an epitope of the CD3 antigen. In certain [aspectsexamples](#), the second antigen binding site comprises: A) a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and B) a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72. In certain [aspectsexamples](#), the second antigen binding site comprises: A) a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and B) a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

[0078] In certain [aspectsexamples](#), the ROR antigen binding molecule comprises an antibody format selected from the group consisting of: full-length antibodies, Fab fragments, Fvs, scFvs, tandem scFvs, Diabodies, scDiabodies, DARTs, tandAbs, and minibodies. In certain [aspectsexamples](#), the ROR antigen binding molecule comprises: a first and a second polypeptide chain, wherein: (a) the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E, wherein the domains are arranged, from N-terminus to C-terminus, in a A-B-D-E orientation, wherein domain A has a variable region domain amino acid sequence, and wherein domain B, domain D, and domain E have a constant region domain amino acid sequence; (b) the second polypeptide chain comprises a domain F and a domain G, wherein the domains are arranged, from N-terminus to C-terminus, in a F-G orientation, and wherein domain F has a variable region domain amino acid sequence and domain G has a constant region domain amino acid sequence c) the first and the second polypeptides are associated through an interaction between the A and the F domain and an interaction between the B domain and the G domain to form the ROR antigen binding molecule, and wherein the interaction between the A domain and the F domain form a first antigen binding site.

[0079] In certain [aspectsexamples](#), the ROR antigen binding molecule further comprises: a third and a fourth polypeptide chain, wherein: (a) the third polypeptide chain comprises a domain H, a

domain I, a domain J, and a domain K, wherein the domains are arranged, from N-terminus to C-terminus, in a H-I-J-K orientation, and wherein domain H has a variable region domain amino acid sequence, and domains I, J, and K have a constant region domain amino acid sequence; (b) the fourth polypeptide chain comprises a domain L and a domain M, wherein the domains are arranged, from N-terminus to C-terminus, in a L-M orientation, and wherein domain L has a variable region domain amino acid sequence and domain M has a constant region amino acid sequence; (c) the third and the fourth polypeptides are associated through an interaction between the H and the L domains and an interaction between the I and the M domains; and (d) the first and the third polypeptides are associated through an interaction between the D domain and the J domain and an interaction between the E domain and the K domain to form the ROR antigen binding molecule, and wherein the interaction between the H domain and the L domain form a second antigen binding site. In certain [aspectsexamples](#), the first antigen binding site is specific for the ROR antigen. In certain [aspectsexamples](#), the second antigen binding site is specific for CD3.

[0080] In certain [aspectsexamples](#), domain B and domain G have a CH3 amino acid sequence.

[0081] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0082] In certain [aspectsexamples](#), the amino acid sequences of the B domain and the G domain are different and separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the B domain interacts with the G domain, and wherein neither the B domain nor the G domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0083] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise mutations that generate engineered disulfide bridges between the B domain and the G domain. In certain [aspectsexamples](#), the mutations of the B domain and the G domain that generate engineered disulfide bridges are a S354C mutation in one of the B domain and G domain, and a 349C in the other domain.

[0084] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations of the B domain and the G domain are a T366W mutation in one of the B domain and G domain, and a T366S, L368A, and aY407V mutation in the other domain.

[0085] In certain [aspectsexamples](#), the orthogonal modifications of the B domain and the G domain comprise charge-pair mutations. In certain [aspectsexamples](#), the charge-pair mutations of the B domain and the G domain are a T366K mutation in one of the B domain and G domain, and a L351D mutation in the other domain.

[0086] In certain [aspectsexamples](#), domain B and domain G have an IgM CH2 amino acid sequence or an IgE CH2 amino acid sequence. In certain [aspectsexamples](#), the IgM CH2 amino acid sequence or the IgE CH2 amino acid sequence comprise orthogonal modifications.

[0087] In certain [aspectsexamples](#), domain I has a CL sequence and domain M has a CH1 sequence. In certain [aspectsexamples](#), domain I has a CH1 sequence and domain M has a CL sequence. In certain [aspectsexamples](#), the CH1 sequence and the CL sequence each comprise one or more orthogonal modifications, wherein a domain having the CH1 sequence does not significantly interact with a domain having a CL sequence lacking the orthogonal modification.

[0088] In certain [aspectsexamples](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, the mutations selected from the group consisting of: an engineered cysteine at position 138 of the CH1 sequence and position 116 of the CL sequence; an engineered cysteine at position 128 of the CH1 sequence and position 119 of the CL sequence, and an engineered cysteine at position 129 of the CH1 sequence and position 210 of the CL sequence.

[0089] In certain [aspectsexamples](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, wherein the mutations comprise and engineered cysteines at position 128 of the CH1 sequence and position 118 of a CL Kappa sequence.

[0090] In certain [aspectsexamples](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, the mutations selected from the group consisting of: a F118C mutation in the CL sequence with a corresponding A141C in the CH1 sequence; a F118C mutation in the CL sequence with a corresponding L128C in the CH1 sequence; and a S162C mutations in the CL sequence with a corresponding P171C mutation in the CH1 sequence.

[0091] In certain [aspectsexamples](#), the orthogonal modifications comprise charge-pair mutations between the at least one CH1 domain and a CL domain, the charge-pair mutations selected from the group consisting of: a F118S mutation in the CL sequence with a corresponding A141L in the CH1 sequence; a F118A mutation in the CL sequence with a corresponding

A141L in the CH1 sequence; a F118V mutation in the CL sequence with a corresponding A141L in the CH1 sequence; and a T129R mutation in the CL sequence with a corresponding K147D in the CH1 sequence.

[0092] In certain [aspectsexamples](#), the orthogonal modifications comprise charge-pair mutations between the at least one CH1 domain and a CL domain, the charge-pair mutations selected from the group consisting of: a N138K mutation in the CL sequence with a corresponding G166D in the CH1 sequence, and a N138D mutation in the CL sequence with a corresponding G166K in the CH1 sequence.

[0093] In certain [aspectsexamples](#), domain A has a VL amino acid sequence and domain F has a VH amino acid sequence. In certain [aspectsexamples](#), domain A has a VH amino acid sequence and domain F has a VL amino acid sequence.

[0094] In certain [aspectsexamples](#), domain H has a VL amino acid sequence and domain L has a VH amino acid sequence. In certain [aspectsexamples](#), domain H has a VH amino acid sequence and domain L has a VL amino acid sequence.

[0095] In certain [aspectsexamples](#), domain D and domain J have a CH2 amino acid sequence.

[0096] In certain [aspectsexamples](#), the E domain has a CH3 amino acid sequence.

[0097] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are identical, wherein the sequence is an endogenous CH3 sequence.

[0098] In certain [aspectsexamples](#), the amino acid sequences of the E domain and the K domain are different. In certain [aspectsexamples](#), the different sequences separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the E domain interacts with the K domain, and wherein neither the E domain nor the K domain significantly interacts with a CH3 domain lacking the orthogonal modification.

[0099] In certain [examplesaspects](#), the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the E domain and the K domain. In certain [aspectsexamples](#), the mutations that generate engineered disulfide bridges are a S354C mutation in one of the E domain and the K domain, and a 349C in the other domain. In certain [examplesaspects](#), the orthogonal modifications in the E domain and the K domain comprise knob-in-hole mutations. In certain [aspectsexamples](#), the knob-in hole mutations are a T366W mutation in one of the E domain or the K domain and a T366S, L368A, and aY407V mutation in the other domain. In certain [examplesaspects](#), the orthogonal modifications in the E domain and the K domain comprise charge-pair

mutations. In certain examplesaspects, the charge-pair mutations are a T366K mutation in one of the E domain or the K domain and a corresponding L351D mutation in the other domain.

[00100] In certain examplesaspects, the amino acid sequences of the E domain and the K domain are endogenous sequences of two different antibody domains, the domains selected to have a specific interaction that promotes the specific association between the first and the third polypeptides. In certain examplesaspects, the two different amino acid sequences are a CH1 sequence and a CL sequence.

[00101] In certain examplesaspects, the ROR antigen binding molecule further comprises a third antigen binding site. In certain examplesaspects, the third antigen binding site is specific for a ROR antigen. In certain examplesaspects, the first antigen binding site and the third antigen binding site are specific for the same ROR antigen. In certain examplesaspects, the first antigen binding site and the third antigen binding site are specific for different ROR antigens.

[00102] In certain examplesaspects, ROR antigen binding molecule comprises a fifth polypeptide chain, wherein (a) the first polypeptide chain further comprises a domain N and a domain O, wherein the domains are arranged, from N-terminus to C-terminus, in a N-O-A-B-D-E orientation, and wherein domain N has a variable region domain amino acid sequence, domain O has a constant region amino acid sequence; (b) the fifth polypeptide chain comprises a domain P and a domain Q, wherein the domains are arranged, from N-terminus to C-terminus, in a P-Q orientation, and wherein domain P has a variable region domain amino acid sequence and domain Q has a constant region amino acid sequence; and (c) the first and the fifth polypeptides are associated through an interaction between the N and the P domains and an interaction between the O and the Q domains to form the ROR antigen binding molecule.

