

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 33328-4940PC	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/US2019/068839	International filing date (day/month/year) 27.12.2019	Priority date (day/month/year) 28.12.2018	
International Patent Classification (IPC) or national classification and IPC INV. C12N9/72			
Applicant Catalyst Biosciences, Inc.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>45</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 02.10.2020		Date of completion of this report 04.12.2020	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Kools, Patrick Telephone No. +31 70 340-1964 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2019/068839

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-297 as originally filed

Sequence listings, SEQ ID NO

1-1044 as originally filed

Claims, Numbers

1-243 filed in electronic form on 02-10-2020

Drawings, Sheets

1/3-3/3 as originally filed

- ☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2019/068839

5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).
6. ☒ With regard to top-up searches (Rules 66.1ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 07.10.2020 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-243</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-243</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-243</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search and/or examination:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
 - d. ☐ furnished to this Authority as an amendment* under PCT Article 34 on :
 - ☐ in the form of an Annex C/ST.25 text file, and preferably identified as "Amended" at the first line of text.
 - ☐ on paper or in the form of an image file.
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 119, 121-137, 141, 143-168, 172-226 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

- D1 DATABASE UniProt [Online] 20 June 2018 (2018-06-20), "SubName: Full=Plasminogen activator, urokinase {ECO:0000313 Ensembl:ENSPAP00000025696}; XP055682907, retrieved from EBI accession no. UNIPROT:A0A2R9BBQ2

- D2 US 2006/142195 A1 (MEDCALF ROBERT L [AU]) 29 June 2006 (2006-06-29) cited in the application

- D3 SHINGO TSUJI ET AL: "The effects of amino-acid mutations on specific interactions between urokinase-type plasminogen activator and its receptor:molecular orbital calculations", JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, ELSEVIER SCIENCE, NEW YORK, NY, US, vol. 29, no. 8, 7 April 2011 (2011-04-07), pages 975-984, XP028223708, ISSN: 1093-3263, DOI: 10.1016/J.JMGM.2011.04.003

- D4 US 5 728 564 A (SAMBROOK JOSEPH F [US] ET AL) 17 March 1998 (1998-03-17)cited in the application

- D5 EP 0 336 508 A1 (LEUVEN K U RES & DEV [BE]; COLLEN DESIRE JOSE [BE]) 11 October 1989 (1989-10-11)

- D6 EP 0 387 380 A1 (BEHRINGWERKE AG [DE]) 19 September 1990 (1990-09-19)

- D7 US 5 472 692 A (LIU JIAN-NING [US] ET AL) 5 December 1995 (1995-12-05)

D8 EP 0 266 032 A1 (BEECHAM GROUP PLC [GB]) 4 May 1988 (1988-05-04)

Novelty, Article 33(2) PCT

D1 discloses a database entry disclosing a sequence fully identical to Seq ID No 2 except for one mutation corresponding to V41L. Due to the amendment in claim 1 this document is not against novelty.

A new sequence search did not reveal any other relevant disclosed sequences.

Inventive step, Article 33(3) PCT

Closest prior art D2 discloses not only t-PA variants but also urokinase variants having modifications. These modifications result, when compared to the wild-type sequence, in an increased enzymatic activity in the presence of fibrin (V420, T421, D422, S423), reduce the stability of the catalytic active conformation in absence of fibrin (position 194) and a point mutation that prevents plasmin catalysis (I275) (see claims 24-30).

The difference resides in the positions of the present substitutions. The technical effect of said mutations is an increased activity/specificity for complement protein C3.

The problem to be solved is the provision of mutant urokinases having an increased activity/specificity for complement protein C3.

The solutions to said problem (as defined in claim 1) are considered inventive. Despite the relative age of the urokinase protein in science, there is little known about certain modifications and their effects. There are reports on specific modifications to the protein (D3-D8), but nothing in the direction of alterations in complement activation. This is also not obvious in view of the knowledge of the skilled person working in the field of serine proteases.

Industrial applicability, Article 33(4) PCT

The application finds its use in the treatment of various diseases related to blood clotting and urokinase activity.

