We claim:

1. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a heavy chain comprising an amino acid sequence shown in SEQ ID NO:1, wherein said amino acid sequence comprises one or more amino acid modifications.
2. The isolated monoclonal antibody of claim 1, wherein the modification is selected from the group consisting of a substitution, an insertion or a deletion.
3. The isolated monoclonal antibody of claim 2, wherein the modification is a substitution.
4. The isolated monoclonal antibody of claim 3, wherein the substitution is at a position selected from the group consisting of Q1, R30 S31, G33, M34, S35, S50, I51, R52, S54, S55, S56, K99 and F104.
5. The isolated monoclonal antibody of claim 4, wherein the substitution is selected from the group consisting of Q1E, R30S, S31P, S31V, G33A, G33K, G33P, M34I, M34K, S35L, S35D, S50A, I51D, I51E, R52S, S54F, S54D, S55A, S55G, S55R, S56G, K99V, K99L, and F104Y.
6. The isolated monoclonal antibody of claim 1, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.
7. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody comprises two or more substitutions selected from the group consisting of Q1E, R30S, S31P, S31V, G33A, G33K, G33P, M34I, M34K, S35L, S35D, S50A, I51D, I51E, R52S, S54F, S54D, S55A, S55G, S55R, S56G, K99V, K99L, and F104Y.
8. The isolated monoclonal antibody of claim 7, wherein the monoclonal antibody comprises the amino acid sequence shown in SEQ ID NO:1, wherein said sequence comprises the following substitutions selected from the group consisting of:

   (a) G33A+S35D+S55R+K99L;

   (b) G33P+I51D+S54F;

   (c) G33P+S35D+S54F+K99L;

   (d) I51D+S54F+K99L;

   (e) M34I+S35D+S55R+K99L;

   (f) M34K+S35D+S55R+K99L;

(g) Q1E+R30S+S35D+S55G+S56G+K99L;

(h) Q1E+R30S+S35D+S55R+S56G+K99L;

(i) Q1E+S31V+S50A+I51D+S55R+S56G+K99V;

(j) Q1E+S35D+S55R+K99L;

(k) R30S+S31V+I51D+S55R+K99V;

(l) R30S+S35D+S55R+K99L;

(m) S31V+G33A+I51D+S55R+K99V;

(n) S31V+G33P+I51D+S54F+K99V;

(o) S31V+G33P+S35D;

(p) S31V+I51D+R52S+S55R+K99V;

(q) S31V+I51D+S54F+K99V;

(r) S31V+I51D+S55R;

(s) S31V+I51D+S55R+K99L;

(t) S31V+I51D+S55R+K99V;

(u) S31V+I51D+S55R+S56G+K99V;

(v) S31V+I51E+S55R+K99V;

(w) S31V+K99V;

(x) S31V+S35D;

(y) S31V+S35D+I51D+K99V;

(z) S31V+S35D+S54F;

(aa) S31V+S35D+S55R;

(bb) S31V+S35L+I51D+S54F+K99V;

(cc) S31V+S35L+I51E+S54F+K99V;

(dd) S31V+S50A+I51D+S55R+K99V;

(ee) S31V+S54F+K99L;

(ff) S35D+I51D+K99L;

(gg) S35D+I51D+S55R+K99V;

(hh) S35D+I51E+S55R+K99L;

(ii) S35D+K99L;

(jj) S35D+R52S+K99L;

(kk) S35D+R52S+S55R+K99L;

(ll) S35D+S50A+K99L;

(mm) S35D+S50A+S55R+K99L;

(nn) S35D+S54F+S55R+K99L;

(oo) S35D+S55G+K99L;

(pp) S35D+S55R+K99L;

(qq) S35D+S55R+S56G+K99L;

(rr) S35D+S56G+K99L; and

(ss) S35L+S54F+K99V.

9. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a light chain comprising an amino acid sequence shown in SEQ ID NO:2, wherein said amino acid sequence comprises one or more amino acid modifications.

10. The isolated monoclonal antibody of claim 9, wherein the modification is selected from the group consisting of a substitution, an insertion or a deletion.

11. The isolated monoclonal antibody of claim 10, wherein the modification is a substitution.

12. The isolated monoclonal antibody of claim 11, wherein the substitution is at a position selected from the group consisting of D1, I2, A13, S21, N26, R28, N29, A32, H33, Y48, Y49, N51, N52, P54, G56, E80, S89, D91, D92, G93, V94, P95 and V96.

13. The isolated monoclonal antibody of claim 12, wherein the substitution is selected from the group consisting of D1S, I2Y, A13S, S21T, N26A, R28P, N29K, A32N, H33Y, Y48F, Y49R, N51S, N51V, N52G, P54L, G56D, E80M, S89A, D91L, D91R, D91W, D91K, D92S, D92T, G93S, V94T, P95V, P95A, V96G, V96M and V96W.