[00103] In certain examplesaspects, (a) the amino acid sequences of domain N and domain A are identical, the amino acid sequences of domain H is different from the sequence of domain N and domain A, the amino acid sequences of domain O and domain B are identical, the amino acid sequences of domain I is different from the sequence of domain O and domain B, the amino acid sequences of domain P and domain F are identical, the amino acid sequences of domain L is different from the sequence of domain P and domain F, the amino acid sequences of domain Q and domain G are identical, the amino acid sequences of domain M is different from the sequence of domain Q and domain G; and (b) wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen

binding site specific for a second antigen, and the interaction between the N domain and the P domain form a third antigen binding site specific for the first antigen. In certain examplesaspects, the first antigen is a ROR antigen. In certain examplesaspects, the second antigen is a CD3 antigen.

[00104] In certain examplesaspects, (a) the amino acid sequences of domain N, domain A, and domain H are different, the amino acid sequences of domain O, domain B, and domain I are different, the amino acid sequences of domain P, domain F, and domain L are different, and the amino acid sequences of domain Q, domain G, and domain M are different; and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the N domain and the P domain form a third antigen binding site specific for a third antigen.

[00105] In certain examplesaspects, the ROR antigen binding molecule comprises a sixth polypeptide chain, wherein: (a) the third polypeptide chain further comprises a domain R and a domain S, wherein the domains are arranged, from N-terminus to C-terminus, in a R-S-H-I-J-K orientation, and wherein domain R has a variable region amino acid sequence and domain S has a constant domain amino acid sequence; (b) the sixth polypeptide chain comprises: a domain T and a domain U, wherein the domains are arranged, from N-terminus to C-terminus, in a T-U orientation, and wherein domain T has a variable region amino acid sequence and domain U has a constant domain amino acid sequence; and (c) the third and the sixth polypeptides are associated through an interaction between the R and the T domains and an interaction between the S and the U domains to form the ROR antigen binding molecule.

[00106] In certain examplesaspects, (a) the amino acid sequences of domain R and domain A are identical, the amino acid sequences of domain H is different from the sequence of domain R and domain A, the amino acid sequences of domain S and domain B are identical, the amino acid sequences of domain I is different from the sequence of domain S and domain B, the amino acid sequences of domain T and domain F are identical, the amino acid sequences of domain L is different from the sequence of domain T and domain F, the amino acid sequences of domain U and domain G are identical, the amino acid sequences of domain M is different from the sequence of domain U and domain G, and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain

form a third antigen binding site specific for the first antigen. In certain examplesaspects, the first antigen is a ROR antigen. In certain aspectsexamples, the second antigen is a CD3 antigen.

[00107] In certain examplesaspects, (a) the amino acid sequences of domain R and domain H are identical, the amino acid sequences of domain A is different from the sequence of domain R and domain H, the amino acid sequences of domain S and domain I are identical, the amino acid sequences of domain B is different from the sequence of domain S and domain I, the amino acid sequences of domain T and domain L are identical, the amino acid sequences of domain F is different from the sequence of domain T and domain L, the amino acid sequences of domain U and domain M are identical, the amino acid sequences of domain G is different from the sequence of domain U and domain M, and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a third antigen binding site specific for the second antigen. In certain examplesaspects, the second antigen is a ROR antigen. In certain aspectsexamples, the first antigen is a CD3 antigen.

[00108] In certain examplesaspects, (a) the amino acid sequences of domain R, domain A, and domain H are different, the amino acid sequences of domain S, domain B, and domain I are different, the amino acid sequences of domain T, domain F, and domain L are different, and the amino acid sequences of domain U, domain G, and domain M are different; and (b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a third antigen binding site specific for a third antigen.

[00109] Also described herein are purified ROR antigen binding molecules, the purified ROR antigen binding molecules comprising any of the ROR antigen binding molecule described herein. In certain aspectsexamples, the purified ROR antigen binding molecules are purified by a purification method comprising a CH1 affinity purification step. In certain examplesaspects, the purification method is a single-step purification method.

[00110] Also described herein are pharmaceutical compositions comprising any of the ROR antigen binding molecules described herein and a pharmaceutically acceptable diluent.

[00111] Also described herein are methods for treating a subject with cancer, the methods comprising administering a therapeutically effective amount of any of the pharmaceutical

compositions described herein. In certain ~~aspects~~examples, the cancer is selected from the group consisting of: pancreatic cancer, ovarian cancer, breast cancer, lung cancer, gastric cancer, melanoma, Ewing sarcoma, chronic lymphocytic leukemia, mantle cell lymphoma, B-ALL, hematological cancer, prostate cancer, colon cancer, renal cancer, and uterine cancer.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[00112] **FIG. 1** shows an alignment of the CH3-CH3 IgG1 dimer pair with CH1-CL. The quaternary structures align with an RMSD of $\sim 1.6 \text{ \AA}^2$.

[00113] **FIG. 2** presents schematic architectures, with respective naming conventions, for various binding molecules (also called antibody constructs) described herein.

[00114] **FIG. 3** presents a higher resolution schematic of polypeptide chains and their domains, with respective naming conventions, for the bivalent 1x1 antibody constructs described herein.

[00115] **FIG. 4** shows the architecture of an exemplary bivalent, monospecific, construct.

[00116] **FIG. 5** shows data from a biolayer interferometry (BLI) experiment, described in Example 1, in which a bivalent monospecific binding molecule having the architecture illustrated in FIG. 4 [polypeptide 1: VL-CH3(Knob)-CH2-CH3 / polypeptide 2: VH-CH3(Hole)] was assayed. The antigen binding site was specific for TNF α . The BLI response from binding molecule immobilization and TNF α binding to the immobilized construct demonstrates robust, specific, bivalent binding to the antigen. The data are consistent with a molecule having a high percentage of intended pairing of polypeptide 1 and polypeptide 2.

[00117] **FIG. 6** illustrates features of an exemplary bivalent 1x1 bispecific binding molecule, “BC1”.

[00118] **FIG. 7A** shows size exclusion chromatography (SEC) analysis of “BC1”, demonstrating that a single-step CH1 affinity purification step (CaptureSelect™ CH1 affinity resin) yields a single, monodisperse peak via gel filtration in which >98% is unaggregated bivalent protein. **FIG. 7B** shows comparative literature data of SEC analysis of a CrossMab bivalent antibody construct [data from Schaefer *et al.* (*Proc Natl Acad Sci USA*. 2011 Jul 5;108(27):11187-92)].

[00119] **FIG. 8A** is a cation exchange chromatography elution profile of “BC1” following one-step purification using the CaptureSelect™ CH1 affinity resin, showing a single tight

WHAT IS CLAIMED IS:

1. A tyrosine-protein kinase transmembrane receptor (ROR) binding molecule, the ROR antigen binding molecule comprising:

a ~~first~~an antigen binding site specific for a ROR antigen, wherein the ~~first~~ antigen binding site comprises:

A) a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6~~ the CDR1 VL comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 269, 275, 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508, 514, 520, 526, 532, and 538; the CDR2 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 270, 276, 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, 527, 533, and 539; and the CDR3 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 271, 277, 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, 528, 534, and 540; and

B) comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6~~ the CDR1 VH comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 266, 272, 278, 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, 523, 529, and 535; the CDR2 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 267, 273, 279, 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464, 470, 476, 482, 488, 494, 500, 506, 512, 518, 524, 530, and 536; and the CDR3 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, 525, 531, and 537,

wherein the ~~first~~ antigen binding site is specific for ROR1 and/or ROR2.

2. A tyrosine-protein kinase transmembrane receptor (ROR) binding molecule, the ROR antigen binding molecule comprising:

a ~~first~~an antigen binding site specific for a ROR antigen, wherein the ~~first~~ antigen binding site comprises:

A) a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6~~ the CDR1 VL comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 269, 275, 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508, 514, 520, 526, 532, and 538; the CDR2 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 270, 276, 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, 527, 533, and 539; and the CDR3 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 271, 277, 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, 528, 534, and 540; and

B) comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6~~ the CDR1 VH comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 266, 272, 278, 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, 523, 529, and 535; the CDR2 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 267, 273, 279, 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464, 470, 476, 482, 488, 494, 500, 506, 512, 518, 524, 530, and 536; and the CDR3 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, 525, 531, and 537,

wherein the ~~first~~ antigen binding site is specific for ROR1.

3. A tyrosine-protein kinase transmembrane receptor (ROR) binding molecule, the ROR antigen binding molecule comprising:

a ~~first~~an antigen binding site specific for a ROR antigen, wherein the ~~first~~ antigen binding site comprises:

A) a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific light chain variable region (VL) from a specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6~~ the CDR1 VL comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 269, 275, 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508, 514, 520, 526, 532, and 538; the CDR2 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 270, 276, 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, 527, 533, and 539; and the CDR3 VL comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 271, 277, 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, 528, 534, and 540; and

B) comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of a specific heavy chain variable region (VH) from the specific ROR antigen binding site, wherein ~~the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6~~ the CDR1 VH comprises an amino acid sequence selected from a group consisting SEQ ID NOs: 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 266, 272, 278, 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, 523, 529, and 535; the CDR2 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 267, 273, 279, 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464, 470, 476, 482, 488, 494, 500, 506, 512, 518, 524, 530, and 536; and the CDR3 VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, 525, 531, and 537,

wherein the ~~first~~ antigen binding site is specific for ROR2.

