What is claimed is:

1. An isolated polypeptide comprising at least one monomer of a single variable domain of a NB agent that specifically binds to human DR5.

2. The polypeptide of claim 1, wherein said single variable domain is selected from the group consisting of a) singe variable domains comprising one or more complementarity determining region 3 (CDR3) sequences selected from any one or more of SEQ ID NOs: 63-68; b) single variable domains comprising one or more complementarity determining region 3 (CDR3) sequences with 90% identity to at least one CDR3 selected from any one or more of SEQ ID NOs: 63-68; and c) single variable domains comprising one or more complementarity determining region 3 (CDR3) sequences with at least 95% identity to at least one CDR3 selected from any one or more of SEQ ID NOs: 63-68.

3. The polypeptide of claim 1, wherein said single variable domain is selected from the group consisting of a) singe variable domains with SEQ ID NOs: 1 – 5, 26, 30 and 87; and b) single variable domains with at least 95% identity to at least one single variable domain with SEQ ID NOs: 1 – 5, 26, 30 and 87.

4. An isolated polypeptide comprising at least three, at least four, or at least five monomeric subunits of a single variables domain that specifically binds to human DR5, wherein said subunits are optionally linked by a polypeptide linker.

5. The polypeptide of claim 4, wherein said polypeptide comprises identical monomers of the single variable domain and wherein said single variable domain is selected from the group consisting of a) singe variable domains with SEQ ID NOs: 1 – 5, 26, 30 and 87; b) single variable domains with at least 90% identity to at least one single variable domain with SEQ ID NOs: 1 – 5, 26, 30 and 87 and c) single variable domains with at least 95% identity to at least one single variable domain with SEQ ID NOs: 1 – 5, 26, 30 and 87.

6. The polypeptide of claim 4 comprising an amino sequence that is selected from one or more subunits of the group consisting of a) amino acid sequences with SEQ ID NO: 6, 9, 12-14, 17, 20, 27 and 31; and b) amino acid sequences with at least 90% identity to said amino acid sequence with SEQ ID NO: 6, 9, 12-14, 17, 20, 27 and 31.

7. The polypeptide of claim 4 that specifically binds to human DR5 and wherein said polypeptide has an in vitro potency (IC_{50}) against a panel of at least 2 tumor cell lines

selected from the group consisting of Colo205, Jurkat, Molt4, H2122, H226 and H2052 that is equal or lower than 100nM.

8. The polypeptide of claim 7, wherein said polypeptide has an in vitro potency that is equal or lower than 10 nM, that is equal or lower than 1 nM, or that is equal or lower than 100 pM.

9. An isolated polypeptide comprising an amino sequence that is selected from the group consisting of one or more amino acid sequences of SEQ ID NO: 1 through 22, 26 through 33, 87 and 88.

10. The isolated polypeptide according to claim 1, comprising at least one complementarity determining region (CDR) having at least 60, 70, 80, 90, 95 or 100 percent sequence identity with at least one of the CDR regions depicted in any of SEQ ID NO: 41 to 44 (CDR1); SEQ ID NO: 51 to 55 (CDR2); SEQ ID NO: 63 to 68 (CDR3), more preferably SEQ ID NO: 51 to 55 and SEQ ID NO: 63 to 68.

11. The isolated polypeptide according to any of the preceding claims that is a humanized immunoglobulin, a camelized immunoglobulin or an immunoglobulin obtainable by affinity optimization technique, or a fragment thereof.

12. The isolated polypeptide according to any of the preceding claims that essentially consists of a light chain variable domain sequence, e.g., a V_L-sequence; or of a heavy chain variable domain sequence, e.g., a V_H-sequence, or is a domain antibody, a single domain antibody, a dAb and a camelid antibody or fragment, including but not limited to a V_{HH} sequence.

13. The isolated polypeptide according to any of the preceding claims that essentially consists of a V_{HH} sequence that,

(a) has at least 90% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's 1-22, 26-40, 87-88, and 103-104, or of the amino acid sequences encoded by at least one of SEQ ID NOS: 96-99, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;

and in which

(b) optionally one or more of the amino acid positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to Kabat numbering are humaneered.

14. The compound that comprises or essentially consists of one or more polypeptide according to any of any preceding claims, and optionally further comprises one or more other groups, residues, moieties or binding units, wherein said compound is capable of enhancing cell apoptosis.

