CLAIMS:

1. A modified urokinase-type plasminogen activator (u-PA) polypeptide, comprising one or more amino acid modifications selected from among modifications corresponding to V41R, R35Q, R35W, R35Y, H37E, H37Y, Y40Q, D60aP, L97bA, L97bG, T97aI and H99Q, and conservative amino acid modifications thereof selected from among R35F or N; H37R, Q, W or F; V41K; D60aS; T97aD, L or V; L97bS; and H99N, whereby the modified u-PA polypeptide has increased activity and/or specificity for a complement protein compared to the ~~unmodified~~ active form of the unmodified u-PA polypeptide, wherein:

further~~the~~ amino acid modifications are selected from among replacements, insertions and deletions in the primary sequence of the modified u-PA polypeptide;

the modified u-PA polypeptide cleaves a complement protein to thereby inhibit or reduce complement activation compared to the unmodified u-PA polypeptide that does not contain the amino acid modifications;

the complement protein is C3;

residues are numbered by chymotrypsin numbering;

the unmodified u-PA polypeptide comprises the sequence set forth in any of SEQ ID NOs: 1-6; and

the modified u-PA polypeptide has at least 90% or 95% sequence identity with a polypeptide of any of SEQ ID Nos. 1-6~~; and~~, or a catalytically active fragment thereof that includes the amino acid replacement position(s).

~~the conservative modifications are selected from among R35Y, W, F or N; H37R, Q, E, W or F; V41K; D60aS; T97aD, L or V; L97bG or S; and H99N.~~

2. The modified u-PA polypeptide of claim 1, comprising one or more amino acid modifications selected from among amino acid modifications corresponding to R35Q, H37Y, V41R, Y40Q, D60aP, L97bA, T97aI, and H99Q.

3. The modified u-PA polypeptide of claim 1 or claim 2, wherein the modified u-PA polypeptide has reduced activity or specificity for cleavage of a substrate sequence in plasminogen compared to the unmodified u-PA polypeptide of any one of SEQ ID NOs:1-6 or catalytically active portion thereof.

4. The modified u-PA polypeptide of any of claims 1-3, wherein the unmodified u-PA polypeptide consists of the sequence of amino acids set forth in any of SEQ ID NOs:1-6.

5. The modified u-PA polypeptide of any of claims 1-4, wherein the modified u-PA polypeptide has 1 or up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid replacements, insertions, or deletions, compared to the unmodified u-PA polypeptide of any of SEQ ID NOs: 1-6 or a catalytically active portion thereof.

6. The modified u-PA polypeptide of any of claims 1-5, comprising the amino acid replacement(s) V41R or V38E/V41R.

7. The modified u-PA polypeptide of claim 6, further comprising the amino acid replacement V38E or H37Y or the replacements H37Y/V38E.

8. The modified u-PA polypeptide of any of claims 1-7, comprising the replacements R35Y/H37K or R35Q/H37K or R35Y/H37K/V38E or R35Q/H37K/V38E.

9. The modified u-PA polypeptide of any of claims 1-8, further comprising the amino acid replacement L97bA; and/or

further comprising R35Q; and/or

further comprising H99Q; and/or

further comprising D60aP; and/or

further comprising T97aI; and/or

further comprising the amino acid replacement T39Y, T39W, or T39F or comprising a conservative replacement selected from T39M or T39L.

10. The modified u-PA polypeptide of any of claims 1-9, comprising the amino acid modifications R35Q/H37Y/V41R or V38E/V41R/Y149R or R35Y/H37S/V38E/V41R or R35Y/H37Y/V38E/V41R.

11. The modified u-PA polypeptide of any of claims 1-7, comprising the amino acid modifications

R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aT/Y60bT/T97aI/L97bA/H99Q/C122S/Y149R or

R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aT/Y60bT/T97aI/L97bA/H99Q/Y149R.

12. The modified u-PA polypeptide of any of claims 1-11, wherein:

the modified u-PA polypeptide comprises the modifications in the protease domain set forth in Table 14; and

has an ED_{50} of 100 nM or less.