4. The ROR antigen binding molecule of any of claims 1-3, wherein the ROR antigen is a domain selected from the group consisting of: a ROR1 Frizzle domain, ROR2 Frizzle domain, a ROR1 Ig-like domain, a ROR2 Ig-like domain, a ROR1 Kringle domain, and a ROR2 Kringle domain.

5. The ROR antigen binding molecule of any of claims 1-4, wherein the ROR antigen comprises a human ROR antigen.

6. The ROR antigen binding molecule of any of claims 1, 4, and 5, wherein the first antigen binding site comprises

~~the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 1, I2A 10, I2A 10 D54E Y55Q, I2A 11, I2A 13, I2A 14, I2A 16, I2A 18, I2A 19, I2A 22, I2A 24, I2A 26, I2A 34, I2A 36, I2C 1, I2C 2, I2C 4, I2C 6, I2C 8, I2C 9, I2C 10, I2C 11, I2C 12, I2C 13, I2C 14, I2C 15, I2C 16, I2C 17, I2C 18, I2C 1 20, I2C 22, I2C 23, or I2C 24 from Table 6(1)~~ CDR1 VH comprising the amino acid sequence of SEQ ID NO: 153, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 154, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 155, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 156, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 157, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 158;

(2) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 207, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 208, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 209, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 210, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 211, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 212;

(3) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 213, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 214, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 215, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 216, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 217, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 218;

(4) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 219, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 220, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 221, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 222, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 223, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 224;

(5) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 231, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 232, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 233, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 234, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 235, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 236;

(6) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 237, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 238, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 239, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 240, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 241, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 242;

(7) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 249, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 250, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 251, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 252, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 253, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 254;

(8) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 261, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 262, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 263, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 264, and CDR2 VL comprising the amino acid sequence of SEQ ID NO: 265;

(9) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 266, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 267, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 268, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 269, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 270, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 271;

(10) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 284, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 285, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 286, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 287, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 288, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 289;

(11) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 296, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 297, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 298, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 299, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 300, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 301;

(12) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 308, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 309, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 310, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 311, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 312, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 313;

(13) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 356, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 357, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 358, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 359, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 360, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 361;

(14) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 368, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 369, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 370, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 371, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 372, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 373;

(15) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 385, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 386, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 387, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 388, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 389, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 390;

(16) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 391, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 392, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 393, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 394, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 395, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 396;

(17) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 403, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 404, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 405, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 406, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 407, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 408;

(18) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 415, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 416, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 417, CDR1 VL comprising the amino acid sequence of SEQ

ID NO: 418, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 419, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 420;

(19) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 427, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 428, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 429, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 430, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 431, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 432;

(20) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 433, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 434, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 435, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 436, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 437, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 438;

(21) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 439, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 440, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 441, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 442, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 443, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 444;

(22) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 445, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 446, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 447, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 448, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 449, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 450;

(23) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 451, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 452, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 453, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 454, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 455, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 456;

(24) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 457, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 458, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 459, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 460, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 461, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 462;

(25) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 463, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 464, CDR3 VH comprising the amino

acid sequence of SEQ ID NO: 465, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 466, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 467, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 468;

(26) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 469, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 470, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 471, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 472, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 473, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 474;

(27) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 475, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 476, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 477, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 478, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 479, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 480;

(28) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 481, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 482, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 483, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 484, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 485, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 486;

(29) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 487, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 488, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 489, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 490, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 491, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 492;

(30) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 499, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 500, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 501, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 502, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 503, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 504;

(31) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 511, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 512, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 513, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 514, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 515, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 516;

(32) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 517, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 518, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 519, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 520, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 521, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 522; or

(33) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 523, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 524, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 525, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 526, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 527, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 528.

7. The ROR antigen binding molecule of any of claims 2, 4, and 5, wherein the first antigen binding site comprises

~~the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 3, I2A 4, I2A 6, I2A 8, I2A 12, I2A 20, I2A 25, I2A 26, I2A 27, I2A 30, I2A 32, I2A 33, or I2A37 from Table 6(1)~~ (1) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 165, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 166, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 167, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 168, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 169, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 170;

(2) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 171, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 172, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 173, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 174, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 175, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 176;

(3) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 183, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 184, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 185, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 186, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 187, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 188;

(4) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 195, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 196, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 197, CDR1 VL comprising the amino acid sequence of SEQ

ID NO: 198, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 199, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 200;

(5) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 225, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 226, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 227, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 228, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 229, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 230;

(6) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 272, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 273, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 274, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 275, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 276, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 277;

(7) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 302, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 303, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 304, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 305, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 306, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 307;

(8) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 308, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 309, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 310, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 311, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 312, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 313;

(9) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 314, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 315, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 316, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 317, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 318, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 319;

(10) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 332, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 333, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 334, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 335, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 336, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 337;

(11) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 344, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 345, CDR3 VH comprising the amino

acid sequence of SEQ ID NO: 346, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 347, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 348, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 349;

(12) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 350, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 351, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 352, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 353, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 354, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 355; or

(13) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 374, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 375, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 376, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 377, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 378, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 379.

8. The ROR antigen binding molecule of any of claims 3, 4, and 5, wherein the ~~first~~ antigen binding site comprises ~~the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2C-3, I2C-5, I2C-7, I2C-19, I2C-21, I2C-25, or I2C-26 from Table 6~~

(1) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 397, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 398, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 399, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 400, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 401, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 402;

(2) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 409, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 410, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 411, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 412, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 413, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 414;

(3) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 421, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 422, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 423, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 424, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 425, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 426;

(4) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 493, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 494, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 495, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 496, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 497, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 498;

(5) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 505, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 506, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 507, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 508, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 509, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 510;

(6) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 529, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 530, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 531, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 532, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 533, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 534; or

(7) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 535, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 536, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 537, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 538, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 539, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 540.

9. The ROR antigen binding molecule of claim 1, wherein the antigen binding site comprises

(1) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 159, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 160, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 161, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 162, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 163, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 164;

(2) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 177, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 178, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 179, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 180, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 181, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 182;

(3) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 189, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 190, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 191, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 192, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 193, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 194;

(4) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 201, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 202, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 203, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 204, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 205, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 206;

(5) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 243, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 244, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 245, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 246, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 247, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 248;

(6) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 255, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 256, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 257, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 258, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 259, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 260;

(7) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 278, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 279, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 280, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 281, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 282, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 283;

(8) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 290, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 291, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 292, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 293, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 294, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 295;

(9) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 320, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 321, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 322, CDR1 VL comprising the amino acid sequence of SEQ

ID NO: 323, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 324, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 325;

(10) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 326, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 327, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 328, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 329, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 330, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 331;

(11) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 338, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 339, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 340, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 341, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 342, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 343;

(12) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 362, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 363, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 364, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 365, CDR2 VL comprising the amino acid sequence of SEQ ID NO: 366, and CDR3 VL comprising the amino acid sequence of SEQ ID NO: 367; or

(13) CDR1 VH comprising the amino acid sequence of SEQ ID NO: 380, CDR2 VH comprising the amino acid sequence of SEQ ID NO: 381, CDR3 VH comprising the amino acid sequence of SEQ ID NO: 382, CDR1 VL comprising the amino acid sequence of SEQ ID NO: 383, and CDR2 VL comprising the amino acid sequence of SEQ ID NO: 384.

10. A nucleic acid encoding the ROR antigen binding molecule of any one of claims 1-9.

11. A vector comprising the nucleic acid of claim 10.

~~9. — The ROR antigen binding molecule of any of claims 1-8, wherein the ROR antigen binding molecule further comprises a second antigen binding site.~~

~~10. — The ROR antigen binding molecule of claim 9, wherein the second antigen binding site is the same as the first antigen binding site.~~

~~11. — The ROR antigen binding molecule of claim 9, wherein the second antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A-1, I2A-10, I2A-10 D54E Y55Q, I2A-11, I2A-13, I2A-14, I2A-16, I2A-~~

~~18, I2A 19, I2A 22, I2A 24, I2A 26, I2A 34, I2A 36, I2C 1, I2C 2, I2C 4, I2C 6, I2C 8, I2C 9, I2C 10, I2C 11, I2C 12, I2C 13, I2C 14, I2C 15, I2C 16, I2C 17, I2C 18, I2C 1 20, I2C 22, I2C 23, or I2C 24 from Table 6.~~

~~12. — The ROR antigen binding molecule of claim 9, wherein the second antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 3, I2A 4, I2A 6, I2A 8, I2A 12, I2A 20, I2A 25, I2A 26, I2A 27, I2A 30, I2A 32, I2A 33, or I2A37 from Table 6.~~

~~13. — The ROR antigen binding molecule of claim 9, wherein the second antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2C 3, I2C 5, I2C 7, I2C 19, I2C 21, I2C 25, or I2C 26 from Table 6.~~

~~14. — The ROR antigen binding molecule of claim 9, wherein the second antigen binding site is specific for a second antigen different from the ROR antigen.~~

~~15. — The ROR antigen binding molecule of claim 14, wherein the second antigen is a CD3 antigen.~~

~~16. — The ROR antigen binding molecule of claim 15, wherein the antigen binding site is specific for an epitope of the CD3 antigen.~~

~~17. — The ROR antigen binding molecule of claim 15, wherein~~

~~the second antigen binding site comprises:~~

~~A) — a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and~~

~~B) — a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.~~

~~18. — The ROR antigen binding molecule of claim 15, wherein~~

~~the second antigen binding site comprises:~~

~~A) — a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and~~

B) — a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

~~19.~~ — The ROR antigen binding molecule of any of claims 1-18, wherein the ROR antigen binding molecule comprises an antibody format selected from the group consisting of: full-length antibodies, Fab fragments, Fvs, scFvs, tandem scFvs, Diabodies, scDiabodies, DARTs, tandAbs, and minibodies.

