

[0007] Previous efforts to multimerize proteins include the use of streptavidin (Kipriyanov et al., *Protein Engineering*, 9(2):203-211 (1996)), helix-turn-helix constructs (Kriangkum et al., *Biomolecular Engineering*, 18:31-40 (2001)), leucine zippers (Kruif et al., *The Journal of Biological Chemistry*, 271(13):7630-7634, 1996 (1996)), barnase/barstar complexes (Deyev et al., *Nature Biotechnology*, 21(12):1486-1492 (2003)), and Dock N Lock technology (protein kinase and A-kinase anchoring protein anchoring domain interactions) (Goldenberg et al., *Journal of Nuclear Medicine*, 49(1):158-163 (2008)).

[0008] However, there remains a need for an efficient means of generating multispecific proteins (e.g., whole antibodies and antibody fragments) that can bind multiple epitopes on the same or different protein.

SUMMARY ~~OF THE INVENTION~~

[0009] ~~In one aspect, the present invention~~disclosure relates to a TTR protein complex, wherein the TTR protein complex comprises TTR subunits A, B, C, and D;
TTR subunits A and B dimerize to form TTR dimer AB;
TTR subunits C and D dimerize to form TTR dimer CD;
TTR dimers AB and CD further dimerize to form TTR tetramer ABCD; and
each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1, except that at least one amino acid in the interface between TTR dimer AB and TTR dimer CD is mutated such that the formation of an ABCD tetramer is favored over the formation of any other tetramer (e.g., an ABAB tetramer or a CDCD tetramer).

[0010] Each of the A, B, C, and D subunits of the TTR protein complex may comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations: C10A, K15A, or both C10A and K15A.

[0011] Thus, in one ~~embodiment~~example, the present ~~invention~~disclosure relates to TTR protein complexes wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 6, 7, 8, 9, 10, 13, 15, 17, 19, 20, 21, 22, 23, 24, 26, 50, 51, 52, 53, 54, 56, 57, 60, 61, 62, 63, 78, 82, 83, 84, 85, 100, 101, 102, 103, 104, 106, 108, 110, 112, 113, 114, 115, 117, 119, 121, 123, 124, 125, 126, and 127 of SEQ ID NO: 1.

[0012] In another ~~embodiment~~example, the present ~~invention~~disclosure relates to a TTR protein complex wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1.

[0013] In another ~~embodiment~~example, the present ~~invention~~disclosure relates to a TTR protein complex wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106,

108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an aspartate, glutamate, arginine, lysine, or histidine.

[0014] In another [embodimentexample](#), the present [inventiondisclosure](#) relates to a TTR protein complex wherein A and B comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an aspartate or glutamate.

[0015] In yet another [embodimentexample](#), the present [inventiondisclosure](#) relates to a TTR protein complex wherein C and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an arginine, lysine, or histidine.

[0016] In a particular [embodimentexample](#), A and B comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an aspartate or glutamate; and C and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an arginine, lysine, or histidine.

[0017] In some [embodimentexamples](#), A and B comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: K15D, L17D, V20D, R21D, G22D, S23D, P24D, S52D, I84D, T106D, A108D, S112D, Y114D, S115D, T119D, V121D, S123D, K15E, L17E, V20E, R21E, G22E, S23E, P24E, D51E, S52E, I84E, T106E, A108E, S112E, Y114E, S115E, T119E, V121E, and S123E. The present [inventiondisclosure](#) also relates to TTR protein complexes wherein A and B comprise at least one mutation in SEQ ID NO: 1, wherein the mutation is selected from the list comprising: L17D, L17E, V20D, V20E, G22D, G22E, S112D, S112E, T119D, T119E, V121D, and V121E.

