polypeptides and two light chain polypeptides) that adopt a three-dimensional structure shaped like a capital letter "Y," which is linked together by disulphide bonds. The "arms" of the "Y" structure contain the variable regions of the antibody and the central cleft region is located at the junction between the two arms of the "Y" structure.

Accordingly, in one ~~aspect~~embodiment, the disclosure features a therapeutic antibody, or a therapeutically- active fragment of the antibody, wherein the antibody or fragment comprises at least two therapeutic peptides and wherein at least one of the therapeutic peptides is incorporated into the constant region of a light chain polypeptide at a position that is structurally permissive to allow for the therapeutic peptide to be presented at the central cleft of the antibody. The therapeutic antibody, or fragment thereof, can also contain a heavy chain polypeptide that contains at least one of the therapeutic peptides. The at least one therapeutic peptide is incorporated into the hinge region as follows: (a) into the hinge region of the heavy chain polypeptide; (b) at the junction between the amino-terminus of the hinge region and the region of the heavy chain polypeptide that is upstream to the hinge region; (c) at the junction between the carboxy-terminus of the hinge region and the region of the heavy chain polypeptide that is downstream of the hinge region; or (d) at a location starting within fewer than 20 amino acids upstream of the amino-terminus, or fewer than 20 amino acids downstream of the carboxy-terminus, of the hinge region of the heavy chain polypeptide.

In one aspect, there is provided a therapeutic antibody, or a therapeutically-active fragment of the antibody, wherein the antibody or fragment comprises at least two therapeutic peptides, wherein at least one of the therapeutic peptides is incorporated into the constant region of a light chain polypeptide of the antibody or fragment as (i) an insertion within a β-turn region of the constant region; (ii) a replacement within a β-turn region of the constant region; (iii) an addition to the carboxy-terminus of the constant region; (iv) an insertion into a position that is downstream from the final β-sheet structure in the constant region; or (v) an addition at a position that is downstream from the final β-sheet structure in the constant region, and wherein the therapeutic antibody or therapeutically-active fragment thereof comprises the variable region of a heavy chain polypeptide and the variable region of a light chain polypeptide.

In another aspect, there is provided a therapeutic antibody, or a therapeutically-active fragment of the antibody, wherein the antibody or fragment comprises a heavy chain polypeptide comprising at least two therapeutic peptides, wherein each therapeutic peptide is a thrombopoietin (TPO) mimetic peptide, wherein at least one of the therapeutic peptides is incorporated: (a) into the

hinge region of the heavy chain polypeptide; (b) at the junction between the amino-terminus of the hinge region and the region of the heavy chain polypeptide that is upstream to the hinge region; (c) at the junction between the carboxy-terminus of the hinge region and the region of the heavy chain polypeptide that is downstream of the hinge region; or (d) at a location starting within fewer than 20 amino acids upstream of the amino- terminus, or fewer than 20 amino acids downstream of the carboxy-terminus, of the hinge region of the heavy chain polypeptide, and wherein the therapeutic antibody or therapeutically-active fragment thereof comprises the variable region of the heavy chain polypeptide.

In yet another aspect, a therapeutic antibody, or a therapeutically-active fragment of the antibody, comprising at least two therapeutic peptides, wherein the therapeutic antibody or therapeutically-active fragment thereof comprises the variable region of a heavy chain polypeptide and the variable region of a light chain polypeptide, and wherein at least one of the therapeutic peptides is incorporated: (a) into the hinge region of the heavy chain polypeptide; (b) at the junction between the amino-terminus of the hinge region and the region of the heavy chain polypeptide that is upstream to the hinge region; (c) at the junction between the carboxy-terminus of the hinge region and the region of the heavy chain polypeptide that is downstream of the hinge region; or (d) at a location starting within fewer than 20 amino acids upstream of the amino- terminus, or fewer than 20 amino acids downstream of the carboxy-terminus, of the hinge region of the heavy chain polypeptide.