~~20.~~ — The ROR antigen binding molecule of any of claims 1-19, wherein the molecule comprises a sequence of one or more constant regions.

~~21.~~ — The ROR antigen binding molecule of claim 20, wherein the constant region is a CH1, CH2, CH3 and/or CL constant region.

~~22.~~ — The ROR antigen binding molecule of any of claims 20-21, wherein the sequence of the constant region comprises one or more of (i) a CH1 constant region sequence that is SEQ ID NO:23, SEQ ID NO:113, SEQ ID NO:131, or SEQ ID NO:149; (ii) a CH2 constant region sequence that is SEQ ID NO:14, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:51, SEQ ID NO:102, SEQ ID NO:110, SEQ ID NO:120, SEQ ID NO:128, SEQ ID NO:138, or SEQ ID NO:146; (iii) a CH3 constant region sequence that is SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:52, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:107, SEQ ID NO:111, SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:125, SEQ ID NO:129, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, or SEQ ID NO:147; and/or (iv) a CL constant region sequence that is SEQ ID NO:19, SEQ ID NO:42, SEQ ID NO:50, SEQ ID NO:109, SEQ ID NO:127, or SEQ ID NO:145.

~~23.~~ — The ROR antigen binding molecule of any of claims 1-22, wherein the ROR antigen binding molecule comprises:

a first and a second polypeptide chain, wherein:

(a) — the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E,

~~wherein the domains are arranged, from N terminus to C terminus, in a A-B-D-E orientation,~~

~~wherein domain A has a variable region domain amino acid sequence, and~~

~~wherein domain B, domain D, and domain E have a constant region domain amino acid sequence;~~

~~(b) — the second polypeptide chain comprises a domain F and a domain G,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a F-G orientation, and~~

~~wherein domain F has a variable region domain amino acid sequence and domain G has a constant region domain amino acid sequence~~

~~(c) — the first and the second polypeptides are associated through an interaction between the A and the F domain and an interaction between the B domain and the G domain to form the ROR antigen binding molecule, and wherein the interaction between the A domain and the F domain form the first antigen binding site.~~

24. — The ROR antigen binding molecule of 23, wherein the ROR antigen binding molecule further comprises:

~~a third and a fourth polypeptide chain, wherein:~~

~~(a) — the third polypeptide chain comprises a domain H, a domain I, a domain J, and a domain K,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a H-I-J-K orientation, and~~

~~wherein domain H has a variable region domain amino acid sequence, and domains I, J, and K have a constant region domain amino acid sequence;~~

~~(b) — the fourth polypeptide chain comprises a domain L and a domain M,
wherein the domains are arranged, from N terminus to C terminus, in a L M-orientation, and
wherein domain L has a variable region domain amino acid sequence and domain M has a constant region amino acid sequence;~~

~~(c) — the third and the fourth polypeptides are associated through an interaction between the H and the L domains and an interaction between the I and the M domains; and~~

~~(d) — the first and the third polypeptides are associated through an interaction between the D domain and the J domain and an interaction between the E domain and the K domain to form the ROR antigen binding molecule, and wherein the interaction between the H domain and the L domain form a second antigen binding site.~~

~~**25.** — The ROR antigen binding molecule of claims 23 or 24, wherein the first antigen binding site is specific for ROR1 and ROR2, ROR1, or ROR2.~~

~~**26.** — The ROR antigen binding molecule of claim 25, wherein the first antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 1, I2A 10, I2A 10 D54E Y55Q, I2A 11, I2A 13, I2A 14, I2A 16, I2A 18, I2A 19, I2A 22, I2A 24, I2A 26, I2A 34, I2A 36, I2C 1, I2C 2, I2C 4, I2C 6, I2C 8, I2C 9, I2C 10, I2C 11, I2C 12, I2C 13, I2C 14, I2C 15, I2C 16, I2C 17, I2C 18, I2C 1 20, I2C 22, I2C 23, or I2C 24 from Table 6.~~

~~**27.** — The ROR antigen binding molecule of claim 25, wherein the first antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 3, I2A 4, I2A 6, I2A 8, I2A 12, I2A 20, I2A 25, I2A 26, I2A 27, I2A 30, I2A 32, I2A 33, or I2A37 from Table 6.~~

~~**28.** — The ROR antigen binding molecule of claim 25, wherein the first antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2C 3, I2C 5, I2C 7, I2C 19, I2C 21, I2C 25, or I2C 26 from Table 6.~~

~~29. — The ROR antigen binding molecule of any one of claims 24–28, wherein the second antigen binding site is specific for CD3.~~

~~30. — The ROR antigen binding molecule of any one of claims 23–28, wherein domain B and domain G have a CH3 amino acid sequence.~~

~~31. — The ROR antigen binding molecule of claim 30, wherein the amino acid sequences of the B domain and the G domain are identical, wherein the sequence is an endogenous CH3 sequence.~~

~~32. — The ROR antigen binding molecule of claim 30, wherein the amino acid sequences of the B domain and the G domain are different and separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the B domain interacts with the G domain, and wherein neither the B domain nor the G domain significantly interacts with a CH3 domain lacking the orthogonal modification.~~

~~33. — The ROR antigen binding molecule of claim 32, wherein the orthogonal modifications of the B domain and the G domain comprise mutations that generate engineered disulfide bridges between the B domain and the G domain.~~

~~34. — The ROR antigen binding molecule of claim 33, wherein the mutations of the B domain and the G domain that generate engineered disulfide bridges are a S354C mutation in one of the B domain and G domain, and a 349C in the other domain.~~

~~35. — The ROR antigen binding molecule of any one of claims 32–34, wherein the orthogonal modifications of the B domain and the G domain comprise knob-in-hole mutations.~~

~~36. — The ROR antigen binding molecule of claim 35, wherein the knob-in-hole mutations of the B domain and the G domain are a T366W mutation in one of the B domain and G domain, and a T366S, L368A, and a Y407V mutation in the other domain.~~

~~37. — The ROR antigen binding molecule of any one of claims 32–36, wherein the orthogonal modifications of the B domain and the G domain comprise charge pair mutations.~~

~~38. — The ROR antigen binding molecule of claim 37, wherein the charge pair mutations of the B domain and the G domain are a T366K mutation in one of the B domain and G domain, and a L351D mutation in the other domain.~~

- ~~39. The ROR antigen binding molecule of any one of claims 23-38, wherein domain B and domain G have an IgM CH2 amino acid sequence or an IgE CH2 amino acid sequence.~~
- ~~40. The ROR antigen binding molecule of claim 39, wherein the IgM CH2 amino acid sequence or the IgE CH2 amino acid sequence comprise orthogonal modifications.~~
- ~~41. The ROR antigen binding molecule of any one of claims 24-40, wherein domain I has a CL sequence and domain M has a CH1 sequence.~~
- ~~42. The ROR antigen binding molecule of any one of claims 24-40, wherein domain I has a CH1 sequence and domain M has a CL sequence.~~
- ~~43. The ROR antigen binding molecule of claim 41 or 42, wherein the CH1 sequence and the CL sequence each comprise one or more orthogonal modifications, wherein a domain having the CH1 sequence does not significantly interact with a domain having a CL sequence lacking the orthogonal modification.~~
- ~~44. The ROR antigen binding molecule of claim 43, wherein the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, the mutations selected from the group consisting of: an engineered cysteine at position 138 of the CH1 sequence and position 116 of the CL sequence; an engineered cysteine at position 128 of the CH1 sequence and position 119 of the CL sequence, and an engineered cysteine at position 129 of the CH1 sequence and position 210 of the CL sequence.~~
- ~~45. The ROR antigen binding molecule of claim 43, wherein the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, wherein the mutations comprise and engineered cysteines at position 128 of the CH1 sequence and position 118 of a CL Kappa sequence.~~
- ~~46. The ROR antigen binding molecule of claim 43, wherein the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the at least one CH1 domain and a CL domain, the mutations selected from the group consisting of: a F118C mutation in the CL sequence with a corresponding A141C in the CH1 sequence; a F118C mutation in the CL sequence with a corresponding L128C in the CH1 sequence; and a S162C mutations in the CL sequence with a corresponding P171C mutation in the CH1 sequence.~~