[0018] In some [embodimentexamples](#), C and D comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: K15R, L17R, V20R, G22R, S23R, P24R, D51R, S52R, I84R, T106R, A108R, S112R, Y114R, S115R, T119R, V121R, S123R, L17K, V20K, R21K, G22K, S23K, P24K, D51K, S52K, I84K, T106K, A108K, S112K, Y114K, S115K, T119K, V121K, S123K, K15H, L17H, V20H, R21H, G22H, S23H, P24H, D51H, S52H, I84H, T106H, A108H, S112H, Y114H, S115H, T119H, V121H, and S123H. The present [inventiondisclosure](#) also relates to TTR protein complexes wherein C and D comprise at least one mutation in SEQ ID NO: 1, wherein the mutation is selected from the list comprising: L17R, L17K, L17H, V20R, V20K, V20H, G22R, G22K, G22H, S112R, S112K, S112H, T119R, T119K, T119H, V121R, V121K, and V121H.

[0019] In other embodimentexamples, both A and B, both C and D, or all four of A, B, C, and D independently comprise one mutation discussed above. In yet other embodimentexamples, both A and B, both C and D, or all four of A, B, C, and D independently comprise two said mutations discussed above.

[0020] In specific embodimentexamples, the present inventiondisclosure relates to a TTR protein complex wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/L17E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/G22D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/G22E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/S112D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/S112E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/T119D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/T119E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/V121D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/V121E, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/L17E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/G22D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/G22E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/S112D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/S112E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/T119D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/T119E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/V121D, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/V121E, and C and D comprise C10A/K15A/L17K (or vice versa);
A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/V20R (or vice versa);
A and B comprise C10A/K15A/L17E, and C and D comprise C10A/K15A/V20R (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/V20R (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/V20R (or vice versa);

[illegible]

A and B comprise C10A/K15A/V121D, and C and D comprise C10A/K15A/V121R (or vice versa);
A and B comprise C10A/K15A/V121E, and C and D comprise C10A/K15A/V121R (or vice versa);
A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/L17E, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/G22D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/G22E, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/S112D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/S112E, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/T119D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/T119E, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/V121D, and C and D comprise C10A/K15A/V121K (or vice versa); or
A and B comprise C10A/K15A/V121E, and C and D comprise C10A/K15A/V121K (or vice versa).

[0021] In other specific embodiment examples, the present invention disclosure relates to a TTR protein complex wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/V121R (or vice versa);
A and B comprise C10A/K15A/L17D, and C and D comprise C10A/K15A/V121K (or vice versa);
A and B comprise C10A/K15A/L17E, and C and D comprise C10A/K15A/V121R (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/V20R (or vice versa);
A and B comprise C10A/K15A/V20D, and C and D comprise C10A/K15A/V20K (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/V20R (or vice versa);
A and B comprise C10A/K15A/V20E, and C and D comprise C10A/K15A/V20K (or vice versa);
A and B comprise C10A/K15A/T119D, and C and D comprise C10A/K15A/L17R (or vice versa);
A and B comprise C10A/K15A/T119D, and C and D comprise C10A/K15A/L17K (or vice versa); or
A and B comprise C10A/K15A/V121E, and C and D comprise C10A/K15A/L17K (or vice versa).

[0022] In some embodiment examples, A and B comprise two mutations in SEQ ID NO: 1, wherein said mutations are selected from the list comprising: L17D/V20D, L17D/V20E, L17E/V20D, L17E/V20E, L17D/T119D, L17D/V121E, L17E/T119D, L17E/V121E, V20D/T119D, V20D/V121E, V20E/T119D, and V20E/V121E.

[0023] In some embodiment examples, C and D comprise two mutations in SEQ ID NO: 1, wherein said mutations are selected from the list comprising: L17K/V20K, L17K/V20R, L17R/V20K, L17R/V20R,

L17K/V121K, L17K/V121R, L17R/V121K, L17R/V121R, V20K/V121K, V20K/V121R, V20R/V121K, and V20R/V121R.