14. The isolated monoclonal antibody of claim 9, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

15. The isolated monoclonal antibody of claim 9, wherein the monoclonal antibody comprises two or more substitutions selected from the group consisting of D1S, I2Y, A13S, S21T, N26A, R28P, N29K, A32N, H33Y, Y48F, Y49R, N51S, N51V, N52G, P54L, G56D, E80M, S89A, D91L, D91R, D91W, D91K, D92S, D92T, G93S, V94T, P95V, P95A, V96G, V96M and V96W

16. The isolated monoclonal antibody of claim 15, wherein the monoclonal antibody comprises the amino acid sequence shown in SEQ ID NO:2, wherein said sequence comprises the following substitutions selected from the group consisting of:

(a) A13S+Y48F+N51V+D91W;

(b) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+E80M+D91L+D92S+V94T+V96W;

(c) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51S+E80M+D91L+D92S+V94T+V96W;

(d) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+D91W;

(e) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(f) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+Y49R+N51S+E80M+D91L+D92S+V94T+V96W;

(g) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+D91W;

(h) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(i) D1S+Y48F+N51V+D91W;

(j) D91L+V96W;

(k) H33Y+Y48F+N51V+D91W;

(l) I2Y+Y48F+N51V+D91W;

(m) N26A+Y48F+N51V+D91W;

(n) N29K+Y48F+N51V+D91W;

(o) N51V+D91K;

(p) N51V+D91W;

(q) R28P+Y48F+N51V+D91W;

(r) S21T+Y48F+N51V+D91W;

(s) Y48F+D91K;

(t) Y48F+D91L+D92S+V96W;

(u) Y48F+D91L+G93S+V96W;

(v) Y48F+D91L+P95V+V96W;

(w) Y48F+D91L+V94T+V96W;

(x) Y48F+D91L+V96W;

(y) Y48F+D91W;

(z) Y48F+N51S+D91L+V96W;

(aa) Y48F+N51V;

(bb) Y48F+N51V+D91L;

(cc) Y48F+N51V+D91L+V96W;

(dd) Y48F+N51V+D91W;

(ee) Y48F+N51V+D91W+D92S;

(ff) Y48F+N51V+D91W+G93S;

(gg) Y48F+N51V+D91W+P95V;

(hh) Y48F+N51V+D91W+V94T;

(ii) Y48F+N51V+E80M+D91W;

(jj) Y48F+N51V+G56D+V96W;

(kk) Y48F+N51V+S89A+D91W;

(ll) Y48F+N51V+S89A+D91W+D92S+G93S+V94T+P95A;

(mm) Y48F+N51V+V96W;

(nn) Y48F+N52G;

(oo) Y48F+N52G+D91L+V96W; and

(pp) Y48F+S89A+D91L+V96W.

17. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises:

(a) a heavy chain comprising an amino acid sequence shown in SEQ ID NO:1, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications; and

(b) a light chain comprising an amino acid sequence shown in SEQ ID NO:2, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

18. The isolated monoclonal antibody of claim 17, wherein the heavy chain modification is a substitution.

19. The isolated monoclonal antibody of claim 18, wherein the heavy chain substitution comprises the substitution selected from the group consisting of Q1E, R30S, S31P, S31V, G33A, G33K, G33P, M34I, M34K, S35L, S35D, S50A, I51D, I51E, R52S, S54F, S54D, S55A, S55G, S55R, S56G, K99V, K99L, and F104Y.

20. The isolated monoclonal antibody of claim 17, wherein the heavy chain comprises the two or more substitutions.

21. The isolated monoclonal antibody of claim 20, wherein the heavy chain comprises the substitutions selected from the group consisting of:

(a) G33A+S35D+S55R+K99L;

(b) G33P+I51D+S54F;

(c) G33P+S35D+S54F+K99L;

(d) I51D+S54F+K99L;

(e) M34I+S35D+S55R+K99L;

(f) M34K+S35D+S55R+K99L;

(g) Q1E+R30S+S35D+S55G+S56G+K99L;

(h) Q1E+R30S+S35D+S55R+S56G+K99L;

(i) Q1E+S31V+S50A+I51D+S55R+S56G+K99V;

(j) Q1E+S35D+S55R+K99L;

(k) R30S+S31V+I51D+S55R+K99V;

(l) R30S+S35D+S55R+K99L;

(m) S31V+G33A+I51D+S55R+K99V;

(n) S31V+G33P+I51D+S54F+K99V;

(o) S31V+G33P+S35D;

(p) S31V+I51D+R52S+S55R+K99V;

(q) S31V+I51D+S54F+K99V;

(r) S31V+I51D+S55R;

(s) S31V+I51D+S55R+K99L;

(t) S31V+I51D+S55R+K99V;

(u) S31V+I51D+S55R+S56G+K99V;

(v) S31V+I51E+S55R+K99V;

(w) S31V+K99V;

(x) S31V+S35D;

(y) S31V+S35D+I51D+K99V;

(z) S31V+S35D+S54F;

(aa) S31V+S35D+S55R;

(bb) S31V+S35L+I51D+S54F+K99V;

(cc) S31V+S35L+I51E+S54F+K99V;

(dd) S31V+S50A+I51D+S55R+K99V;

(ee) S31V+S54F+K99L;

(ff) S35D+I51D+K99L;

(gg) S35D+I51D+S55R+K99V;

(hh) S35D+I51E+S55R+K99L;

(ii) S35D+K99L;

(jj) S35D+R52S+K99L;

(kk) S35D+R52S+S55R+K99L;

(ll) S35D+S50A+K99L;

(mm) S35D+S50A+S55R+K99L;

(nn) S35D+S54F+S55R+K99L;

(oo) S35D+S55G+K99L;

(pp) S35D+S55R+K99L;

(qq) S35D+S55R+S56G+K99L;

(rr) S35D+S56G+K99L; and

(ss) S35L+S54F+K99V.