13. The modified u-PA polypeptide of claim 12, comprising the amino acid replacement(s) V41R or V38E/V41R.

14. The modified u-PA polypeptide of claim 13, further comprising an amino acid replacement at one or more of positions R35, H37 and V38.

15. The modified u-PA polypeptide of any of claims 1-14, comprising the modifications selected from:
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L;
R35W/R36Q/H37S/V38P/T39Y/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K82R/T97aI/L97bA/H99Q/K110aR/C122S/Y149R/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K/K179R;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K92R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35V/R36H/H37G/V38E/T39W/Y40H/V41R/Y60bW/T97aI/L97bA/H99Q/C122S/Y149E/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K92S/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K61R/K62R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K/K179S;
R35W/H37P/R37aN/V38E/T39Y/V41R/D60aP/Y60bL/T97aI/L97bA/H99Q/C122S;
F30Y/R35W/R36T/H37S/V38S/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157R/Q192Y;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K61S/K62S/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
R35A/H37E/R37aG/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L;
R35W/R36Q/H37S/V38T/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151P/M157R;
F30Y/R35W/H37Y/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R;
V38E/T39W/V41R/D60aW/Y60bP/L97bG/H99L/C122S;
R35W/R36K/H37S/V38E/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157S/Q192H;
R35Q/H37Y/R37aP/V38E/T39Y/V41R/D60aQ/Y60bP/T97aI/L97bA/H99Q/C122S/Y149R;

I17V/F30Y/R35Q/R36H/H37W/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/M157K/T158A;
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192H;
F30Y/R35W/R36H/H37D/V38E/T39Y/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
R35W/R36N/H37S/V38E/T39Y/Y40M/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157S;
R35Y/H37D/V38E/T39W/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/K82S/T97aI/L97bA/H99Q/K110aS/C122S/Y149R/M157K;
R35W/H37P/R37aN/V38E/T39Y/V41R/D60aP/Y60bL/D97T/T97aE/L97bG/A98S/H99L/C122S;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/Y149R/M157K;
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S;
F30Y/R35W/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/M157K;
R35H/V38E/T39Y/V41R/D60aP/Y60bQ/L97bA/H99Q/C122S/T158A;
R35Q/R36H/H37Y/V38E/T39Y/Y40L/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
R35W/H37P/R37aG/V38E/T39Y/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R;
V38D/V41Q/D60aH/Y60bS/T97aW/L97bR/H99E/C122S/Y151L/E175D/R217E/K224R;
F30Y/R35W/R36H/H37P/R37aQ/V38E/T39Y/Y40F/V41R/Y60bQ/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36Q/H37S/V38P/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157R;
F30H/R35W/R36T/H37S/V38P/T39Y/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157S;
F30Y/R35W/R36H/H37D/V38E/T39Y/Y40H/V41R/Y60bD/T97aI/L97bA/H99Q/C122S/M157K;
F30Y/R35Y/R36H/H37N/V38E/T39F/Y40F/V41R/K61E/R72H/T97aI/L97bA/H99Q/C122S/Y149R/M157K/Q169K;
R35W/R36Q/H37S/V38S/T39Y/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157S/Q192H;

R35W/H37G/R37aE/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192T;
R35W/H37P/R37aN/V38E/T39Y/V41R/D60aP/Y60bL/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R35W/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S;
F30Y/R35V/R36H/H37G/V38E/T39W/Y40H/V41R/Y60bA/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36H/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R;
F30Y/R35W/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R;
F30Y/R35W/R36H/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/M157K;
F30Y/R35W/R36H/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S;
F30Y/R35W/R36S/H37S/V38Q/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157S/Q192N;
F30Y/R35W/R36H/H37P/R37aD/V38E/T39Y/Y40F/V41R/D60aE/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
R35Q/H37Y/R37aS/V38E/T39Y/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R;
R37aS/V38E/Y40V/V41R/H99L/C122S/Y151L/R217V;
V38D/V41R/L97bG/H99Q/C122S/Y151L/R217E;
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S;
F30Y/R35V/R36H/H37D/V38E/T39W/Y40H/V41R/Y60bP/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
I17V/F30Y/R35Q/R36H/H37W/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/M157K;
F30Y/R35V/R36H/H37S/V38E/T39F/Y40H/V41R/Y60bS/T97aM/L97bA/H99Q/C122S/Y149W/M157K;
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R;
N26D/F30Y/R35Y/R36H/H37E/V38E/T39F/Y40F/V41R/K61E/T97aI/L97bA/H99Q/R110dS/P114S/C122S/Y149R/M157K;
F30Y/R35W/R36H/H37P/R37aE/V38E/T39Y/Y40F/V41R/Y60bA/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
R35L/H37D/R37aN/V38E/T39Y/V41R/D60aP/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R35W/R36H/H37P/V38E/T39Y/Y40F/V41R/Y60bS/T97aE/L97bA/H99Q/C122S/Y149K/M157K;
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/T97aI/L97bA/H99Q/C122S/Y149R;