[0024] The present invention disclosure also comprises embodiment examples wherein each of A, B, C, and D in the TTR protein complex comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

A and B comprise C10A/K15A/L17D/V20D, and C and D comprise C10A/K15A/L17K/V20K (or vice versa);

A and B comprise C10A/K15A/L17D/V20E, and C and D comprise C10A/K15A/L17K/V20R (or vice versa);

A and B comprise C10A/K15A/L17E/V20D, and C and D comprise C10A/K15A/L17R/V20K (or vice versa);

A and B comprise C10A/K15A/L17E/V20E, and C and D comprise C10A/K15A/L17R/V20R (or vice versa);

A and B comprise C10A/K15A/L17D/T119D, and C and D comprise C10A/K15A/L17K/V121K (or vice versa);

A and B comprise C10A/K15A/L17D/V121E, and C and D comprise C10A/K15A/L17K/V121R (or vice versa);

A and B comprise C10A/K15A/L17E/T119D, and C and D comprise C10A/K15A/L17R/V121K (or vice versa);

A and B comprise C10A/K15A/L17E/V121E, and C and D comprise C10A/K15A/L17R/V121R (or vice versa);

A and B comprise C10A/K15A/V20D/T119D, and C and D comprise C10A/K15A/V20K/V121K (or vice versa);

A and B comprise C10A/K15A/V20D/V121E, and C and D comprise C10A/K15A/V20K/V121R (or vice versa);

A and B comprise C10A/K15A/V20E/T119D, and C and D comprise C10A/K15A/V20R/V121K (or vice versa); or

A and B comprise C10A/K15A/V20E/V121E, and C and D comprise C10A/K15A/V20R/V121R (or vice versa)

[0025] In some embodiment examples, the TTR protein complex is attached to 1, 2, 3, 4, 5, 6, 7, or 8 bioactive proteins, peptides, or small molecules. In some embodiment examples, the TTR protein complex is attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins or peptides. In other embodiment examples, the TTR protein complex is attached to 1, 2, 3, or 4 antigen binding proteins or peptides. The antigen binding proteins or peptides may be attached to the TTR protein complex at the C-terminus of a TTR subunit or the

N-terminus of a TTR subunit. In addition, the TTR protein complex may be directly attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins or peptides; or may be attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins or peptides via a linker. In particular [embodimentexample](#), the TTR protein complex is directly attached to 1, 2, 3, or 4 antigen binding proteins or peptides; or is attached to 1, 2, 3, or 4 antigen binding proteins or peptides via a linker.

[0026] The linker may be an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids. In other [embodimentexamples](#), the linker is an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 amino acids. In other [embodimentexamples](#), the linker is an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids. In yet other [embodimentexamples](#), the linker is an amino acid-based linker comprising 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids. In particular [embodimentexamples](#), the linker is G, GG, GGG, GGGG, GGGGG, GGGGGG, GGGGGGG, GGGGGGGG, GGGGGGGGG, or GGGGGGGGGG. In other particular [embodimentexamples](#), the linker is selected from the list comprising: GG, GGGG, GGGSGG, GGGSGGGG, and GGAGGGAGGG.

[0027] Other suitable linkers include a $G(G_xB_y)_rG_z$ linker wherein G = glycine; B = any amino acid; $x = 1-15$; $y = 1-5$; $z = 1-15$; and $r = 1-20$. In another [embodimentexample](#), the linker is a $G(G_xB_y)_rG_z$ linker wherein B = Q, S, A, E, P, T, K, R, D or N; $x = 4$; $y = 1$; $z = 4$; and $r = 1$.

[0028] In some [embodimentexamples](#) of the present [inventiondisclosure](#), the TTR protein complex is attached to two antigen binding proteins, wherein each antigen binding protein binds a different antigen. In other [embodimentexamples](#) of the present [inventiondisclosure](#), the TTR protein complex is attached to four antigen binding proteins, wherein the antigen binding proteins bind to at least two different antigens (e.g., one antigen binding protein binds to a first antigen and three antigen binding proteins bind to a second antigen; or two antigen binding proteins bind to a first antigen and two antigen binding proteins bind to a second antigen).