22. The isolated monoclonal antibody of claim 17, wherein the light chain modification is a substitution.

23. The isolated monoclonal antibody of claim 22, wherein the light chain substitution comprises the substitution selected from the group consisting of D1S, I2Y, A13S, S21T, N26A, R28P, N29K, A32N, H33Y, Y48F, Y49R, N51S, N51V, N52G, P54L, G56D, E80M, S89A, D91L, D91R, D91W, D91K, D92S, D92T, G93S, V94T, P95V, P95A, V96G, V96M and V96W.

24. The isolated monoclonal antibody of claim 17, wherein the light chain comprises two or more substitutions.

25. The isolated monoclonal antibody of claim 24, wherein the light chain comprises the substitutions selected from the group consisting of:

(a) A13S+Y48F+N51V+D91W;

(b) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+E80M+D91L+D92S+V94T+V96W;

(c) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51S+E80M+D91L+D92S+V94T+V96W;

(d) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+D91W;

(e) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(f) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+Y49R+N51S+E80M+D91L+D92S+V94T+V96W;

(g) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+D91W;

(h) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(i) D1S+Y48F+N51V+D91W;

(j) D91L+V96W;

(k) H33Y+Y48F+N51V+D91W;

(l) I2Y+Y48F+N51V+D91W;

(m) N26A+Y48F+N51V+D91W;

(n) N29K+Y48F+N51V+D91W;

(o) N51V+D91K;

(p) N51V+D91W;

(q) R28P+Y48F+N51V+D91W;

(r) S21T+Y48F+N51V+D91W;

(s) Y48F+D91K;

(t) Y48F+D91L+D92S+V96W;

(u) Y48F+D91L+G93S+V96W;

(v) Y48F+D91L+P95V+V96W;

(w) Y48F+D91L+V94T+V96W;

(x) Y48F+D91L+V96W;

(y) Y48F+D91W;

(z) Y48F+N51S+D91L+V96W;

(aa) Y48F+N51V;

(bb) Y48F+N51V+D91L;

(cc) Y48F+N51V+D91L+V96W;

(dd) Y48F+N51V+D91W;

(ee) Y48F+N51V+D91W+D92S;

(ff) Y48F+N51V+D91W+G93S;

(gg) Y48F+N51V+D91W+P95V;

(hh) Y48F+N51V+D91W+V94T;

(ii) Y48F+N51V+E80M+D91W;

(jj) Y48F+N51V+G56D+V96W;

(kk) Y48F+N51V+S89A+D91W;

(ll) Y48F+N51V+S89A+D91W+D92S+G93S+V94T+P95A;

(mm) Y48F+N51V+V96W;

(nn) Y48F+N52G;

(oo) Y48F+N52G+D91L+V96W; and

(pp) Y48F+S89A+D91L+V96W.

26. The isolated monoclonal antibody of claim 17, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

27. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises an amino acid sequence shown in SEQ ID NO:3 comprising one or more amino acid modifications.

28. The isolated monoclonal antibody of claim 27, wherein the modification is selected from the group consisting of a substitution, an insertion or a deletion.

29. The isolated monoclonal antibody of claim 28, wherein the modification is a substitution.

30. The isolated monoclonal antibody of claim 29, wherein the substitution is at a position selected from the group consisting of Q1, S30, N32, S37, G44, I53, K55, S57, K58, N61, D62, H103, H107, G109 and Y112.

31. The isolated monoclonal antibody of claim 30, wherein the substitution is selected from the group consisting of Q1E, S30R, N32D, N32E, S33G, S37N, G44S, I53T, K55Y, S57K, S57R, K58M, N61G, N61T, D62I, D62R, D62Q, D62L, D62S, D62V, D62N, D62K, H103D, H103G, H107M, G109A and Y112D.

32. The isolated monoclonal antibody of claim 27, wherein the monoclonal antibody comprises two or more substitutions selected from the group consisting of Q1E, S30R, N32D, N32E, S33G, S37N, G44S, I53T, K55Y, S57K, S57R, K58M, N61G, N61T, D62I, D62R, D62Q, D62L, D62S, D62V, D62N, D62K, H103D, H103G, H107M, G109A and Y112D

33. The isolated monoclonal antibody of claim 32, wherein the monoclonal antibody comprises the amino acid sequence shown in SEQ ID NO:3, wherein said sequence comprises the following substitutions selected from the group consisting of:

(a) D62Q+H107M+Y112D;

(b) D62Q+Y112D;

(c) D62R+H107M+Y112D;

(d) D62R+Y112D;

(e) D62S+H107M+Y112D;

(f) N32D+D62K+Y112D;

(g) N32D+D62Q+H107M+Y112D;

(h) N32D+D62Q+Y112D;

(i) N32D+D62R+H103D;

(j) N32D+D62R+H103D+H107M+Y112D;

(k) N32D+D62R+H107M;

(l) N32D+D62R+H107M+Y112D;

(m) N32D+D62R+Y112D;

(n) N32D+D62S+H107M+Y112D;

(o) N32D+G44S+D62R+Y112D;

(p) N32D+I53T+D62Q+Y112D;

(q) N32D+I53T+D62R+Y112D;

(r) N32D+K55Y+D62Q+Y112D;

(s) N32D+K55Y+D62R+Y112D;

(t) N32D+S37N+D62R+Y112D;

(u) Q1E+N32D+D62R+Y112D;

(v) Q1E+N32D+G44S+K55Y+D62R+Y112D;

(w) N32D+G44S+K55Y+D62R+Y112D

(x) S30R+S57K;

(y) N61G+D62V; and

(z) K58M+D62N.

