

CLAIMS

1. A method of reducing immunogenicity, comprising administering to a patient receiving or having received a biological therapeutic agent, an effective amount of B cell inhibitor that is non-depletional.
2. The method of claim 1, wherein the biological therapeutic agent is selected from one or more of: gene therapy, gene editing therapy, messenger RNA (mRNA) therapy, oncolytic viruses, enzyme replacement therapy, antibody therapy, protein therapeutics, and cell therapy.
3. The method of claim 1, wherein the biological therapeutic agent is gene therapy.
4. The method of any one of claims 1-3, wherein the B cell inhibitor is a CD32B×CD79B bi-specific antibody capable of immunospecifically binding an epitope of CD32B and an epitope of CD79B.
5. The method of claim 4, wherein the CD32B×CD79B bi-specific antibody comprises:
 - (A) a VL_{CD32B} domain that comprises the amino acid sequence of SEQ ID NO: 1;
 - (B) a VH_{CD32B} domain that comprises the amino acid sequence of SEQ ID NO: 2;
 - (C) a VL_{CD79B} domain that comprises the amino acid sequence of SEQ ID NO: 3; and
 - (D) a VH_{CD79B} domain that comprises the amino acid sequence of SEQ ID NO: 4.
6. The method of claim 4, wherein said CD32B x CD79B bi-specific antibody is an Fc diabody comprising:
 - (A) a first polypeptide chain that comprises the amino acid sequence of SEQ ID NO: 5;
 - (B) a second polypeptide chain that comprises the amino acid sequence of SEQ ID NO: 6; and
 - (C) a third polypeptide chain that comprises the amino acid sequence of SEQ ID NO: 7.
7. The method of claim 6, comprising administering the Fc diabody at a dose of between about 5 mg/kg and about 40 mg/kg, and at a dosage regimen of between one dose per 2 week and one dose per 6 weeks.
8. The method of claim 6, comprising administering the Fc diabody at a dose of about 10 mg/kg, and at a dosage regimen of one dose per 4 weeks.
9. The method of claim 6, comprising administering 3 doses of the Fc diabody at a dose of about 10 mg/kg at 2-6 week intervals.
10. The method of claim 9, comprising administering a first dose about 2-6 weeks prior to administration of the biological therapeutic agent, a second dose at about the same time as

administration of the biological therapeutic agent, and a third dose about 2-6 weeks after administration of the biological therapeutic agent.

11. The method of claim 6, wherein the Fc diabody results in inhibition of its own immunogenicity upon administration, with lower prevalence and/or titers of anti-drug antibodies (ADA) at increased doses.

12. The method of claim 11, wherein the ADA does not neutralize the Fc diabody.

13. The method of claim 6, wherein the Fc diabody, in a dose-dependent fashion, binds to at least 80% B cells upon administration, and remains bound to at least 50% of the B cells for at least 4 weeks after last administration.

14. The method of claim 6, wherein the Fc diabody results in sustained inhibition of immunoglobulin production without depleting circulating B cells.

15. The method of claim 14, wherein the immunoglobulin includes IgM, IgA, IgG and IgE.

16. The method of any one of claims 1-15, further comprising monitoring the patient by examining the presence of specific antibodies against the biological therapeutic agent.

17. The method of claim 16, further comprising administering one or more dose of the B cell inhibitor to further modulate immunogenicity.

18. The method of any one of claims 1-15, further comprising co-administering one or more immune-modulators.

19. The method of claim 18, wherein the one or more immune-modulators are selected from sirolimus, rapamycin, abatacept, teplizumab and immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*.