R35H/V38E/T39Y/V41R/D60aP/Y60bQ/L97bA/H99Q/C122S/T158S/E167K;
R35Q/H37Y/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R35Y/R36H/H37D/V38E/T39W/Y40H/V41R/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35Y/R36H/H37E/V38E/T39F/Y40F/V41R/K61E/T97aI/L97bA/H99Q/C122S/Y149R/M157K/T242A;
F30Y/R35L/V38D/Y40H/V41R/L97bA/H99Q/C122S/M157K/T158A;
F30Y/R35Y/R36H/H37P/R37aQ/V38E/T39Y/Y40F/V41R/Y60bH/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
V38D/V41R/L97bR/H99E/C122S/Y151L/R217E;
H37G/R37aD/G37bD/V38F/T39H/V41R/Y60bK/T97aS/L97bR/H99E/C122S/Y151L/E175D/R217E/K224R;
R35Y/H37V/R37aW/V38E/T39Y/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y151L/Q192T;
F30Y/R35M/R36H/H37G/V38E/T39F/Y40H/V41R/Y60bP/T97aF/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36Q/H37S/V38T/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157K/Q192T;
R35W/H37D/R37aP/V38E/T39W/V41R/D60aR/Y60bS/T97aI/L97bA/H99Q/C122S/Y149R;
I17V/F30Y/R35W/R36H/H37E/V38E/T39W/Y40H/V41R/Y60bQ/T97aE/L97bA/H99Q/C122S/Y149K/M157K;
I17V/F30Y/R35Q/H37W/V38D/Y40H/V41R/Y60bN/L97bA/H99Q/C122S/Y149H/M157K/T158A;
R35H/V38E/T39Y/V41R/D60aP/Y60bQ/L97bA/H99Q/C122S/I138V/E167K;
F30Y/R35W/R36Q/H37S/V38E/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157T/Q192H;
R35H/G37bD/V38E/T39Y/V41R/D60aP/Y60bQ/L97bA/H99Q/C122S/T158S;
R35H/H37P/R37aG/V38E/T39F/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R35W/R36H/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
V38D/T39Y/Y40L/V41R/L97bI/H99E/C122S/R217E;
F30Y/R36H/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/M157K/T158A;