34. The isolated monoclonal antibody of claim 27, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

35. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises an amino acid sequence shown in SEQ ID NO:4 comprising one or more amino acid modifications.

36. The isolated monoclonal antibody of claim 35, wherein the modification is selected from the group consisting of a substitution, an insertion or a deletion.

37. The isolated monoclonal antibody of claim 36, wherein the modification is a substitution.

38. The isolated monoclonal antibody of claim 37, wherein the substitution is at a position selected from the group consisting of M4, V30, F31, S32, D33, N35, T36, Y37, N39, L42, K44, Q50, L51, Y54, K55, G56, S57, A60, S61, D97 and S98.

39. The isolated monoclonal antibody of claim 38, wherein the substitution is selected from the group consisting of M4I, M4L, V30L, F31I, F31M, F31Y, F31H, S32L, S32R, S32Y, D33F, D33R, N35I, N35L, N35T, N35V, T36N, Y37F, N39D, L42Q, K44R, Q50R, L51R, Y54F, K55L, G56D, G56A, G56V, S57Y, A60D, S61C, D97M, D97T and S98H.

40. The isolated monoclonal antibody of claim 35, wherein the monoclonal antibody comprises two or more substitutions selected from the group consisting of M4I, M4L, V30L, F31I, F31M, F31Y, F31H, S32L, S32R, S32Y, D33F, D33R, N35I, N35L, N35T, N35V, T36N, Y37F, N39D, L42Q, K44R, Q50R, L51R, Y54F, K55L, G56D, G56A, G56V, S57Y, A60D, S61C, D97M, D97T and S98H.

41. The isolated monoclonal antibody of claim 40, wherein the monoclonal antibody comprises the amino acid sequence shown in SEQ ID NO:4, wherein said sequence comprises the following substitutions selected from the group consisting of:

(a) D33F+N35I;

(b) D33F+N35I+D97T;

(c) D33F+N35T+Y37F;

(d) D33R+N35I;

(e) D33R+N35I+D97T;

(f) D33R+N35T;

(g) F31H+S32R+D33F+N35I+D97T;

(h) F31I+D33F+N35I;

(i) F31I+D33F+N35I+D97T;

(j) F31I+D33F+N35I+K44R;

(k) F31I+D33F+N35I+L42Q;

(l) F31I+D33F+N35I+S98H;

(m) F31I+D33F+N35I+T36N;

(n) F31I+D33R;

(o) F31I+D33R+N35I;

(p) F31I+N35I;

(q) F31I+S32R+D33F+N35I+D97T;

(r) F31I+S32R+D33F+N35T;

(s) F31I+S32R+D33R+N35I+D97T;

(t) F31I+S32R+N35I+D97T;

(u) F31M+D33F;

(v) F31M+D33F+N35I;

(w) F31M+D33F+N35T;

(x) F31M+D33F+N35T+Y37F;

(y) F31M+D33R;

(z) F31M+D33R+N35I;

(aa) F31M+S32L+D33R+N35I+D97T;

(bb) F31M+S32R+D33F+D97T;

(cc) F31M+S32R+D33F+N35I;

(dd) F31M+S32R+D33F+N35I+D97T;

(ee) F31M+S32R+D33R;

(ff) F31M+S32R+D33R+N35I;

(gg) F31M+S32R+D33R+N35I+D97T;

(hh) F31M+S32R+D33R+N35T;

(ii) F31Y+S32R+D33F+N35I+D97T;

(jj) M4I+S32R+D33F+N35I+D97T;

(kk) M4L+S32R+D33F+N35I+D97T;

(ll) N35T+D97T;

(mm)S32R+D33F;

(nn) S32R+D33F+N35I;

(oo) S32R+D33F+N35I+A60D+D97T;

(pp) S32R+D33F+N35I+D97T;

(qq) S32R+D33F+N35I+D97T+S98H;

(rr) S32R+D33F+N35I+G56V+D97T;

(ss) S32R+D33F+N35I+K44R+D97T;

(tt) S32R+D33F+N35I+K55L+D97T;

(uu) S32R+D33F+N35I+L42Q+D97T;

(vv) S32R+D33F+N35I+L51R+D97T;

(ww) S32R+D33F+N35I+N39D+D97T;

(xx) S32R+D33F+N35I+Q50R+D97T;

(yy) S32R+D33F+N35I+T36N+D97T;

(zz) S32R+D33F+N35T;

(aaa) S32R+D33R;

(bbb) S32R+D33R+N35I;

(ccc) S32R+D33R+N35I+D97T;

(ddd) S32R+D33R+N35T;

(eee) S32R+N35I;

(fff) S32R+N35T;

(ggg) S32R+N35T+D97T;

(hhh) V30L+F31I+D33F+N35I;

(iii) V30L+S32R+D33F+N35I+D97T;

(jjj) V30L+S32R+D33F+N35I+T36N+D97T;

(kkk) V30L+S32R+N35I+T36N;

(lll) N35V+G56D;

(mmm) N35L+G56A; and

(nnn) D33F+Y54F.