In yet another aspect, there is provided a composition comprising the therapeutic antibody, or therapeutically-active fragment, as disclosed herein, and a pharmaceutically acceptable carrier.

In yet another aspect, there is provided the use of a composition comprising a therapeutically-effective amount of the therapeutic antibody, or therapeutically-active fragment thereof, as disclosed herein, in the manufacture of a medicament for increasing platelet production in a subject in need thereof.

In yet another aspect, there is provided an isolated polypeptide comprising the amino acid sequence depicted in SEQ ID NO:10 or SEQ ID NO:12.

In yet another aspect, there is provided an isolated nucleic acid encoding a polypeptide comprising the amino acid sequence depicted in SEQ ID NO:10 or SEQ ID NO:12.

In another ~~aspect~~embodiment, the disclosure features a therapeutic antibody, or a therapeutic ally- active fragment of the antibody, wherein the antibody or fragment comprises at least two therapeutic peptides and wherein a heavy chain polypeptide of the antibody

comprises at least one of the therapeutic peptides incorporated into the heavy chain as follows: (a) into the hinge region of the heavy chain polypeptide; (b) at the junction between the amino-terminus of the hinge region and the region of the heavy chain polypeptide that is upstream to the hinge region; (c) at the junction between the carboxy-terminus of the hinge region and the region of the heavy chain polypeptide that is downstream of the hinge region; or (d) at a location starting within fewer than 20 amino acids upstream of the amino-terminus, or fewer than 20 amino acids downstream of the carboxy-terminus, of the hinge region of the heavy chain polypeptide. The therapeutic antibody, or therapeutically-active fragment thereof, can

In another ~~aspect~~embodiment, the disclosure features a composition of any of the therapeutic antibodies or therapeutically-active fragments thereof and a pharmaceutically acceptable carrier. For example, in some embodiments the compositions can contain any of the TPO mimetic antibodies described herein.

In some embodiments, any of the compositions described herein can be formulated for use as a single dose. In some embodiments, any of the compositions described herein can be formulated for use in multiple doses.

In some embodiments, any of the compositions described herein can also contain at least one active agent for reducing the side-effects of radiation exposure or for reducing the side-effects of chemotherapy. The at least one active agent can be selected from the group consisting of an antibiotic, an anesthetic, an antiemetic, a steroid, a chelating agent, and a diuretic.

In some embodiments, any of the compositions described herein can also include at least one additional active agent for increasing platelet production in a subject. The at least one additional active agent can be, e.g., eltrombopag, oprelvekin, romiplostim, pegfilgrastim, an erythropoietin- stimulating agent (ESA), or any other suitable agent described herein or known in the art.

In yet another ~~aspect~~embodiment, the disclosure features a method for increasing platelet production in a subject. The method includes the step of administering to a subject in need thereof a therapeutically-effective amount of a composition comprising any of the TPO mimetic antibodies or therapeutically-active fragments thereof described herein.

In another ~~aspect~~embodiment the disclosure features a method for increasing platelet production in a subject, which method includes administering to a subject in need thereof a composition comprising a therapeutically-effective amount of any of the TPO mimetic antibodies or therapeutically-active fragments thereof described herein.

In some embodiments of any of the methods described herein, the subject is a mammal, e.g., a human or a non-human primate. In some embodiments of any of the methods described herein, the subject is a non-human mammal.

In some embodiments of any of the methods described herein, the subject has a disorder related to insufficient platelet counts. The disorder can be, e.g., any one of Bernard-Soulier syndrome, idiopathic thrombocytopenic purpura, Wiskott-Aldrich syndrome, hypersplenism, thrombotic microangiopathies, disseminated intravascular

two, three, four, five, six, seven, eight, nine, 10, or 15 or more) dose(s) of the composition.

In some embodiments of any of the methods described herein, the composition can be administered to the subject: (i) prior to and (ii) during or following the chemotherapy or the radiotherapy regimen.

In some embodiments of any of the methods described herein, the chemotherapy or radiotherapy regimen can be (i) more potent or (ii) administered more frequently to a subject than would be safely possible in the absence of administering the composition.