15. The compound of any of claims 14, wherein said at least three, four, five or more monovalent binding polypeptides are all directed against the same binding region of human DR5.

16. The compound of any of claims 14, wherein said at least one monovalent binding polypeptide is directed against one binding region of DR5 and at least one other monovalent binding polypeptide is directed against another distinct binding region of DR5 or a binding region of another DR5.

17. The polypeptide according to any of claim 1 for use as a drug.

18. The polypeptide of claim 17, for use as an anti-cancer therapeutic.

19. A polypeptide of claim 18 and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

20. A method for the prevention and/or treatment of a disorder that can be treated by enhancement of cell apoptosis, said method comprising administering, to a subject in need thereof, a pharmaceutically effective amount of at least one polypeptide according to any above claim.

21. The method of claim 20, wherein said disorder is a proliferative disease that is responsive to agonism of DR5 activity.

22. The method of claim 21, wherein said proliferative disease is selected from:

a) one or more solid cancers selected from primary and metastatic cancers such as renal cell carcinoma, and cancers of the lung (e.g., small cell lung cancer "SCLC" and non-small cell lung cancer "NSCLC"), pancreas, hematopoietic malignancy, glioma, astrocytoma, mesothelioma, colorectal cancers, prostate cancer, osteosarcoma, melanoma, lymphoma lymphoma (including but not limited to Burkitt's Lymphoma), breast cancer, endometrial cancer, liver cancer, gastric cancer, skin cancer, ovarian cancer and squamous cell cancers of any origin (including but not limited to squamous cell cancers of the lung, head and neck, breast, thyroid, cervix, skin, and/or esophageal);

b) one or more liquid cancers selected from leukemias including especially a T-cell leukemia such as acute T-cell leukemia (T-ALL), acute B-cell leukemia (B-ALL), chronic

myelogenous leukemia (CML), acute myelogenous leukemia (AML), plasma cell myeloma and multiple myeloma (MM); and

c) one or more non-cancer indications, said indications comprising one or more of inflammatory and autoimmune diseases, such as systemic lupus erythematosus, Hashimoto's disease, rheumatoid arthritis, graft-versus-host disease, Sjogren's syndrome, pernicious anemia, Addison disease, scleroderma, Goodpasture's syndrome, Crohn's disease, autoimmune hemolytic anemia, sterility, myasthenia gravis, multiple sclerosis, Basedow's disease, thrombotic throbocytopenia, thrombopenia purpurea, insulin-dependent diabetes mellitus, allergy; asthma, atopic disease; arteriosclerosis; myocarditis; cardiomyopathy; globerula nephritis; and hypoplastic anemia.

23. The method of claim 22, wherein the proliferative disease is pancreatic cancer.

24. The method of claim 22, wherein the proliferative disease is T-ALL.

25. The method of claim 22, wherein the proliferative disease is mesothelioma.

26. The method of claim 22, wherein the proliferative disease is squamous cell carcinoma of any tissue origin.

27. The method of claim 22, wherein the proliferative disease is AML.

28. The method of claim 22, wherein the proliferative disease is melanoma.

29. The method of claim 22, wherein the proliferative disease is myeloma.

30. The isolated polypeptides according to any one or more of the preceding claims wherein the CDRs are calculated according to either Kabat and/or Chothia rules.

31. The NB construct according to any one or more of the preceding claims that binds the DR5 epitope as provided in Table 29A or that binds the DR5 epitope as provided in Table 30A.

What is claimed is:

1. An isolated polypeptide comprising at least one monomer of a single variable domain comprising the sequence of the complementarity determining region 3 (CDR3) sequence of SEQ ID NO: 66, the sequence of the complementarity determining region 2 (CDR2) sequence of SEQ ID NO: 53, and the sequence of the complementarity determining region 1 (CDR1) sequence of SEQ ID NO: 43, wherein the isolated polypeptide specifically binds to human DR5.

2. The polypeptide of claim 1, wherein said single variable domain comprises:

(a) the sequence of SEQ ID NO: 30; or

(b) the sequence of SEQ ID NO: 30 wherein one or more of the amino acid positions 1-30, 36-49, 66-97 and/or 112-122 have been substituted, modified or deleted and/or wherein one or more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97 and/or 112-122.