42. The isolated monoclonal antibody of claim 35, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

43. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises:

(a) a heavy chain comprising an amino acid sequence shown in SEQ ID NO:3, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications; and

(b) a light chain comprising an amino acid sequence shown in SEQ ID NO:4, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

44. The isolated monoclonal antibody of claim 43, wherein the heavy chain modification is a substitution.

45. The isolated monoclonal antibody of claim 44, wherein the heavy chain substitution comprises the substitution selected from the group consisting of Q1E, S30R, N32D, N32E, S33G, S37N, G44S, I53T, K55Y, S57K, S57R, K58M, N61G, N61T, D62I, D62R, D62Q, D62L, D62S, D62V, D62N, D62K, H103D, H103G, H107M, G109A and Y112D.

46. The isolated monoclonal antibody of claim 43, wherein the heavy chain comprises the two or more substitutions.

47. The isolated monoclonal antibody of claim 46, wherein the heavy chain comprises the substitutions selected from the group consisting of:

(a) D62Q+H107M+Y112D;

(b) D62Q+Y112D;

(c) D62R+H107M+Y112D;

(d) D62R+Y112D;

(e) D62S+H107M+Y112D;

(f) N32D+D62K+Y112D;

(g) N32D+D62Q+H107M+Y112D;

(h) N32D+D62Q+Y112D;

(i) N32D+D62R+H103D;

(j) N32D+D62R+H103D+H107M+Y112D;

(k) N32D+D62R+H107M;

(l) N32D+D62R+H107M+Y112D;

(m) N32D+D62R+Y112D;

(n) N32D+D62S+H107M+Y112D;

(o) N32D+G44S+D62R+Y112D;

(p) N32D+I53T+D62Q+Y112D;

(q) N32D+I53T+D62R+Y112D;

(r) N32D+K55Y+D62Q+Y112D;

(s) N32D+K55Y+D62R+Y112D;

(t) N32D+S37N+D62R+Y112D;

(u) Q1E+N32D+D62R+Y112D;

(v) Q1E+N32D+G44S+K55Y+D62R+Y112D;

(w) N32D+G44S+K55Y+D62R+Y112D

(x) S30R+S57K;

(y) N61G+D62V; and

(z) K58M+D62N.

48. The isolated monoclonal antibody of claim 43, wherein the light chain modification is a substitution.

49. The isolated monoclonal antibody of claim 48, wherein the light chain substitution comprises the substitution selected from the group consisting M4I, M4L, V30L, F31I, F31M, F31Y, F31H, S32L, S32R, S32Y, D33F, D33R, N35I, N35L, N35T, N35V, T36N, Y37F, N39D, L42Q, K44R, Q50R, L51R, Y54F, K55L, G56D, G56A, G56V, S57Y, A60D, S61C, D97M, D97T and S98H.

50. The isolated monoclonal antibody of claim 43, wherein the light chain comprises two or more substitutions.

51. The isolated monoclonal antibody of claim 50, wherein the light chain comprises the substitutions selected from the group consisting of:

(a) D33F+N35I;

(b) D33F+N35I+D97T;

(c) D33F+N35T+Y37F;

(d) D33R+N35I;

(e) D33R+N35I+D97T;

(f) D33R+N35T;

(g) F31H+S32R+D33F+N35I+D97T;

(h) F31I+D33F+N35I;

(i) F31I+D33F+N35I+D97T;

(j) F31I+D33F+N35I+K44R;

(k) F31I+D33F+N35I+L42Q;

(l) F31I+D33F+N35I+S98H;

(m) F31I+D33F+N35I+T36N;

(n) F31I+D33R;

(o) F31I+D33R+N35I;

(p) F31I+N35I;

(q) F31I+S32R+D33F+N35I+D97T;

(r) F31I+S32R+D33F+N35T;

(s) F31I+S32R+D33R+N35I+D97T;

(t) F31I+S32R+N35I+D97T;

(u) F31M+D33F;

(v) F31M+D33F+N35I;

(w) F31M+D33F+N35T;

(x) F31M+D33F+N35T+Y37F;

(y) F31M+D33R;

(z) F31M+D33R+N35I;

(aa) F31M+S32L+D33R+N35I+D97T;

(bb) F31M+S32R+D33F+D97T;

(cc) F31M+S32R+D33F+N35I;

(dd) F31M+S32R+D33F+N35I+D97T;

(ee) F31M+S32R+D33R;

(ff) F31M+S32R+D33R+N35I;

(gg) F31M+S32R+D33R+N35I+D97T;

(hh) F31M+S32R+D33R+N35T;

(ii) F31Y+S32R+D33F+N35I+D97T;

(jj) M4I+S32R+D33F+N35I+D97T;