[0029] The antigen binding proteins may be antibodies. In other [embodimentexamples](#), the antigen binding proteins are Fabs or scFvs. In a particular [embodimentexample](#) the antigen binding proteins are Fabs. In other [embodimentexamples](#), the antigen binding proteins are a mixture of antibodies and Fabs.

[0030] [In another aspect, the present inventiondisclosure](#) also includes pharmaceutical compositions comprising any of the TTR protein complexes discussed herein.

[0031] [In a further aspect, the present disclosure provides a use of a TTR protein complex as disclosed herein in the manufacture of a pharmaceutical composition for the treatment of cancer. In a further aspect, the present disclosure provides a TTR protein complex as disclosed herein for use in therapy.](#) In

addition, the present ~~invention~~disclosure includes methods of treating cancer using any of the TTR protein complexes discussed herein. The TTR protein complexes of the present ~~invention~~disclosure may be used in the treatment of cancer. The present ~~invention~~disclosure also includes any of the TTR protein complexes discussed herein for use in the treatment of cancer.

~~[0031]~~ ——— **[0032]** In a further aspect, the present disclosure provides one or more isolated nucleic acid(s) encoding a TTR subunit, a TTR subunit fused or linked to an antigen binding protein or peptide (such as an antibody or Fab), or a TTR protein complex as disclosed herein. In another ~~embodiment~~example, the present ~~invention~~disclosure includes one or more isolated nucleic acid(s) encoding any of the TTR protein complexes discussed herein. In a further aspect, the present disclosure provides an expression vector comprising a nucleic acid as disclosed herein. In addition, the present ~~invention~~disclosure includes expression vector(s) comprising a nucleic acid encoding any of the TTR protein complexes discussed herein. In yet another aspect, ~~T~~the present ~~invention~~disclosure further includes a recombinant host cell comprising such nucleic acid(s) or vector(s). In some ~~embodiment~~examples, the host cell is a Chinese hamster ovary (CHO) cell, E5 cell, baby hamster kidney (BHK) cell, monkey kidney (COS) cell, human hepatocellular carcinoma cell, or human embryonic kidney 293 (HEK 293) cell.

[0033] In ~~some embodiments~~ yet another aspect, the present ~~invention~~disclosure relates to a method of making a TTR protein complex described herein, wherein the method comprises: a) culturing a recombinant host cell; and b) isolating the TTR protein complex from the culture.

CLAIMS

What is claimed:

1. A transthyretin (TTR) protein complex, wherein said TTR protein complex comprises TTR subunits A, B, C, and D;
wherein TTR subunits A and B dimerize to form TTR dimer AB;
wherein TTR subunits C and D dimerize to form TTR dimer CD;
wherein TTR dimers AB and CD further dimerize to form TTR tetramer ABCD; and
wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1, except that at least one amino acid in the interface between TTR dimer AB and TTR dimer CD is mutated such that the formation of an ABCD tetramer is favored over the formation of an ABAB tetramer or a CDCD tetramer.
2. The TTR protein complex according to claim 1, wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations: C10A, K15A, or both a C10A and a K15A mutation.
3. The TTR protein complex according to claim 1 or 2, wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 6, 7, 8, 9, 10, 13, 15, 17, 19, 20, 21, 22, 23, 24, 26, 50, 51, 52, 53, 54, 56, 57, 60, 61, 62, 63, 78, 82, 83, 84, 85, 100, 101, 102, 103, 104, 106, 108, 110, 112, 113, 114, 115, 117, 119, 121, 123, 124, 125, 126, and 127 of SEQ ID NO: 1.
4. The TTR protein complex according to claim 3, wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1.
5. The TTR protein complex according to any one of claims 1-4, wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1,
wherein said amino acid is mutated to an aspartate or glutamate.
6. The TTR protein complex according to any one of claims 1-4, wherein both A and B, both C and D, or all four of A, B, C, and D comprise a mutation at one or more amino acids positions selected from

the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1,

wherein said amino acid is mutated to an arginine, lysine, or histidine.