In some embodiments, any of the methods described herein can also include administering to the subject at least one additional agent for reducing the side-effects of a chemotherapy regimen or a radiotherapy regimen. The at least one agent can be selected from the group consisting of an antibiotic, an anesthetic, an antiemetic, and a steroid such as an androstenediol. In some embodiments, any of the methods described herein can also include administering to the subject at least one additional agent for increasing platelet production. The at least one additional agent for increasing platelet production can be one selected from the group consisting of eltrombopag, oprelvekin, romiplostim, pegfilgrastim, and an ESA.

In some embodiments, any of the methods described herein can also include, after administering the composition, monitoring the subject for an increase in platelet levels.

In yet another ~~aspect~~embodiment, the disclosure features a method for increasing platelet production in a subject, which method includes administering to a subject in need thereof a single dose of a platelet production-increasing amount of a TPO mimetic antibody, or a therapeutic ally- active fragment thereof, described herein. The disclosure also features a method for treating a subject for radiation exposure or a platelet level-decreasing chemotherapy regimen. The method includes administering to a subject a single dose of a platelet production-increasing amount of a TPO mimetic antibody, or a therapeutic ally-active fragment thereof, described herein. The subject can be one who has undergone, who is likely to undergo, or is scheduled to undergo, a chemotherapy or radiotherapy regimen. The subject can be one who has been, who is likely to be, or is scheduled to be, exposed to radiation.

In yet another ~~aspect~~embodiment, the disclosure features a method for increasing platelet production in a subject, which method includes administering to a subject in need thereof multiple (e.g., at least two, three, four, five, six, seven, eight, nine, 10, 11, or 12 or more) doses of a platelet production-increasing amount of a TPO mimetic antibody, or a therapeutic ally- active ~~fragment~~ thereof, described herein. The disclosure also features a method for treating a subject for radiation exposure or a platelet level-decreasing chemotherapy regimen. The method includes administering to a subject multiple doses of a platelet production-increasing amount of a TPO mimetic antibody, or a therapeutic ally-active fragment thereof, described herein. The subject can be one who has undergone, who is likely to undergo, or is scheduled to undergo, a chemotherapy or radiotherapy regimen. The subject can be one who has been, who is likely to be, or is scheduled to be, exposed to radiation.

In another ~~aspect~~embodiment, the disclosure features a nucleic acid encoding a polypeptide containing at least one (e.g., at least two, three, four, five, six, or eight) TPO mimetic peptide(s), wherein the amino acid sequence of the polypeptide is at least 80 (e.g., at least 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100) % identical to the amino acid sequence depicted in SEQ ID NO: 10 or SEQ ID NO: 12. In some embodiments, the nucleic acid encodes a polypeptide having an amino acid sequence that is at least 80% identical to amino acids 1-214 of SEQ ID NO: 10 or at least 80% identical to amino acids 1-218 of SEQ ID NO: 10, wherein amino acids 219-232 of SEQ ID NO: 10 are 100% identical between the amino acid sequence and SEQ ID NO: 10. In some embodiments, the nucleic acid encodes a polypeptide having an amino acid sequence that is at least 80% identical to amino acids 1-234 of SEQ ID NO: 12 and at least 80% identical to amino acids 249-461 of SEQ ID NO: 12, wherein amino acids 235-248 of SEQ ID NO: 12 are 100% identical between the amino acid sequence and SEQ ID NO: 12. In some embodiments, the nucleic acid encodes an amino acid sequence that is at least 80% identical to amino acids 1-232 of SEQ ID NO: 12 and at least 80% identical to amino acids 251-461 of SEQ ID NO: 12, wherein amino acids 235-248 of SEQ ID NO: 12 are 100% identical between the amino acid sequence and SEQ ID NO: 12.

Percent (%) amino acid sequence or nucleic acid sequence identity is defined as the percentage of amino acids, or nucleic acids, in a candidate sequence that are identical to the amino acids or nucleic acids in a reference sequence, after aligning the