(kk) M4L+S32R+D33F+N35I+D97T;

(ll) N35T+D97T;

(mm)S32R+D33F;

(nn) S32R+D33F+N35I;

(oo) S32R+D33F+N35I+A60D+D97T;

(pp) S32R+D33F+N35I+D97T;

(qq) S32R+D33F+N35I+D97T+S98H;

(rr) S32R+D33F+N35I+G56V+D97T;

(ss)S32R+D33F+N35I+K44R+D97T;

(tt) S32R+D33F+N35I+K55L+D97T;

(uu) S32R+D33F+N35I+L42Q+D97T;

(vv) S32R+D33F+N35I+L51R+D97T;

(ww) S32R+D33F+N35I+N39D+D97T;

(xx) S32R+D33F+N35I+Q50R+D97T;

(yy) S32R+D33F+N35I+T36N+D97T;

(zz) S32R+D33F+N35T;

(aaa) S32R+D33R;

(bbb) S32R+D33R+N35I;

(ccc) S32R+D33R+N35I+D97T;

(ddd) S32R+D33R+N35T;

(eee) S32R+N35I;

(fff) S32R+N35T;

(ggg) S32R+N35T+D97T;

(hhh) V30L+F31I+D33F+N35I;

(iii) V30L+S32R+D33F+N35I+D97T;

(jjj) V30L+S32R+D33F+N35I+T36N+D97T;

(kkk) V30L+S32R+N35I+T36N;

(lll) N35V+G56D;

(mmm) N35L+G56A; and

(nnn) D33F+Y54F.

52. The isolated monoclonal antibody of claim 43, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

53. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises:

(a) a heavy chain comprising an amino acid sequence shown in SEQ ID NO:1, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications; and

(b) a light chain comprising an amino acid sequence shown in SEQ ID NO:4, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

54. The isolated monoclonal antibody of claim 53, wherein the heavy chain modification is a substitution.

55. The isolated monoclonal antibody of claim 54, wherein the heavy chain substitution comprises the substitution selected from the group consisting of Q1E, R30S, S31P, S31V, G33A, G33K, G33P, M34I, M34K,S35L, S35D, S50A, I51D, I51E, R52S, S54F, S54D, S55A, S55G, S55R, S56G, K99V, K99L, and F104Y.

56. The isolated monoclonal antibody of claim 53, wherein the heavy chain comprises the two or more substitutions.

57. The isolated monoclonal antibody of claim 56, wherein the heavy chain comprises the substitutions selected from the group consisting of:

(a) G33A+S35D+S55R+K99L;

(b) G33P+I51D+S54F;

(c) G33P+S35D+S54F+K99L;

(d) I51D+S54F+K99L;

(e) M34I+S35D+S55R+K99L;

(f) M34K+S35D+S55R+K99L;

(g) Q1E+R30S+S35D+S55G+S56G+K99L;

(h) Q1E+R30S+S35D+S55R+S56G+K99L;

(i) Q1E+S31V+S50A+I51D+S55R+S56G+K99V;

(j) Q1E+S35D+S55R+K99L;

(k) R30S+S31V+I51D+S55R+K99V;

(l) R30S+S35D+S55R+K99L;

(m)S31V+G33A+I51D+S55R+K99V;

(n) S31V+G33P+I51D+S54F+K99V;

(o) S31V+G33P+S35D;

(p) S31V+I51D+R52S+S55R+K99V;

(q) S31V+I51D+S54F+K99V;

(r) S31V+I51D+S55R;

(s) S31V+I51D+S55R+K99L;

(t) S31V+I51D+S55R+K99V;

(u) S31V+I51D+S55R+S56G+K99V;

(v) S31V+I51E+S55R+K99V;

(w) S31V+K99V;

(x) S31V+S35D;

(y) S31V+S35D+I51D+K99V;

(z) S31V+S35D+S54F;

(aa) S31V+S35D+S55R;

(bb) S31V+S35L+I51D+S54F+K99V;

(cc) S31V+S35L+I51E+S54F+K99V;

(dd) S31V+S50A+I51D+S55R+K99V;

(ee) S31V+S54F+K99L;

(ff) S35D+I51D+K99L;

(gg) S35D+I51D+S55R+K99V;

(hh) S35D+I51E+S55R+K99L;

(ii) S35D+K99L;

(jj) S35D+R52S+K99L;

(kk) S35D+R52S+S55R+K99L;

(ll) S35D+S50A+K99L;

(mm)S35D+S50A+S55R+K99L;

(nn) S35D+S54F+S55R+K99L;

(oo) S35D+S55G+K99L;

(pp) S35D+S55R+K99L;

(qq) S35D+S55R+S56G+K99L;

(rr) S35D+S56G+K99L; and

(ss) S35L+S54F+K99V.

58. The isolated monoclonal antibody of claim 53, wherein the light chain modification is a substitution.

59. The isolated monoclonal antibody of claim 58, wherein the light chain substitution comprises the substitution selected from the group consisting of M4I, M4L, V30L, F31I, F31M, F31Y, F31H, S32L, S32R, S32Y, D33F, D33R, N35I, N35L, N35T, N35V, T36N, Y37F, N39D, L42Q, K44R, Q50R, L51R, Y54F, K55L, G56D, G56A, G56V, S57Y, A60D, S61C, D97M, D97T and S98H.