F30H/R35W/R36H/H37S/V38E/T39Y/Y40M/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
R35V/R36H/H37D/V38E/T39W/Y40M/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
R35W/R36K/H37S/V38A/T39Y/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157R/Q192T;
F30Y/R35W/R36H/H37D/V38E/T39Y/Y40H/V41R/Y60bA/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36H/H37S/V38E/T39Y/Y40F/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/N145S/S146V/T147M/D148G/Y149Q/L150F/M157K;
F30Y/R35Y/R36H/H37K/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/Y149R/M157K;
F30Y/R35I/R36H/H37D/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
R35V/V38E/Y40Q/V41L/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R;
R35Q/H37Y/R37aP/V38E/T39Y/V41R/D60aN/Y60bN/T97aI/L97bA/H99Q/C122S/Y149R;
V38E/Y40Q/V41L/L97bG/H99Q/C122S/R217T;
R35H/V38E/T39Y/V41R/T56S/D60aP/Y60bQ/L97bA/H99Q/C122S/T158S;
F30H/R35Q/H37W/V38D/V41R/L97bA/H99Q/C122S/Y151L/M157K;
R35Q/H37Y/V38E/T39Y/V41R/D60aP/T97aI/L97bA/H99Q/C122S/Y149R;
R35W/H37P/R37aN/V38E/T39Y/V41K/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192A;
V38D/V41R/Y60bR/T97aW/L97bR/H99E/C122S/E175D/R217E/K224R;
F30Y/R35W/R36H/H37S/V38E/Y40H/Y60bN/T97aI/L97bA/H99Q/C122S/Y149R;
V38D/V41L/Y60bP/T97aM/L97bR/H99E/C122S/Y151L/E175D/R217E/K224R;
F30Y/R35W/R36H/H37D/V38E/T39F/Y40H/V41R/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36H/H37N/V38E/T39Y/Y40F/V41R/Y60bS/T97aE/L97bA/H99Q/C122S/Y149K/M157K;
F30Y/R35W/R36K/H37S/V38D/T39Y/Y40L/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151L/M157R/Q192T;
V41R/H99Q/C122S/Y151L/R217V;
V38E/Y40P/V41L/L97bG/H99L/C122S/Y151Q/R217E;
V38E/Y40L/V41R/H99L/C122S/Y151L/R217S;
V38E/Y40Q/V41L/L97bG/H99Q/C122S/Y151P/R217T;
V38E/T39Y/V41R/D60aW/Y60bP/L97bR/H99I/C122S;

R35W/H37D/R37aP/V38E/T39W/V41R/Y60bA/T97aI/L97bA/H99Q/C122S/Y149R;
F30Y/R36H/H37F/V38E/T39Y/Y40H/V41R/Y60bD/T97aV/L97bA/H99Q/C122S/Y149L/M157K;
F30Y/R35W/R36H/H37E/S37dP/V38E/T39W/Y40H/V41R/Y60bQ/T97aE/L97bA/H99Q/C122S/Y149K/M157K;
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aA/Y60bP/T97aI/L97bA/H99Q/C122S/Y149R;
R36H/V38D/V41R/A96D/D97E/A98G/T97adel/H99L/L97bdel/C122S/T178S/R217D;
V38D/V41R/L97bG/H99Q/C122S/Y151L/R217A;
F30H/R35Q/R36H/H37Y/V38E/T39Y/Y40L/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;
F30Y/R35W/R36K/H37E/V38E/T39W/Y40H/V41R/Y60bQ/K61E/I65T/T97aE/L97bA/H99Q/C122S/Y149K/M157K;
F30Y/R35W/R36H/H37D/V38E/T39Y/Y40H/V41R/Y60bS/T97aL/L97bA/H99Q/C122S/Y149L/M157K;
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V38E/Y40Q/V41L/L97bA/H99Q/C122S;
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49K/M157K;
R35Q/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R;
V38E/T39L/V41R/D60aN/Y60bP/L97bG/H99Q/C122S;
F30Y/R36H/H37A/V38E/T39Y/Y40H/V41R/Y60bQ/T97aV/L97bA/H99Q/C122S/Y149R/
M157K;
F30Y/R35W/R36H/H37E/R37aP/V38E/T39Y/Y40F/V41R/Y60bN/T97aE/L97bA/H99Q/C1
22S/Y149Q/M157K;
H37T/R37aL/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192R;
H37G/R37aD/V38F/T39H/V41R/Y60bK/T97aS/L97bR/H99E/C122S/Y151L/E175D/Q192T
/R217E/K224R;
F30Y/R35W/R36H/H37S/V38E/Y40H/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
V38D/T39W/Y40L/V41R/T97aL/L97bA/H99Q/C122S;
H37G/R37aD/G37bD/T39H/V41R/Y60bK/T97aS/L97bR/H99E/C122S/Y151L/E175D/Q192
T/R217E/K224R;

T39Y/V41R/L97bA/H99Q/C122S;
V38D/T39L/Y40L/V41R/T97aW/L97bA/H99Q/C122S;
F30Y/R36H/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/Y149N/L150V/M157K;
R35S/V38D/L97bA/H99Q/C122S/Y151L/M157Y;
R37aS/V38D/T39Y/Y40F/V41R/H99L/C122S/R217T;
Y40Q/V41L/Y60bE/L97bA/H99Q/C122S/Y149R; and
Y40H/V41T/L97bG/H99Q/C122S/R217T; and
a modified u-PA polypeptide comprising any of the preceding modifications except the cysteine residue at position 122 is not modified and
~~any of these polypeptides in which C122S~~ is C122C, by chymotrypsin numbering.