7. The TTR protein complex according to any one of claims 1-6, wherein A and B comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1,

wherein said amino acid is mutated to an aspartate or glutamate.

8. The TTR protein complex according to any one of claims 1-7, wherein C and D comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1,

wherein said amino acid is mutated to an arginine, lysine, or histidine.

9. The TTR protein complex according to any one of claims 1-4 wherein:

A and B comprise a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an aspartate or glutamate; and

C and D comprises a mutation at one or more amino acids positions selected from the list comprising: 15, 17, 20, 21, 22, 23, 24, 51, 52, 84, 106, 108, 112, 114, 115, 119, 121, and 123 of SEQ ID NO: 1, wherein said amino acid is mutated to an arginine, lysine, or histidine.

10. The TTR protein complex according to any one of claims 1-7 and 9, wherein A and B comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: K15D, L17D, V20D, R21D, G22D, S23D, P24D, S52D, I84D, T106D, A108D, S112D, Y114D, S115D, T119D, V121D, S123D, K15E, L17E, V20E, R21E, G22E, S23E, P24E, D51E, S52E, I84E, T106E, A108E, S112E, Y114E, S115E, T119E, V121E, and S123E.

11. The TTR protein complex according to claim 10, wherein A and B comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: L17D, L17E, V20D, V20E, G22D, G22E, S112D, S112E, T119D, T119E, V121D, and V121E.

12. The TTR protein complex according to any one of claims 1-6, 8, and 9, wherein C and D comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: K15R, L17R, V20R, G22R, S23R, P24R, D51R, S52R, I84R, T106R, A108R, S112R, Y114R, S115R, T119R, V121R, S123R, L17K, V20K, R21K, G22K, S23K, P24K, D51K, S52K, I84K,

T106K, A108K, S112K, Y114K, S115K, T119K, V121K, S123K, K15H, L17H, V20H, R21H, G22H, S23H, P24H, D51H, S52H, I84H, T106H, A108H, S112H, Y114H, S115H, T119H, V121H, and S123H.

13. The TTR protein complex according to claim 12, wherein C and D comprise at least one mutation in SEQ ID NO: 1, wherein said mutation is selected from the list comprising: L17R, L17K, L17H, V20R, V20K, V20H, G22R, G22K, G22H, S112R, S112K, S112H, T119R, T119K, T119H, V121R, V121K, and V121H.

14. The TTR protein complex according to any one of claims 1-13, wherein both A and B, both C and D, or all four of A, B, C, and D independently comprise one said mutation.

15. The TTR protein complex according to any one of claims 1-13, wherein both A and B, both C and D, or all four of A, B, C, and D independently comprise two said mutations.

16. The TTR protein complex according to any one of claims 1-15, wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

both A and B comprise C10A/K15A/L17D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/L17E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/V20D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/V20E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/G22D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/G22E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/S112D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/S112E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/T119D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/T119E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/V121D, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/V121E, and both C and D comprise C10A/K15A/L17R;
both A and B comprise C10A/K15A/L17D, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/L17E, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/V20D, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/V20E, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/G22D, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/G22E, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/S112D, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/S112E, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/T119D, and both C and D comprise C10A/K15A/L17K;
both A and B comprise C10A/K15A/T119E, and both C and D comprise C10A/K15A/L17K;

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[illegible]

both A and B comprise C10A/K15A/L17E, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/V20D, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/V20E, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/G22D, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/G22E, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/S112D, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/S112E, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/T119D, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/T119E, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/V121D, and both C and D comprise C10A/K15A/V121K; or
 both A and B comprise C10A/K15A/V121E, and both C and D comprise C10A/K15A/V121K.