60. The isolated monoclonal antibody of claim 53, wherein the light chain comprises two or more substitutions.

61. The isolated monoclonal antibody of claim 60, wherein the light chain comprises the substitutions selected from the group consisting of:

(a) D33F+N35I;

(b) D33F+N35I+D97T;

(c) D33F+N35T+Y37F;

(d) D33R+N35I;

(e) D33R+N35I+D97T;

(f) D33R+N35T;

(g) F31H+S32R+D33F+N35I+D97T;

(h) F31I+D33F+N35I;

(i) F31I+D33F+N35I+D97T;

(j) F31I+D33F+N35I+K44R;

(k) F31I+D33F+N35I+L42Q;

(l) F31I+D33F+N35I+S98H;

(m) F31I+D33F+N35I+T36N;

(n) F31I+D33R;

(o) F31I+D33R+N35I;

(p) F31I+N35I;

(q) F31I+S32R+D33F+N35I+D97T;

(r) F31I+S32R+D33F+N35T;

(s) F31I+S32R+D33R+N35I+D97T;

(t) F31I+S32R+N35I+D97T;

(u) F31M+D33F;

(v) F31M+D33F+N35I;

(w) F31M+D33F+N35T;

(x) F31M+D33F+N35T+Y37F;

(y) F31M+D33R;

(z) F31M+D33R+N35I;

(aa) F31M+S32L+D33R+N35I+D97T;

(bb) F31M+S32R+D33F+D97T;

(cc) F31M+S32R+D33F+N35I;

(dd) F31M+S32R+D33F+N35I+D97T;

(ee) F31M+S32R+D33R;

(ff) F31M+S32R+D33R+N35I;

(gg) F31M+S32R+D33R+N35I+D97T;

(hh) F31M+S32R+D33R+N35T;

(ii) F31Y+S32R+D33F+N35I+D97T;

(jj) M4I+S32R+D33F+N35I+D97T;

(kk) M4L+S32R+D33F+N35I+D97T;

(ll) N35T+D97T;

(mm) S32R+D33F;

(nn) S32R+D33F+N35I;

(oo) S32R+D33F+N35I+A60D+D97T;

(pp) S32R+D33F+N35I+D97T;

(qq) S32R+D33F+N35I+D97T+S98H;

(rr) S32R+D33F+N35I+G56V+D97T;

(ss) S32R+D33F+N35I+K44R+D97T;

(tt) S32R+D33F+N35I+K55L+D97T;

(uu) S32R+D33F+N35I+L42Q+D97T;

(vv) S32R+D33F+N35I+L51R+D97T;

(ww) S32R+D33F+N35I+N39D+D97T;

(xx) S32R+D33F+N35I+Q50R+D97T;

(yy) S32R+D33F+N35I+T36N+D97T;

(zz) S32R+D33F+N35T;

(aaa) S32R+D33R;

(bbb) S32R+D33R+N35I;

(ccc) S32R+D33R+N35I+D97T;

(ddd) S32R+D33R+N35T;

(eee) S32R+N35I;

(fff) S32R+N35T;

(ggg) S32R+N35T+D97T;

(hhh) V30L+F31I+D33F+N35I;

(iii) V30L+S32R+D33F+N35I+D97T;

(jjj) V30L+S32R+D33F+N35I+T36N+D97T;

(kkk) V30L+S32R+N35I+T36N;

(lll) N35V+G56D;

(mmm) N35L+G56A; and

(nnn) D33F+Y54F.

62. The isolated monoclonal antibody of claim 53, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

63. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises:

(a) a heavy chain comprising an amino acid sequence shown in SEQ ID NO:3, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications; and

(b) a light chain comprising an amino acid sequence shown in SEQ ID NO:2, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

64. The isolated monoclonal antibody of claim 63, wherein the heavy chain modification is a substitution.

65. The isolated monoclonal antibody of claim 64, wherein the heavy chain substitution comprises the substitution selected from the group consisting of Q1E, S30R, N32D, N32E, S33G, S37N, G44S, I53T, K55Y, S57K, S57R, K58M, N61G, N61T, D62I, D62R, D62Q, D62L, D62S, D62V, D62N, D62K, H103D, H103G, H107M, G109A and Y112D.

66. The isolated monoclonal antibody of claim 63, wherein the heavy chain comprises the two or more substitutions.

67. The isolated monoclonal antibody of claim 66, wherein the heavy chain comprises the substitutions selected from the group consisting of:

(a) D62Q+H107M+Y112D;

(b) D62Q+Y112D;

(c) D62R+H107M+Y112D;

(d) D62R+Y112D;

(e) D62S+H107M+Y112D;

(f) N32D+D62K+Y112D;

(g) N32D+D62Q+H107M+Y112D;

(h) N32D+D62Q+Y112D;

(i) N32D+D62R+H103D;

(j) N32D+D62R+H103D+H107M+Y112D;

(k) N32D+D62R+H107M;

(l) N32D+D62R+H107M+Y112D;

(m) N32D+D62R+Y112D;

(n) N32D+D62S+H107M+Y112D;

(o) N32D+G44S+D62R+Y112D;

(p) N32D+I53T+D62Q+Y112D;

(q) N32D+I53T+D62R+Y112D;

(r) N32D+K55Y+D62Q+Y112D;

(s) N32D+K55Y+D62R+Y112D;

(t) N32D+S37N+D62R+Y112D;

(u) Q1E+N32D+D62R+Y112D;

(v) Q1E+N32D+G44S+K55Y+D62R+Y112D;

(w) N32D+G44S+K55Y+D62R+Y112D

(x) S30R+S57K;

(y) N61G+D62V; and

(z) K58M+D62N.