3. An isolated polypeptide comprising at least three, at least four, or at least five monomeric subunits of a single variable domain that specifically binds to human DR5, wherein said subunits are linked by a linker, and wherein the variable domain comprises the sequence of the complementarity determining region 3 (CDR3) sequence of SEQ ID NO: 66, the sequence of the complementarity determining region 2 (CDR2) sequence of SEQ ID NO: 53, and the sequence of the complementarity determining region 1 (CDR1) sequence of SEQ ID NO: 43.

4. The polypeptide of claim 1, wherein said single variable domain comprises the sequence of SEQ ID NO: 30.

5. The polypeptide of claim 3 wherein the single variable domain comprises the amino acid sequence of SEQ ID NO: 30 wherein one or more of the amino acid positions 1-30, 36-49, 66-97 and/or 112-122 have been substituted, modified or deleted, and/or wherein one or

more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97 and/or 112-122.

6. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 5, 20, 21, 22, 30, 31, 32, 33, or 87.

7. A composition comprising an isolated polypeptide comprising at least one monomer of a single variable domain that specifically binds to human DR5, wherein the single variable domain comprises complementarity determining region (CDR) sequences having the sequences of SEQ ID NO: 43 (CDR1); SEQ ID NO: 53 (CDR2); and SEQ ID NO: 66 (CDR3), further comprising at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

8. The isolated polypeptide according to claim 1 that is a humanized immunoglobulin, a camelized immunoglobulin or an immunoglobulin obtainable by an affinity optimization technique, or a fragment thereof.

9. An isolated polypeptide that has:

(a) the amino acid sequence of SEQ ID NO: 30; or

(b) the amino acid sequence of SEQ ID NO: 30, in which one or more of the amino acid positions 11, 37, 44, 45, 47, 83, 84, 112, 113 and 117 of SEQ ID NO: 30 are humaneered, substituted, modified or deleted and/or wherein one or more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97 and/or 112-122, wherein the isolated polypeptide specifically binds to human DR5.

10. An isolated polypeptide comprising one or more copies of:

(a) the sequence of SEQ ID NO: 30; and/or

(b) the sequence of SEQ ID NO: 30 wherein one or more of the amino acid positions 1-30, 36-49, 66-97 and/or 112-122 have been substituted, modified or deleted, and/or wherein one or more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97

and/or 112-122, and wherein the isolated polypeptide is capable of enhancing cell apoptosis and wherein the isolated polypeptide specifically binds to human DR5.

11. The polypeptide according to claim 10, wherein the polypeptide comprises at least three, four, five or more copies of the sequence of SEQ ID NO: 30 wherein one or more of the amino acid positions 1-30, 36-49, 66-97 and/or 112-122 have been substituted, modified or deleted, and/or wherein one or more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97 and/or 112-122, and wherein the copies constitute monovalent binding polypeptides that are all directed against the same binding region of human DR5.

12. An isolated polypeptide comprising at least three, four, five or more copies of the sequence of SEQ ID NO: 30 wherein one or more of the amino acid positions 1-30, 36-49, 66-97 and/or 112-122 have been substituted, modified or deleted and/or wherein one or more amino acids have been inserted between any amino acids at 1-30, 36-49, 66-97 and/or 112-122, wherein the isolated polypeptide is capable of enhancing cell apoptosis and wherein the copies constitute monovalent binding polypeptides that are all directed against the same binding region of human DR5, and wherein the said isolated polypeptide specifically binds to human DR5.

13. The polypeptide according to claim 10 for use as a drug.

14. The polypeptide of claim 10, for use as an anti-cancer therapeutic.

15. A composition comprising the polypeptide of claim 10, further comprising at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

16. A polypeptide comprising the CDR1 sequence of SEQ ID NO: 43, the CDR2 sequence of SEQ ID NO: 53, and the CDR3 sequence of SEQ ID NO: 66, wherein the polypeptide is capable of contacting, within 5 Angstroms, amino acids H86, S88, E89, D90, D93, I95, K98, Q101, D102, L111, F112, R115, and R118 of a DR5 polypeptide of SEQ ID NO: 89.

17. The polypeptide of claim 3 wherein the single variable domain comprises the amino acid sequence of SEQ ID NO: 30.