16. The modified u-PA polypeptide of any of claims 1-15, comprising the amino acid modifications R35Q/H37Y/T39Y/V41R or R35Q/H37Y/T39Y/V41R/C122S or R35Q/H37Y/T39Y/V41R/L97bA/H99Q/C122S or R35Q/H37Y/T39Y/V41R/L97bA/H99Q or R37aS/V41R/L97bG/H99Q or R37aS/V41R/L97bG/H99Q/C122S or T39Y/V41R/Y60bQ/L97bA/H99Q or T39Y/V41R/Y60bQ/L97bA/H99Q/C122S, or T39Y/V41R/D60aP/L97bA/H99Q/C122S or T39Y/V41R/D60aP/L97bA/H99Q.

17. The modified u-PA polypeptide any of claims 1-16, comprising the amino acid modifications Y40Q/V41L/L97bA/C122S or Y40Q/V41R/L97bA/C122S or Y40Q/V41L/L97bA or Y40Q/V41R/L97bA or Y40Q/V41L/L97bA/H99Q/C122S or Y40Q/V41R/L97bA/H99Q/C122S or Y40Q/V41L/L97bA/H99Q or Y40Q/V41R/L97bA/H99Q or T39Y/V41L/L97bA/H99Q/C122S or T39Y/V41R/L97bA/H99Q/C122S or T39Y/V41L/L97bA/H99Q or T39Y/V41R/L97bA/H99Q.

18. The modified u-PA polypeptide of any of claims 1-16, comprising the amino acid modifications
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aT/Y60bT/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aT/Y60bT/T97aI/L97bA/H99Q/Y149R.

19. The modified u-PA polypeptide of any of claims 1-16 and 18, comprising the amino acid modifications:

R35Y/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L;
or
R35Q/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/T97aI/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/L97bA/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/H99Q/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/C122S/Y149R; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S; or
R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aA/Y60bP/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35L/H37D/R37aS/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35M/H37G/R37aD/V38E/T39W/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R
;
or
R35Q/H37G/R37aP/V38E/T39Y/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35A/H37G/R37aE/V38E/T39F/V41R/D60aE/Y60bP/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35Q/H37S/R37aE/V38E/T39Y/V41R/D60aP/Y60bS/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35Q/H37T/R37aP/V38E/T39Y/V41R/D60aE/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35Q/H37G/R37aE/V38E/T39H/V41R/D60aP/Y60bA/T97aI/L97bA/H99Q/C122S/Y149R;
or
R35W/H37D/R37aS/V38E/T39Y/V41R/D60aE/Y60bS/T97aI/L97bA/H99Q/C122S/Y149R;
or

R35Q/H37G/R37aE/V38E/T39Y/V41R/D60aP/Y60bT/T97aI/L97bA/H99Q/C122S/Y149R; or
R35W/H37P/R37aN/V38E/T39Y/V41R/D60aP/Y60bL/D97T/T97aE/L97bG/A98S/H99L/C122S; or
R35W/H37P/R37aN/V38E/T39Y/V41K/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192A; or
R35Y/H37V/R37aW/V38E/T39Y/V41R/D60aP/Y60bE/T97aI/L97bA/H99Q/C122S/Y151L/Q192T; or
R35Y/H37S/R37aP/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L; or
R35W/H37P/R37aN/V38E/T39Y/V41K/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y151L/Q192T; or a modified u-PA polypeptide comprising any of the preceding modifications except the cysteine residue at position 122 is not modified and~~or each of the preceding in which C122S~~ is C122C, by chymotrypsin numbering.