17. The TTR protein complex according to any one of claims 1-15, wherein:

both A and B comprise C10A/K15A/L17D, and both C and D comprise C10A/K15A/V121R;
 both A and B comprise C10A/K15A/L17D, and both C and D comprise C10A/K15A/V121K;
 both A and B comprise C10A/K15A/L17E, and both C and D comprise C10A/K15A/V121R;
 both A and B comprise C10A/K15A/V20D, and both C and D comprise C10A/K15A/V20R;
 both A and B comprise C10A/K15A/V20D, and both C and D comprise C10A/K15A/V20K;
 both A and B comprise C10A/K15A/V20E, and both C and D comprise C10A/K15A/V20R;
 both A and B comprise C10A/K15A/V20E, and both C and D comprise C10A/K15A/V20K;
 both A and B comprise C10A/K15A/T119D, and both C and D comprise C10A/K15A/L17R;
 both A and B comprise C10A/K15A/T119D, and both C and D comprise C10A/K15A/L17K; or
 both A and B comprise C10A/K15A/V121E, and both C and D comprise C10A/K15A/L17K.

18. The TTR protein complex according to any one of claims 1-15, wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

both A and B comprise C10A/K15A/L17D/V20D, and both C and D comprise C10A/K15A/L17K/V20K;
 both A and B comprise C10A/K15A/L17D/V20E, and both C and D comprise C10A/K15A/L17K/V20R;
 both A and B comprise C10A/K15A/L17E/V20D, and both C and D comprise C10A/K15A/L17R/V20K;
 both A and B comprise C10A/K15A/L17E/V20E, and both C and D comprise C10A/K15A/L17R/V20R;
 both A and B comprise C10A/K15A/L17D/T119D, and both C and D comprise C10A/K15A/L17K/V121K;

both A and B comprise C10A/K15A/L17D/V121E, and both C and D comprise C10A/K15A/L17K/V121R;

both A and B comprise C10A/K15A/L17E/T119D, and both C and D comprise C10A/K15A/L17R/V121K;

both A and B comprise C10A/K15A/L17E/V121E, and both C and D comprise C10A/K15A/L17R/V121R;

both A and B comprise C10A/K15A/V20D/T119D, and both C and D comprise C10A/K15A/V20K/V121K;

both A and B comprise C10A/K15A/V20D/V121E, and both C and D comprise C10A/K15A/V20K/V121R;

both A and B comprise C10A/K15A/V20E/T119D, and both C and D comprise C10A/K15A/V20R/V121K; or

both A and B comprise C10A/K15A/V20E/V121E, and both C and D comprise C10A/K15A/V20R/V121R.

19. The TTR protein complex according to any one of claims 1-15, wherein each of A, B, C, and D comprise the amino acid sequence of SEQ ID NO: 1 with the following mutations:

both A and B comprise C10A/K15A/V20E/T119D, and both C and D comprise C10A/K15A/V20R/V121K;

both A and B comprise C10A/K15A/L17D/T119D, and both C and D comprise C10A/K15A/L17K/V121K;

both A and B comprise C10A/K15A/L17E/T119D, and both C and D comprise C10A/K15A/L17R/V121K;

both A and B comprise C10A/K15A/L17E/V20D, and both C and D comprise C10A/K15A/L17R/V20K;

both A and B comprise C10A/K15A/L17D/V20D, and both C and D comprise C10A/K15A/L17K/V20K; or

both A and B comprise C10A/K15A/L17E/V121E, and both C and D comprise C10A/K15A/L17R/V121R.

20. The TTR protein complex according to any one of claims 1-19, wherein said TTR protein complex is attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins or peptides.

21. The TTR protein complex according to claim 20, wherein said TTR protein complex is attached to 1, 2, 3, or 4 antigen binding proteins or peptides.

22. The TTR protein complex according to claim 20 or 21, wherein said antigen binding protein or peptide is attached to the TTR protein complex at the C-terminus of a TTR subunit.

23. The TTR protein complex according to claim 20 or 21, wherein said antigen binding protein or peptide is attached to the TTR protein complex at the N-terminus of a TTR subunit.