~~47. The ROR antigen binding molecule of any of claims 43-46, wherein the orthogonal modifications comprise charge pair mutations between the at least one CH1 domain and a CL domain, the charge pair mutations selected from the group consisting of: a F118S mutation in the CL sequence with a corresponding A141L in the CH1 sequence; a F118A mutation in the CL sequence with a corresponding A141L in the CH1 sequence; a F118V mutation in the CL sequence with a corresponding A141L in the CH1 sequence; and a T129R mutation in the CL sequence with a corresponding K147D in the CH1 sequence.~~

~~48. The ROR antigen binding molecule of any of claims 43-46, wherein the orthogonal modifications comprise charge pair mutations between the at least one CH1 domain and a CL domain, the charge pair mutations selected from the group consisting of: a N138K mutation in the CL sequence with a corresponding G166D in the CH1 sequence, and a N138D mutation in the CL sequence with a corresponding G166K in the CH1 sequence.~~

~~49. The ROR antigen binding molecule of any of claims 23-48, wherein domain A has a VL amino acid sequence and domain F has a VH amino acid sequence.~~

~~50. The ROR antigen binding molecule of any of claims 23-48, wherein domain A has a VH amino acid sequence and domain F has a VL amino acid sequence.~~

~~51. The ROR antigen binding molecule of any of claims 24-45, wherein domain H has a VL amino acid sequence and domain L has a VH amino acid sequence.~~

~~52. The ROR antigen binding molecule of any of claims 24-45, wherein domain H has a VH amino acid sequence and domain L has a VL amino acid sequence.~~

~~53. The ROR antigen binding molecule of any of claims 24, wherein domain D and domain J have a CH2 amino acid sequence.~~

~~54. The ROR antigen binding molecule of any one of claims 23-53, wherein the E domain has a CH3 amino acid sequence.~~

~~55. The ROR antigen binding molecule of any one of claims 24-54, wherein the amino acid sequences of the E domain and the K domain are identical, wherein the sequence is an endogenous CH3 sequence.~~

~~56. The ROR antigen binding molecule of any one of claims 24-54, wherein the amino acid sequences of the E domain and the K domain are different.~~

~~57. — The ROR antigen binding molecule of claim 56, wherein the different sequences separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the E domain interacts with the K domain, and wherein neither the E domain nor the K domain significantly interacts with a CH3 domain lacking the orthogonal modification.~~

~~58. — The ROR antigen binding molecule of claim 57, wherein the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the E domain and the K domain.~~

~~59. — The ROR antigen binding molecule of claim 58, wherein the mutations that generate engineered disulfide bridges are a S354C mutation in one of the E domain and the K domain, and a 349C in the other domain.~~

~~60. — The ROR antigen binding molecule of any one of claims 57-59, wherein the orthogonal modifications in the E domain and the K domain comprise knob-in-hole mutations.~~

~~61. — The ROR antigen binding molecule of claim 60, wherein the knob-in-hole mutations are a T366W mutation in one of the E domain or the K domain and a T366S, L368A, and a Y407V mutation in the other domain.~~

~~62. — The ROR antigen binding molecule of any one of claims 57-61, wherein the orthogonal modifications in the E domain and the K domain comprise charge pair mutations.~~

~~63. — The ROR antigen binding molecule of claim 62, wherein the charge pair mutations are a T366K mutation in one of the E domain or the K domain and a corresponding L351D mutation in the other domain.~~

~~64. — The ROR antigen binding molecule of claim 56, wherein the amino acid sequences of the E domain and the K domain are endogenous sequences of two different antibody domains, the domains selected to have a specific interaction that promotes the specific association between the first and the third polypeptides.~~

~~65. — The ROR antigen binding molecule of claim 64, wherein the two different amino acid sequences are a CH1 sequence and a CL sequence.~~

~~66. — The ROR antigen binding molecule of any one of claims 1-65, wherein the ROR antigen binding molecule further comprises a third antigen binding site.~~

~~67.~~—The ROR antigen binding molecule of claim 54, wherein the third antigen binding site is specific for ROR1 and ROR2, ROR1, or ROR2.

~~68.~~—The ROR antigen binding molecule of claim 67, wherein the third antigen binding site is the same as the first antigen binding site.

~~69.~~—The ROR antigen binding molecule of claim 67 or 68, wherein the third antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 1, I2A 10, I2A 10 D54E Y55Q, I2A 11, I2A 13, I2A 14, I2A 16, I2A 18, I2A 19, I2A 22, I2A 24, I2A 26, I2A 34, I2A 36, I2C 1, I2C 2, I2C 4, I2C 6, I2C 8, I2C 9, I2C 10, I2C 11, I2C 12, I2C 13, I2C 14, I2C 15, I2C 16, I2C 17, I2C 18, I2C 1 20, I2C 22, I2C 23, or I2C 24 from Table 6.

~~70.~~—The ROR antigen binding molecule of claim 67 or 68, wherein the third antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2A 3, I2A 4, I2A 6, I2A 8, I2A 12, I2A 20, I2A 25, I2A 26, I2A 27, I2A 30, I2A 32, I2A 33, or I2A37 from Table 6.

~~71.~~—The ROR antigen binding molecule of claim 67 or 68, wherein the third antigen binding site comprises the CDR1, CDR2, and CDR3 VH sequences and the CDR1, CDR2, and CDR3 VL sequences of I2C 3, I2C 5, I2C 7, I2C 19, I2C 21, I2C 25, or I2C 26 from Table 6.

~~72.~~—The ROR antigen binding molecule of any one of claims 66-71, wherein the ROR antigen binding molecule comprises a fifth polypeptide chain, wherein

(a) —the first polypeptide chain further comprises a domain N and a domain O, wherein the domains are arranged, from N-terminus to C-terminus, in a N-O-A-B-D-E orientation, and

wherein domain N has a variable region domain amino acid sequence, domain O has a constant region amino acid sequence;

(b) —the fifth polypeptide chain comprises

a domain P and a domain Q, wherein the domains are arranged, from N terminus to C terminus, in a P-Q orientation, and

wherein domain P has a variable region domain amino acid sequence and domain Q has a constant region amino acid sequence; and

(c) — the first and the fifth polypeptides are associated through an interaction between the N and the P domains and an interaction between the O and the Q domains to form the ROR antigen binding molecule.

73. — The ROR antigen binding molecule of claim 72, wherein:

(a) — the amino acid sequences of domain N and domain A are identical,

the amino acid sequences of domain H is different from the sequence of domain N and domain A,

the amino acid sequences of domain O and domain B are identical,

the amino acid sequences of domain I is different from the sequence of domain O and domain B,

the amino acid sequences of domain P and domain F are identical,

the amino acid sequences of domain L is different from the sequence of domain P and domain F,

the amino acid sequences of domain Q and domain G are identical,

the amino acid sequences of domain M is different from the sequence of domain Q and domain G; and

(b) — wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction

between the N domain and the P domain form a third antigen binding site specific for the first antigen.

~~74. — The ROR antigen binding molecule of claim 73, wherein the first antigen is a ROR antigen.~~

~~75. — The ROR antigen binding molecule of claim 73 or 74, wherein the second antigen is a CD3 antigen.~~

~~76. — The ROR antigen binding molecule of claim 58, wherein:~~

~~(a) — the amino acid sequences of domain N, domain A, and domain H are different,~~

~~the amino acid sequences of domain O, domain B, and domain I are different,~~

~~the amino acid sequences of domain P, domain F, and domain L are different, and~~

~~the amino acid sequences of domain Q, domain G, and domain M are different; and~~

~~(b) — the interaction between the A domain and the F domain form a first antigen-~~

~~binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-~~

~~binding site specific for a second antigen, and~~

~~the interaction between the N domain and the P domain form a third antigen binding-~~

~~site specific for a third antigen.~~

~~77. — The ROR antigen binding molecule of any one of claims 66-69, wherein the ROR antigen binding molecule comprises a fifth polypeptide chain, wherein:~~

~~(a) — the third polypeptide chain further comprises a domain R and a domain S,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a R-S-H-I-J-K orientation, and~~

~~wherein domain R has a variable region amino acid sequence and domain S has a constant domain amino acid sequence;~~

~~(b) — the fifth polypeptide chain comprises:~~

~~a domain T and a domain U,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a T U orientation, and~~

~~wherein domain T has a variable region amino acid sequence and domain U has a constant domain amino acid sequence; and~~

~~(c) — the third and the fifth polypeptides are associated through an interaction between the R and the T domains and an interaction between the S and the U domains to form the ROR antigen binding molecule.~~

78. — ~~The ROR antigen binding molecule of claim 77, wherein:~~

~~(a) — the amino acid sequences of domain R and domain A are identical,~~

~~the amino acid sequences of domain H is different from the sequence of domain R and domain A,~~