20. The modified u-PA polypeptide of claim 1-16, 18 and19, comprising the amino acid modifications R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R or R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/Y149R, wherein the unmodified u-PA polypeptide comprises the sequence of amino acid residues ~~protease domain~~ set forth in SEQ ID NO:2 or SEQ ID NO:5, or comprises the ~~mature unmodified u-PA polypeptide~~sequence of amino acid residues set forth in SEQ ID NO:3 or SEQ ID NO:6.

21. The modified u-PA polypeptide of any of claims 1-20, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 8-44, 171, 176, 183, 184, 198, 199, 208, 211, 216-219, 221-228, 230-233, 240, 242, 243, 249, 260-265, 267, 268, 270-273, 275-292, 299, 300, 307, 309, 311-315, 324-326, 329, 330, 335, 337-341, 346-351, 356-360, 363-365, 368-374, 376, 377, 381, 382, 387, 389, 390, 397, 398-404, 417, 436, 445-448, 466, 469, 475, 481, 484-487, 494-496, 498, 500, 503-511, 513-520, 523, 534, 535, 538, 540-547, 550-553, 555, 557, 561, 562, 564, 565, 568, 576, 584-587, 591, 592, 594, 595, 597, 598, 600, 601, 603-608, 611-625, 627-629, 633, 645, 647-651, 653, 655-658, 661, 663-722, 724-729, 731-754, 792-802, 807, 818, 820-824, 826, 827, 829-836, 839, 841, 842, 849, 850, 855, 868-879, 881-884, 886, 891, 893, 900-904, 921, 924-926, 932, 934-940, 942-944, 946-961, 963, 967, 972, 973, 975, and 977-987, or the same sequences, except the residue at position C122 is C (Cys).

22. The modified u-PA polypeptide of any of claims 1-21, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:21 or 987, or the sequence of amino acid residues set forth in SEQ ID NO:21 or 987 except the cysteine residue at position 122 is not modified and is C122C, by chymotrypsin numbering.

23. The modified u-PA polypeptide of any of claims 1-21, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:18, or the sequence of amino acid residues set forth in SEQ ID NO:18 except the cysteine residue at position 122 is not modified and is C122C, by chymotrypsin numbering.

24. The modified u-PA polypeptide of any of claims 1-23 that cleaves within residues QHARASHLG (residues 737-745) of human C3 (SEQ ID NO:47).

25. The modified u-PA polypeptide of any of claims 1-24 that is conjugated to another moiety or polymer either directly or via a linker.

26. The modified u-PA polypeptide of claim 25, wherein the polypeptide is conjugated to a moiety, whereby the polypeptide is PEGylated.

27. The modified u-PA polypeptide of any of claims 1-26 that comprises a polymer that increases serum half-life and/or reduces immunogenicity or both.

28. The modified u-PA polypeptide of claim 27 that is linked directly or indirectly to a polymer that is serum albumin.

29. The modified u-PA polypeptide of claim 28, wherein:

the serum albumin is a human serum albumin (HSA); and the HSA comprises the sequence set forth in SEQ ID NO: 991, or ~~a form that~~ has at least 90% or at least 95% sequence identity to the sequence set forth in SEQ ID NO: 991~~thereto~~.

30. The modified u-PA polypeptide of claim 27, wherein the polymer is a multimerization domain.

31. The modified u-PA polypeptide of claim 30, wherein the multimerization domain is an Fc domain that comprises the sequence set forth in SEQ ID NO: 50 or SEQ ID NO:992 or ~~a form that~~ has at least 95% sequence identity to the sequence set forth in SEQ ID NO: 50 or SEQ ID NO:992~~thereto~~.

32. The modified u-PA polypeptide of any of claims 27-31, wherein the polymer is linked directly to the modified u-PA polypeptide or the polymer is linked via a peptide linker to the modified u-PA polypeptide.

33. The modified u-PA polypeptide of claim 32, wherein the polymer is linked to the modified u-PA polypeptide via a linker that comprises Gly and/or Ser.

34. The modified u-PA polypeptide of claim 33, wherein the linker comprises (GS)n or (G)n(S)n or (GGS)n or (SGG)n or (GGSSGG)n or (AGS)n, wherein n is 1 to 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or a linker containing up to 25 residues containing one or more of S, G, E and K.