68. The isolated monoclonal antibody of claim 63, wherein the light chain modification is a substitution.

69. The isolated monoclonal antibody of claim 68, wherein the light chain substitution comprises the substitution selected from the group consisting of D1S, I2Y, A13S, S21T, N26A, R28P, N29K, A32N, H33Y, Y48F, Y49R, N51S, N51V, N52G, P54L, G56D, E80M, S89A, D91L, D91R, D91W, D91K, D92S, D92T, G93S, V94T, P95V, P95A, V96G, V96M and V96W.

70. The isolated monoclonal antibody of claim 63, wherein the light chain comprises two or more substitutions.

71. The isolated monoclonal antibody of claim 70, wherein the light chain comprises the substitutions selected from the group consisting of:

(a) A13S+Y48F+N51V+D91W;

(b) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+E80M+D91L+D92S+V94T+V96W;

(c) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51S+E80M+D91L+D92S+V94T+V96W;

(d) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+D91W;

(e) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(f) D1S+I2Y+A13S+S21T+R28P+N29K+Y48F+Y49R+N51S+E80M+D91L+D92S+V94T+V96W;

(g) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+D91W;

(h) D1S+I2Y+A13S+S21T+R28P+Y48F+N51V+E80M+S89A+D91W+D92S+G93S+V94T;

(i) D1S+Y48F+N51V+D91W;

(j) D91L+V96W;

(k) H33Y+Y48F+N51V+D91W;

(l) I2Y+Y48F+N51V+D91W;

(m) N26A+Y48F+N51V+D91W;

(n) N29K+Y48F+N51V+D91W;

(o) N51V+D91K;

(p) N51V+D91W;

(q) R28P+Y48F+N51V+D91W;

(r) S21T+Y48F+N51V+D91W;

(s) Y48F+D91K;

(t) Y48F+D91L+D92S+V96W;

(u) Y48F+D91L+G93S+V96W;

(v) Y48F+D91L+P95V+V96W;

(w) Y48F+D91L+V94T+V96W;

(x) Y48F+D91L+V96W;

(y) Y48F+D91W;

(z) Y48F+N51S+D91L+V96W;

(aa) Y48F+N51V;

(bb) Y48F+N51V+D91L;

(cc) Y48F+N51V+D91L+V96W;

(dd) Y48F+N51V+D91W;

(ee) Y48F+N51V+D91W+D92S;

(ff) Y48F+N51V+D91W+G93S;

(gg) Y48F+N51V+D91W+P95V;

(hh) Y48F+N51V+D91W+V94T;

(ii) Y48F+N51V+E80M+D91W;

(jj) Y48F+N51V+G56D+V96W;

(kk) Y48F+N51V+S89A+D91W;

(ll) Y48F+N51V+S89A+D91W+D92S+G93S+V94T+P95A;

(mm)Y48F+N51V+V96W;

(nn) Y48F+N52G;

(oo) Y48F+N52G+D91L+V96W; and

(pp) Y48F+S89A+D91L+V96W.

72. The isolated monoclonal antibody of claim 63, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

73. The antibody of claim any of the preceding claims, wherein blood clotting time in the presence of the antibody is shortened.

74. The antibody of any of the preceding claims, wherein the antibody has an increased affinity to TFPI.

75. The antibody of any of the preceding claims, wherein the antibody has an increased blocking activity of TFPI.

76. A pharmaceutical composition comprising a therapeutically effective amount of the monoclonal antibody of any of claims 1-72 and a pharmaceutically acceptable carrier.

77. A method for treating genetic or acquired deficiencies or defects in coagulation comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 76 to a patient.

78. The method of claim 77, wherein the method treats hemophilia A, B or C.

79. A method for shortening bleeding time comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 76 to a patient.

80. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a heavy chain comprising an amino acid sequence shown in SEQ ID NO:1, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications.

81. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a light chain comprising an amino acid sequence shown in SEQ ID NO:2, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

82. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a heavy chain comprising an amino acid sequence shown in SEQ ID NO:3, wherein said heavy chain amino acid sequence comprises one or more amino acid modifications.

83. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a light chain comprising an amino acid sequence shown in SEQ ID NO:4, wherein said light chain amino acid sequence comprises one or more amino acid modifications.

84. A vector comprising the nucleic acid molecule of claims 80, 81, 82 or 83.

85. A host cell comprising the vector of claim 84.

86. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:5, 6, 7, 8, 9, 10, 11, 19, 20, 21, 22, 23, 24, 25, and 26.

87. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor wherein the antibody comprises a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:12, 13, 14, 15, 16, 17, 18, 27, 28, 29, 30, 31, 32, 33, and 34.

CLAIMS

1. An invention not claimed in any divisional application.