~~the amino acid sequences of domain S and domain B are identical,~~

~~the amino acid sequences of domain I is different from the sequence of domain S and domain B,~~

~~the amino acid sequences of domain T and domain F are identical,~~

~~the amino acid sequences of domain L is different from the sequence of domain T and domain F,~~

~~the amino acid sequences of domain U and domain G are identical,~~

~~the amino acid sequences of domain M is different from the sequence of domain U and domain G, and~~

~~(b) — the interaction between the A domain and the F domain form a first antigen-binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen, and~~

~~the interaction between the R domain and the T domain form a third antigen-binding site specific for the first antigen.~~

~~79. — The ROR antigen binding molecule of claim 78, wherein the first antigen is a ROR-antigen.~~

~~80. — The ROR antigen binding molecule of claim 78 or 79, wherein the second antigen is a CD3 antigen.~~

~~81. — The ROR antigen binding molecule of any one of claims 77-80, wherein the molecule comprises five polypeptide chains and wherein chain 1 comprises SEQ ID NO:96, chain 2 comprises SEQ ID NO:97, chain 3 comprises SEQ ID NO:98, chain 4 comprises SEQ ID NO:99, and chain 5 comprises SEQ ID NO:97.~~

~~82. — The ROR antigen binding molecule of any one of claims 77-80, wherein the molecule comprises five polypeptide chains and wherein chain 1 comprises SEQ ID NO:114, chain 2 comprises SEQ ID NO:115, chain 3 comprises SEQ ID NO:116, chain 4 comprises SEQ ID NO:117, and chain 5 comprises SEQ ID NO:115.~~

~~83. — The ROR antigen binding molecule of any one of claims 77-80, wherein the molecule comprises five polypeptide chains and wherein chain 1 comprises SEQ ID NO:132, chain 2 comprises SEQ ID NO:133, chain 3 comprises SEQ ID NO:134, chain 4 comprises SEQ ID NO:135, and chain 5 comprises SEQ ID NO:133.~~

~~84. — The ROR antigen binding molecule of claim 77, wherein:~~

~~(a) — the amino acid sequences of domain R and domain H are identical,~~

~~the amino acid sequences of domain A is different from the sequence of domain R and domain H,~~

~~the amino acid sequences of domain S and domain I are identical,~~

~~the amino acid sequences of domain B is different from the sequence of domain S and domain I,~~

~~the amino acid sequences of domain T and domain L are identical,~~

~~the amino acid sequences of domain F is different from the sequence of domain T and domain L,~~

~~the amino acid sequences of domain U and domain M are identical,~~

~~the amino acid sequences of domain G is different from the sequence of domain U and domain M, and~~

~~(b) — the interaction between the A domain and the F domain form a first antigen-binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen, and~~

~~the interaction between the R domain and the T domain form a third antigen binding-site specific for the second antigen.~~

85. — ~~The ROR antigen binding molecule of claim 84, wherein the second antigen is a ROR antigen.~~

86. — ~~The ROR antigen binding molecule of claim 85, wherein the first antigen is a CD3 antigen.~~

87. — ~~The ROR antigen binding molecule of claim 77, wherein:~~

~~(a) — the amino acid sequences of domain R, domain A, and domain H are different,~~

~~the amino acid sequences of domain S, domain B, and domain I are different,~~

~~the amino acid sequences of domain T, domain F, and domain L are different, and~~

~~the amino acid sequences of domain U, domain G, and domain M are different; and~~

~~(b) — the interaction between the A domain and the F domain form a first antigen-binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen, and~~

~~the interaction between the R domain and the T domain form a third antigen binding site specific for a third antigen.~~

~~**88.** — A tyrosine protein kinase transmembrane receptor (ROR) antigen binding molecule, the ROR antigen binding molecule comprising:~~

~~a first and a second polypeptide chain, wherein:~~

~~(a) — the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a A-B-D-E orientation, and~~

~~wherein domain A has a VL amino acid sequence, domain B has a CH3 amino acid sequence, domain D has a CH2 amino acid sequence, domain E has a constant region domain amino acid sequence;~~

~~(b) — the second polypeptide chain comprises a domain F and a domain G,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a F-G orientation, and~~

wherein domain F has a VH amino acid sequence and domain G has a CH3 amino acid sequence; and

(e) — the first and the second polypeptides are associated through an interaction between the A and the F domains and an interaction between the B and the G domains to form the ROR antigen binding molecule, wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a ROR antigen.

89. — A tyrosine protein kinase transmembrane receptor (ROR) antigen binding molecule, the ROR antigen binding molecule comprising:

a first, second, third, and fourth polypeptide chain, wherein:

(a) — the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E,

wherein the domains are arranged, from N terminus to C terminus, in a A-B-D-E orientation, and

domain A has a VL amino acid sequence, domain B has a CH3 amino acid sequence, domain D has a CH2 amino acid sequence, and domain E has a constant region domain amino acid sequence;

(b) — the second polypeptide chain comprises a domain F and a domain G,

wherein the domains are arranged, from N terminus to C terminus, in a F-G orientation, and

wherein domain F has a VH amino acid sequence and domain G has a CH3 amino acid sequence;

(c) — the third polypeptide chain comprises a domain H, a domain I, a domain J, and a domain K,

~~wherein the domains are arranged, from N terminus to C terminus, in a H I J K orientation, and~~

~~wherein domain H has a variable region domain amino acid sequence, domain I has a constant region domain amino acid sequence, domain J has a CH₂ amino acid sequence, and K has a constant region domain amino acid sequence;~~

~~(d) — the fourth polypeptide chain comprises a domain L and a domain M,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a L M orientation, and~~

~~wherein domain L has a variable region domain amino acid sequence and domain M has a constant region domain amino acid sequence;~~

~~(e) — the first and the second polypeptides are associated through an interaction between the A and the F domains and an interaction between the B and the G domains;~~

~~(f) — the third and the fourth polypeptides are associated through an interaction between the H and the L domains and an interaction between the I and the M domains; and~~

~~(g) — the first and the third polypeptides are associated through an interaction between the D and the J domains and an interaction between the E and the K domains to form the ROR antigen binding molecule,~~

~~wherein the interaction between the A domain and the F domain form a first antigen binding site, the interaction between the H domain and the L domain form a second antigen binding site, and~~

~~wherein the first antigen binding site, the second antigen binding site, or the first and the second antigen binding site are specific for a ROR antigen.~~

~~90. — The ROR antigen binding molecule of claim 89, wherein the first antigen binding site is specific for the ROR antigen.~~

- ~~91. The ROR antigen binding molecule of claim 89 or 90, wherein the second antigen binding site is specific for the ROR antigen.~~
- ~~92. The ROR antigen binding molecule of claim 89, wherein the first and the second antigen binding site is specific for the ROR antigen.~~
- ~~93. The ROR antigen binding molecule of any of claims 88-92, wherein the ROR antigen is ROR1.~~
- ~~94. The ROR antigen binding molecule of any of claims 88-92, wherein the ROR antigen is ROR2.~~
- ~~95. The ROR antigen binding molecule of any of claims 88-92, wherein the ROR antigen is ROR1 and ROR2.~~
- ~~96. The ROR antigen binding molecule of any of claims 88-92, wherein the ROR antigen is a domain selected from the group consisting of: a ROR1 Frizzle domain, ROR2 Frizzle domain, a ROR1 Ig-like domain, a ROR2 Ig-like domain, a ROR1 Kringle domain, and a ROR2 Kringle domain.~~
- ~~97. The ROR antigen binding molecule of any of claims 93-96, wherein the ROR antigen comprises a human ROR antigen.~~
- ~~98. The ROR antigen binding molecule of any of claims 88-97,~~
~~wherein Domain A comprises a CDR1, a CDR2, and a CDR3 amino acid sequences~~
~~of a specific light chain variable region (VL) from a specific ROR antigen binding site,~~
~~wherein the CDR1, CDR2, and CDR3 VL sequences are selected from Table 6, and~~
~~wherein Domain F comprises a CDR1, a CDR2, and a CDR3 amino acid sequences of~~
~~a specific heavy chain variable region (VH) from the specific ROR antigen binding site,~~
~~wherein the CDR1, CDR2, and CDR3 VH sequences are selected from Table 6.~~
- ~~99. The ROR antigen binding molecule of claim 98, wherein the specific ROR antigen binding site is I2A-10 or I2A-27.~~
- ~~100. The ROR antigen binding molecule of any of claims 89-99, wherein~~

~~the second antigen binding site comprises:~~

~~A) within the third polypeptide chain a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and~~

~~B) within the fourth polypeptide chain a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.~~

~~101. The ROR antigen binding molecule of any of claims 89-99, wherein~~

~~the second antigen binding site comprises:~~

~~A) within the fourth polypeptide chain a specific light chain variable region (VL) amino acid sequence selected from the group consisting of: SEQ ID NO:69 and SEQ ID NO:73; and~~