35. The modified u-PA of any of claims 27-34, comprising the sequence of amino acid residues set forth in any of SEQ ID NOs: 1001-1003, and 1024-1029, and multimers thereof ~~and sequences having at least 99% sequence identity thereto~~.

36. A fusion protein, comprising a modified u-PA polypeptide or a catalytically active portion of a modified u-PA polypeptide of any of claims 1-35 that is fused to a non-protease polypeptide or a portion thereof.

37. The fusion protein of claim 36, wherein the non-protease polypeptide is a multimerization domain or a protein transduction domain (PTD).

38. The fusion protein of claim 36 or claim 37 that comprises a heterologous activation sequence or a u-PA activation sequence.

39. The fusion protein of claim 38, wherein the activation sequence comprises a cysteine, and the modified u-PA polypeptide comprises a free cysteine, whereby, upon activation, the resulting activated polypeptide comprises two chains.

40. The fusion protein of claim 38 or claim 39, wherein the activation sequence is a u-PA activation sequence or a furin activation sequence.

41. The fusion protein of claim 40, wherein the activation sequence is a furin activation sequence that comprises QSGQKTLRRRKR (SEQ ID NO:996) or QCGQKTLRRRKR (SEQ ID NO:995) or QSGQKTLRRKR (SEQ ID NO: 1044) ~~or a furin activation sequence having at least 98% sequence identity thereto~~.

42. A fusion protein, comprising a modified u-PA polypeptide or catalytically active portion thereof of any of claims 1-34, wherein the fusion protein comprises a signal sequence and the modified u-PA polypeptide or catalytically active portion thereof.

43. The fusion protein of claim 42, wherein the signal sequence is from Il-2, u-PA, or IgGκ.

44. The fusion protein of claim 42 or claim 43, further comprising a fusion partner.

45. The fusion protein of claim 44, wherein the fusion partner is albumin, or an Fc domain, or a single chain antibody or other antigen binding fragment of an antibody, or a hyaluronic acid binding domain (HABD).

46. The fusion protein of claim 45, wherein the fusion partner is a HABD that is Tumor Necrosis factor-Stimulated Gene-6 (TSG-6), or is human serum albumin (HSA), or is IgG Fc, or is an anti-type II collagen antibody scFv fragment, or is an anti-VEGFR antibody or fragment thereof.

47. The fusion protein of any of claims 42-46, comprising an activation sequence.

48. The fusion protein of claim 47, wherein the activation sequence comprises a cysteine, and the modified u-PA polypeptide comprises a free cysteine, whereby, upon activation, the resulting activated polypeptide comprises two chains.

49. The fusion protein of claim 47 or claim 48, wherein the activation sequence is a u-PA activation sequence or a furin activation sequence.

50. The fusion protein of any of claims 47-49, wherein the activation sequence has the sequence set forth in any of SEQ ID NOs:995-998, 1041, and 1044~~, or a sequence having at least 98% or 99% sequence identity thereto~~.

51. The fusion protein of any of claims 42-50, comprising an activation sequence, a modified u-PA polypeptide, and HSA.

52. The fusion protein of any of claims 42-51, comprising the sequence of amino acids set forth in any of SEQ ID NOs: 1006, 1007, 1009, and 1010, or the sequence of amino acid residues set forth in SEQ ID NO: 1006, 1007, 1009, and 1010 except the cysteine residue at position 122 of the u-PA polypeptide is not modified and is C122C, by chymotrypsin numbering.

53. The fusion protein of any of claims 42-49 and, comprising the sequence of amino acids set forth in any of SEQ ID NOs: 1004-1019 and 1034-1040, or the sequence of amino acid residues set forth in SEQ ID NO: 1004-1019 and 1034-1040 except the cysteine residue at position 122 of the u-PA polypeptide is not modified and is C122C, by chymotrypsin numbering.

54. The fusion protein of claim 42, comprising the sequence of amino acids set forth in SEQ ID NO:1015 or 1019, or the sequence of amino acid residues set forth in SEQ ID NO:1015 or 1019 except the cysteine residue at position 122 of the u-PA polypeptide is not modified and is C122C, by chymotrypsin numbering.