24. The TTR protein complex according to any one of claims 20-23, wherein said TTR protein complex is:

directly attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins; or
attached to 1, 2, 3, 4, 5, 6, 7, or 8 antigen binding proteins via a linker.

25. The TTR protein complex according to any one of claims 20-23, wherein said TTR protein complex is:

directly attached to 1, 2, 3, or 4 antigen binding proteins; or
attached to 1, 2, 3, or 4 antigen binding proteins via a linker.

26. The TTR protein complex according to claim 25, wherein said linker is an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids.

27. The TTR protein complex according to claim 26, wherein said linker is an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 amino acids.

28. The TTR protein complex according to claim 27, wherein said linker is an amino acid-based linker comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids.

29. The TTR protein complex according to claim 28, wherein said linker is an amino acid-based linker comprising 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

30. The TTR protein complex according to claim 26, wherein said linker is G, GG, GGG, GGGG, GGGGG, GGGGGG, GGGGGGG, GGGGGGGG, GGGGGGGGG, or GGGGGGGGGG.

31. The TTR protein complex according to claim 26, wherein said linker is $G(G_xB_y)_rG_z$ and wherein:

G = glycine;
B = any amino acid;
x = 1-15;
y = 1-5;

z = 1-15; and
r = 1-20.

32. The TTR protein complex according to claim 30, wherein:

B = Q, S, A, E, P, T, K, R, D or N;
x = 4;
y = 1;
z = 4; and
r = 1.

33. The TTR protein complex according to claim 26, wherein said linker is selected from the list comprising: GG, GGGG, GGGSGG, GGGSGGGG, and GGAGGGAGGG.

34. The TTR protein complex according to any one of claims 20-33, wherein said TTR protein complex is attached to two antigen binding proteins, wherein said antigen binding proteins bind different antigens.

35. The TTR protein complex according to any one of claims 20-33, wherein said TTR protein complex is attached to four antigen binding proteins, wherein said antigen binding proteins bind to at least two different antigens.

36. The TTR protein complex according to any one of claims 20-35, wherein the antigen binding proteins are antibodies.

37. The TTR protein complex according to any one of claims 20-35, wherein the antigen binding proteins are Fabs or scFvs.

38. The TTR protein complex according to claim 37, wherein the antigen binding proteins are Fabs.

39. The TTR protein complex according to any one of claims 20-35, wherein the antigen binding proteins are a mixture of antibodies and Fabs.

40. A pharmaceutical composition comprising a TTR protein complex according to any one of claims 1-39.

~~41. A method of treating cancer using a TTR protein complex according to any one of claims 1-39.~~

~~42-41.~~ Use of a TTR protein complex according to any one of claims 1-39 in the manufacture of a pharmaceutical composition for the treatment of cancer.

~~43.42.~~ A TTR protein complex according to any one of claims 1-39 for use in ~~the treatment of~~
~~cancer~~therapy.

~~44.43.~~ One or more isolated nucleic acid(s) encoding a TTR subunit, a TTR subunit fused or
linked to an antigen binding protein or peptide (such as an antibody or Fab), or a TTR protein complex
according to any one of claims 1-39.

~~45.44.~~ An expression vector comprising a nucleic acid of claim ~~44~~43.

~~46.45.~~ A recombinant host cell comprising a nucleic acid of claim ~~44~~43 or a vector of claim
~~45~~44.

~~47.46.~~ The recombinant host cell of claim 45, wherein said host cell is a Chinese hamster ovary
(CHO) cell, E5 cell, baby hamster kidney (BHK) cell, monkey kidney (COS) cell, human hepatocellular
carcinoma cell, or human embryonic kidney 293 (HEK 293) cell.

~~48.47.~~ A method of making a TTR protein complex according to any one of claims 1-39, said
method comprising:

- a) culturing the recombinant host cell of claim ~~46~~45 or ~~47~~46; and
- b) isolating the TTR protein complex from said culture.