~~B) within the third polypeptide chain a specific heavy chain variable region (VH) amino acid sequence selected from the group consisting of: SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.~~

~~102. The ROR antigen binding molecule of any one of claims 88-100, wherein the amino acid sequences of the B domain and the G domain are identical, wherein the sequence is an endogenous CH3 sequence.~~

~~103. The ROR antigen binding molecule of any one of claims 88-100, wherein the amino acid sequences of the B domain and the G domain are different and separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the B domain interacts with the G domain, and wherein neither the B domain nor the G domain significantly interacts with a CH3 domain lacking the orthogonal modification.~~

- ~~104.~~ The ROR antigen binding molecule of claim 103, wherein the orthogonal modifications of the B domain and the G domain comprise mutations that generate engineered disulfide bridges between the B domain and the G domain.
- ~~105.~~ The ROR antigen binding molecule of claim 104, wherein the mutations of the B domain and the G domain that generate engineered disulfide bridges are a S354C mutation in one of the B domain and G domain, and a 349C in the other domain.
- ~~106.~~ The ROR antigen binding molecule of any one of claims 103-105, wherein the orthogonal modifications of the B domain and the G domain comprise knob-in-hole mutations.
- ~~107.~~ The ROR antigen binding molecule of claim 106, wherein the knob-in-hole mutations are a T366W mutation in one of the B domain and G domain, and a T366S, L368A, and aY407V mutation in the other domain.
- ~~108.~~ The ROR antigen binding molecule of any one of claims 103-107, wherein the orthogonal modifications of the B domain and the G domain comprise charge pair mutations.
- ~~109.~~ The ROR antigen binding molecule of claim 108, wherein the charge pair mutations are a T366K mutation in one of the B domain and G domain, and a L351D mutation in the other domain.
- ~~110.~~ The ROR antigen binding molecule of any one of claims 88-109, wherein the E domain has a CH3 amino acid sequence.
- ~~111.~~ The ROR antigen binding molecule of any one of claims 88-110, wherein the amino acid sequences of the E domain and the K domain are identical, wherein the sequence is an endogenous CH3 sequence.
- ~~112.~~ The ROR antigen binding molecule of any one of claims 88-110, wherein the amino acid sequences of the E domain and the K domain are different.
- ~~113.~~ The ROR antigen binding molecule of claim 112, wherein the different sequences separately comprise respectively orthogonal modifications in an endogenous CH3 sequence, wherein the E domain interacts with the K domain, and wherein neither the

~~E domain nor the K domain significantly interacts with a CH3 domain lacking the orthogonal modification.~~

~~114. The ROR antigen binding molecule of claim 113, wherein the orthogonal modifications comprise mutations that generate engineered disulfide bridges between the E domain and the K domain.~~

~~115. The ROR antigen binding molecule of claim 114, wherein the mutations that generate engineered disulfide bridges are a S354C mutation in one of the E domain and the K domain, and a 349C in the other domain.~~

~~116. The ROR antigen binding molecule of any one of claims 113-115, wherein the orthogonal modifications in the E domain and the K domain comprise knob-in-hole mutations.~~

~~117. The ROR antigen binding molecule of claim 116, wherein the knob-in-hole mutations are a T366W mutation in one of the E domain or the K domain and a T366S, L368A, and aY407V mutation in the other domain.~~

~~118. The ROR antigen binding molecule of any one of claims 113-117, wherein the orthogonal modifications in the E domain and the K domain comprise charge pair mutations.~~

~~119. The ROR antigen binding molecule of claim 118, wherein the charge pair mutations are a T366K mutation in one of the E domain or the K domain and a corresponding L351D mutation in the other domain.~~

~~120. The ROR antigen binding molecule of claim 112, wherein the amino acid sequences of the E domain and the K domain are endogenous sequences of two different antibody domains, the domains selected to have a specific interaction that promotes the specific association between the first and the third polypeptides.~~

~~121. The ROR antigen binding molecule of claim 120, wherein the two different amino acid sequences are a CH1 sequence and a CL sequence.~~

~~122. The ROR antigen binding molecule of any one of claims 89-121, wherein domain I has a CL sequence and domain M has a CH1 sequence.~~

~~123.~~ The ROR antigen binding molecule of any one of claims 89-122, wherein domain H has a VL sequence and domain L has a VH sequence.

~~124.~~ The ROR antigen binding molecule of any one of claims 89-123, wherein:

domain H has a VL amino acid sequence;

domain I has a CL amino acid sequence;

domain K has a CH3 amino acid sequence;

domain L has a VH amino acid sequence;

and domain M has a CH1 amino acid sequence.

~~125.~~ The ROR antigen binding molecule of any one of claims 89-124, further comprising:

a fifth polypeptide chain, wherein:

(a) — the first polypeptide chain further comprises a domain N and a domain O,

wherein the domains are arranged, from N terminus to C terminus, in a N-O-A-B-D-E orientation, and

wherein domain N has a variable region domain amino acid sequence, domain O has a constant region domain amino acid sequence;

(b) — the ROR antigen binding molecule further comprises a fifth polypeptide chain, comprising:

a domain P and a domain Q, wherein the domains are arranged, from N terminus to C terminus, in a P-Q orientation, and

wherein domain P has a variable region domain amino acid sequence and domain Q has a constant region domain amino acid sequence; and

(c) — the first and the fifth polypeptides are associated through an interaction between the N and the P domains and an interaction between the O and the Q domains to form the ROR antigen binding molecule.

126. — The ROR antigen binding molecule of claim 125, wherein:

(a) — the amino acid sequences of domain N and domain A are identical,
the amino acid sequences of domain H is different from the sequence of domain N and domain A,
the amino acid sequences of domain O and domain B are identical,
the amino acid sequences of domain I is different from the sequence of domain O and domain B,
the amino acid sequences of domain P and domain F are identical,
the amino acid sequences of domain L is different from the sequence of domain P and domain F,
the amino acid sequences of domain Q and domain G are identical,
the amino acid sequences of domain M is different from the sequence of domain Q and domain G; and

(b) — wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and the interaction between the N domain and the P domain form a third antigen binding site specific for the first antigen.

127. — The ROR antigen binding molecule of claim 126, wherein the first antigen is the ROR antigen.

~~128. The ROR antigen binding molecule of claim 126 or 127, wherein the second antigen is a CD3 antigen.~~

~~129. The ROR antigen binding molecule of claim 125, wherein:~~

~~(a) the amino acid sequences of domain N, domain A, and domain H are different,~~

~~the amino acid sequences of domain O, domain B, and domain I are different,~~

~~the amino acid sequences of domain P, domain F, and domain L are different, and~~

~~the amino acid sequences of domain Q, domain G, and domain M are different;~~

~~(b) the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen binding site specific for a second antigen, and~~

~~the domain N and domain P form a third antigen binding site specific for a third antigen, and~~

~~(c) the first, the second, or the third antigen is the ROR antigen.~~

~~130. The ROR antigen binding molecule of any one of claims 89-124, further comprising:~~

~~a fifth polypeptide chain, wherein:~~

~~(a) the third polypeptide chain further comprises a domain R and a domain S,~~

~~wherein the domains are arranged, from N-terminus to C-terminus, in a R-S-H-I-J-K orientation, and~~

~~wherein domain R has a variable region domain amino acid sequence and domain S has a constant domain amino acid sequence;~~

~~(b) the ROR antigen binding molecule further comprises a fifth polypeptide chain, comprising:~~

~~a domain T and a domain U,~~

~~wherein the domains are arranged, from N terminus to C terminus, in a T U orientation, and~~

~~wherein domain T has a variable region domain amino acid sequence and domain U has a constant domain amino acid sequence; and~~

~~(e) — the third and the fifth polypeptides are associated through an interaction between the R and the T domains and an interaction between the S and the U domains to form the ROR antigen binding molecule.~~

131. ~~The ROR antigen binding molecule of claim 130, wherein:~~

~~(a) — the amino acid sequences of domain R and domain A are identical,~~

~~the amino acid sequences of domain H is different from the sequence of domain R and domain A,~~

~~the amino acid sequences of domain S and domain B are identical,~~

~~the amino acid sequences of domain I is different from the sequence of domain S and domain B,~~

~~the amino acid sequences of domain T and domain F are identical,~~

~~the amino acid sequences of domain L is different from the sequence of domain T and domain F,~~

~~the amino acid sequences of domain U and domain G are identical,~~

~~the amino acid sequences of domain M is different from the sequence of domain U and domain G and~~

~~(b) — the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen; and~~

~~the interaction between the R domain and the T domain form a third antigen binding site specific for the first antigen.~~

~~132. The ROR antigen binding molecule of claim 131, wherein the first antigen is the ROR antigen.~~

~~133. The ROR antigen binding molecule of claim 131 or 132, wherein the second antigen is a CD3 antigen.~~

~~134. The ROR antigen binding molecule of claim 130, wherein~~

~~(a) the amino acid sequences of domain R and domain H are identical,~~

~~the amino acid sequences of domain A is different from the sequence of domain R and domain H,~~