55. The fusion protein of any of claims 52-54 that does not have a signal sequence or from which the signal sequence has been removed upon expression.

56. A fusion protein that is a two-chain activated form of the fusion protein of any of claims 36-55.

57. The fusion protein of claim 56, comprising the sequence of amino acids set forth in any of SEQ ID NOs. 1005, 1011, 1014, 1015, 1016, 1019, and 1036, but lacking the signal sequence.

58. The fusion protein of claim 56, wherein the B chain starts at residues IIGG of the modified u-PA polypeptide and ends at the C-terminus of the fusion protein.

59. The fusion protein of any of claims 56-58, comprising the modified u-PA polypeptide and HSA.

60. The fusion protein of any of claims 56-59, comprising a modified u-PA polypeptide comprising an A chain of residues 21-178, and a B chain of residues 179 to the C-terminus of the protein with a disulfide linkage between residues 168-299.

61. The fusion protein of any of claims 42-60 that is a two chain activated fusion protein, comprising a modified u-PA polypeptide comprising an A chain and a B chain, wherein the A chain consists of residues 21-178 of SEQ ID No. 1015, and B chain consists of residues 179-1022 of SEQ ID NO:1015; and the A and B chains are linked via a disulfide bridge between C168 and C299 of SEQ ID NO:1015.

62. The fusion protein of any of claims 42-61 that is a dimer via interaction of complementary multimerization domains, wherein the fusion protein comprises a multimerization domain.

63. The fusion protein of claim 62, wherein the multimerization domain is an Fc domain.

64. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified u-PA polypeptide of any of claims 1-35 or encoding a fusion protein of any of claims 36-63.

65. A vector, comprising the nucleic acid molecule of claim 64.

66. The vector of claim 65 that is an expression vector or is a gene therapy vector.

67. Use of the modified u-PA polypeptide of any of claims 1-35 or a fusion protein of any of claims 36-63 or a nucleic acid molecule of claim 64 or vector of claim 65 for formulation of a medicament for treating a disease or condition mediated by or involving complement activation, wherein inhibition of complement activation effects treatment or amelioration of the disease or condition.

68. The modified u-PA polypeptide of any of claims 1-35, or a fusion protein of any of claims 36-63 or a nucleic acid molecule of claim 64 or vector of claim 65 for use ~~for~~in treating a disease or condition mediated by or involving complement activation, wherein

inhibition of complement activation effects treatment or amelioration of the disease or condition.

69. A pharmaceutical composition, comprising a modified u-PA polypeptide of any of claims 1-35 or a fusion protein of any of claims 36-63 in a pharmaceutically acceptable vehicle.

70. The pharmaceutical composition of claim 69, wherein the modified u-PA polypeptide or fusion protein is in a two-chain activated form.

71. The pharmaceutical composition of claim 69, wherein the modified u-PA polypeptide or fusion protein comprises a protease domain of SEQ ID NO:21 or SEQ ID NO:987, or comprises the sequence set forth in SEQ ID NO:1015 or 1019, or comprises the sequence set forth in any of SEQ ID NOs: 21, 987, 1015 and 1019 except the cysteine residue at position 122 is not modified and is C122C, by chymotrypsin numbering.

72. The use of claim 67 or modified u-PA polypeptide or fusion protein of claim 68, wherein the disease or condition is selected from among inflammatory diseases and conditions.

73. The use or modified u-PA polypeptide or fusion protein of any of claims 67, 68 and 72, wherein the disease or condition is selected from among: Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), sepsis, rheumatoid arthritis (RA), a cardiovascular disease, membranoproliferative diseases and conditions, ophthalmic or ocular diseases or disorders, membranoproliferative glomerulonephritis (MPGN), multiple sclerosis (MS), myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), transplanted organ rejection, and ischemia-reperfusion injury.

74. The use or modified u-PA polypeptide or fusion protein of any of claims 67, 68, and 72, wherein the disease or condition is an ocular or ophthalmic disease or is rejection or inflammation due to a transplanted organ.

75. The use or modified u-PA polypeptide or fusion protein of claim 74, wherein the disease or condition is a diabetic retinopathy or age-related macular degeneration (AMD).