~~the amino acid sequences of domain S and domain I are identical,~~

~~the amino acid sequences of domain B is different from the sequence of domain S and domain I,~~

~~the amino acid sequences of domain T and domain L are identical,~~

~~the amino acid sequences of domain F is different from the sequence of domain T and domain L,~~

~~the amino acid sequences of domain U and domain M are identical,~~

~~the amino acid sequences of domain G is different from the sequence of domain U and domain M, and~~

~~(b) the interaction between the A domain and the F domain form a first antigen-binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen, and~~

~~the interaction between the R domain and the T domain form a third antigen binding site specific for the second antigen.~~

~~135. The ROR antigen binding molecule of claim 134, wherein the second antigen is the ROR antigen.~~

~~136. The ROR antigen binding molecule of claim 134 or 135, wherein the first antigen is a CD3 antigen.~~

~~137. The ROR antigen binding molecule of claim 130, wherein~~

~~(a) the amino acid sequences of domain R, domain A, and domain H are different,~~

~~the amino acid sequences of domain S, domain B, and domain I are different,~~

~~the amino acid sequences of domain T, domain F, and domain L are different, and~~

~~the amino acid sequences of domain U, domain G, and domain M are different;~~

~~(b) the interaction between the A domain and the F domain form a first antigen-binding site specific for a first antigen,~~

~~the interaction between the H domain and the L domain form a second antigen-binding site specific for a second antigen, and~~

~~the interaction between the R domain and the T domain form a third antigen binding site specific for a third antigen; and~~

~~(c) the first, the second, or the third antigen is the ROR antigen.~~

~~138. The ROR antigen binding molecule of any one of claims 89-124, further comprising:~~

~~a fifth and a sixth polypeptide chain, wherein:~~

(a) — the first polypeptide chain further comprises a domain N and a domain O,
wherein the domains are arranged, from N terminus to C terminus, in a N-O-A-B-D-E
orientation;

(b) — the third polypeptide chain further comprises a domain R and a domain S,
wherein the domains are arranged, from N terminus to C terminus, in a R-S-H-I-J-K
orientation;

(c) — the ROR antigen binding molecule further comprises a fifth and a sixth
polypeptide chain, wherein:

the fifth polypeptide chain comprises a domain P and a domain Q, wherein the
domains are arranged, from N terminus to C terminus, in a P-Q orientation, and

the sixth polypeptide chain comprises a domain T and a domain U,
wherein the domains are arranged, from N terminus to C terminus, in a T-U
orientation; and

(d) — the first and the fifth polypeptides are associated through an interaction
between the N and the P domains and an interaction between the O and the Q domains, and

the third and the sixth polypeptides are associated through an interaction between the
R and the T domains and an interaction between the S and the U domains to form the ROR
antigen binding molecule.

139. — The ROR antigen binding molecule of claim 138, wherein:

- (a) — the amino acid sequences of domain N and domain A are identical,
- the amino acid sequences of domain H and domain R are identical,
- the amino acid sequences of domain O and domain B are identical,
- the amino acid sequences of domain I and domain S are identical,

~~the amino acid sequences of domain P and domain F are identical,~~
~~the amino acid sequences of domain L and domain T are identical,~~
~~the amino acid sequences of domain Q and domain G are identical,~~
~~the amino acid sequences of domain M and domain U are identical; and~~

~~(b) — wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the domain N and domain P form a second antigen binding site specific for the first antigen, the interaction between the H domain and the L domain form a third antigen binding site specific for a second antigen, and the interaction between the R domain and the T domain form a fourth antigen binding site specific for the second antigen.~~

140. ~~The ROR antigen binding molecule of claim 138, wherein:~~

~~(a) — the amino acid sequences of domain H and domain A are identical,~~
~~the amino acid sequences of domain N and domain R are identical,~~
~~the amino acid sequences of domain I and domain B are identical,~~
~~the amino acid sequences of domain O and domain S are identical,~~
~~the amino acid sequences of domain L and domain F are identical,~~
~~the amino acid sequences of domain P and domain T are identical,~~
~~the amino acid sequences of domain M and domain G are identical,~~
~~the amino acid sequences of domain Q and domain U are identical; and~~

~~(b) — wherein the interaction between the A domain and the F domain form a first antigen binding site specific for a first antigen, the domain N and domain P form a second antigen binding site specific for a second antigen, the interaction between the H domain and the L domain form a third antigen binding site specific for the first antigen, and the~~

interaction between the R domain and the T domain form a fourth antigen binding site specific for the second antigen.

~~141. The ROR antigen binding molecule of any of the above claims, wherein the sequence that forms the junction between the A domain and the B domain is IKRTPREP or IKRTVREP.~~

~~142. The ROR antigen binding molecule of any of the above claims, wherein the sequence that forms the junction between the F domain and the G domain is SSASPREP.~~

~~143. The ROR antigen binding molecule of any of the above claims, wherein at least one CH3 amino acid sequence has a C terminal tripeptide insertion connecting the CH3 amino acid sequence to a hinge amino acid sequence, wherein the tripeptide insertion is selected from the group consisting of PGK, KSC, and GEC.~~

~~144. The ROR antigen binding molecule of any of the above claims, wherein the sequences are human sequences.~~

~~145. The ROR antigen binding molecule of any of the above claims, wherein at least one CH3 amino acid sequence is an IgG sequence.~~

~~146. The ROR antigen binding molecule of claim 145, wherein the IgG sequences are IgG1 sequences.~~

~~147. The ROR antigen binding molecule of any of the above claims, wherein at least one CH3 amino acid sequence has one or more isoallotype mutations.~~

~~148. The ROR antigen binding molecule of claim 147, wherein the isoallotype mutations are D356E and L358M.~~

~~149. The ROR antigen binding molecule of any of the above claims, wherein the CL amino acid sequence is a Ckappa sequence.~~

~~150. The ROR antigen binding molecule of any of the above claims, wherein the CH2 sequences have one or more engineered mutations that reduce Fc effector function.~~

~~151. The ROR antigen binding molecule of claim 150, wherein the one or more engineered mutations are at position L234, L235, and P329.~~

~~152.~~ The ROR antigen binding molecule of claim 151, wherein the one or more engineered mutations are L234A, L235A, and P329G.

~~153.~~ The ROR antigen binding molecule of claim 151, wherein the one or more engineered mutations are L234A, L235A, and P329K.

~~154.~~ A purified ROR antigen binding molecule, the purified ROR antigen binding molecule comprising the ROR antigen binding molecule of any one of claims 1-153.

~~155.~~ The purified ROR antigen binding molecule of claim 154, wherein the purified ROR antigen binding is purified by a purification method comprising a CH1 affinity purification step.

~~156.~~ The purified ROR antigen binding molecule of claim 154 or 155, wherein the purification method is a single step purification method.

~~157~~12. A pharmaceutical composition comprising the ROR antigen binding molecule of any one of claims 1-~~156~~9, the nucleic acid of claim 10, or the vector of claim 11, and a pharmaceutically acceptable diluent.

~~158~~13. A method for treating a subject with cancer, the method comprising administering a therapeutically effective amount of Use of the pharmaceutical composition of claim ~~157~~12 in the production of a medicament for treating a subject with cancer to the subject.

~~159~~14. The method use of claim ~~158~~13, wherein the cancer is an ROR antigen expressing cancer.

~~160~~15. The method use of claim ~~159~~14, wherein the cancer expresses an ROR1 antigen.

~~161~~16. The method use of claim ~~159~~14, wherein the cancer expresses and ROR2 antigen.

~~162~~17. The method use of claim ~~159~~14, wherein the cancer expresses an ROR1 antigen and an ROR2 antigen.

~~163~~18. The method use of any of claims ~~158-162~~13-17, wherein the cancer is selected from the group consisting of: pancreatic cancer, ovarian cancer, breast cancer, lung cancer, gastric cancer, melanoma, Ewing sarcoma, chronic lymphocytic leukemia, mantle cell lymphoma, B-ALL, hematological cancer, prostate cancer, colon cancer, renal cancer, thyroid cancer, liver

cancer, urothelial carcinoma, melanoma, endometrial cancer, clear cell renal cell carcinoma, clear cell carcinoma, and uterine cancer.

~~16419~~. The ~~method-use~~ of any one of claims ~~158-163~~13-18, wherein the pharmaceutical composition is to be administered in combination with an additional therapy.

~~16520~~. The ~~method-use~~ of claim ~~16419~~, wherein the additional therapy is surgery, radiotherapy, endocrine therapy, immunotherapy, or chemotherapy.

~~16621~~. The ~~method-use~~ of claim ~~16520~~, wherein the immunotherapy is an immunotherapeutic agent.

~~16722~~. The ~~method-use~~ of claim ~~16621~~, wherein the immunotherapeutic agent is an immune checkpoint inhibitor.

~~16823~~. The ~~method-use~~ of claim ~~16621~~, wherein the immunotherapeutic agent is a vaccine.

~~16924~~. The ~~method-use~~ of claim ~~16520~~, wherein the chemotherapy is a cytotoxic agent or a chemotherapeutic agent.