Item VIII

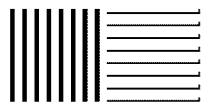
Certain observations on the international application

Claim 1 also refers to substitutions with non-natural amino acids. Using the description it is clear what is intended.

The expression "numbering according to chymotrypsin" is considered clear to the skilled person.

Claims 58 and 59 refer to an incubation test giving a time period, but no temperature indication. This missing information could be important.

Claims 120, and 234-243 use the expression "for use for treating". Depending on the Patent Law of a designated state, this wording could have different interpretation.



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Munich, October 2, 2020

Our Ref.: 223 260 m10/m30/liw
International Application PCT/US2019/068839
CATALYST BIOSCIENCES, INC.

Representation as sub-agent to represent the applicant specifically
before the EPO as IPEA is hereby taken over by

Hoffmann Eitle PartmbB
Association No. 151

A demand for international preliminary examination is hereby made
pursuant to Art. 31(1) PCT.

Please debit the handling fee and international preliminary
examination fee from our deposit account in accordance with the
enclosed electronic debit instructions.

Applicant submits the following under Article 34(2)(b) PCT, in
response to the Written Opinion of the International Searching
Authority mailed May 11, 2020.

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1 Amendments to the Claims

An amended set of claims 1-243 is enclosed for the examination under Chapter II of the PCT. A second copy showing the amendments is also enclosed, for the Examiner's convenience.

All amendments are made without prejudice to any of the Applicant's rights. No subject matter is abandoned by the present claim amendments. The Applicant reserves the right to reinstate any subject matter contained in any part of the application as originally filed during the future prosecution of this application, including in the national or regional phases, or in applications derived from this application, including continuations or divisional applications based on this application.

Claim 1 has been amended to remove the V41L modification, and to incorporate dependent claim 4 to recite that the complement protein is C3. Further basis can also be found throughout the application as filed, which describes that urokinase-type plasminogen activator (u-PA) is modified to cleave C3 at a site whereby complement activation is inhibited or reduced compared to an unmodified u-PA polypeptide that does not contain the modification(s). See, for example, at page 5, line 20 to page 6, line 18, which recites (**emphasis added**):

Among the modified urokinase-type plasminogen activator (u-PA) polypeptides provided herein are those that contain one or more amino acid modifications selected from among replacements corresponding to R35Q, H37Y, V41R, V41L, Y40Q, D60aP, L97bA, T97aI, and H99Q, and conservative amino acid modifications therefor, whereby the modified u-PA polypeptide has increased activity/specificity for a complement protein compared to the unmodified active form of the u-PA polypeptide, where: the amino acid modifications are selected from among replacements, insertions and deletions; corresponding residues can be determined by alignment with the mature form of u-PA; 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; residues are numbered by chymotrypsin numbering; the unmodified u-PA polypeptide

comprises the sequence set forth in any of SEQ ID NOs.: 1-6 (wild-type human full-length u-PA, wild-type protease (catalytic) domain u-PA, wild-type mature u-PA, full-length u-PA with the replacement corresponding to C122S, protease domain u-PA with the replacement corresponding to C122S, and mature u-PA with the replacement corresponding to C122S) and catalytically active fragment thereof that includes the amino acid replacement(s). The conservative modifications are selected from among R35Y, W, F or N; H37 R, Q, E, W or F, V41K, D60aS, T97aD, L or V, L97bG or S and H99N, by chymotrypsin numbering.

*In particular, among these modified urokinase-type plasminogen activator (uPA) polypeptides are those **containing one or more amino acid modifications selected from among replacements corresponding to R35Q, H37Y, V41R, V41L, Y40Q, D60aP, L97bA, T97aI, and H99Q.***

*The modified u-PA polypeptides have reduced activity and/or specificity for cleavage of a substrate sequence in plasminogen. **The complement protein for which the polypeptides have increased specificity/activity is C3;** cleavage inactivates C3. Exemplary of cleavage sites is within the active site of C3. Among the modified u-PA polypeptides are those that have increased activity for cleavage of C3 that is least 3-fold greater than the unmodified u-PA polypeptide of SEQ ID NO:5 (protease domain with the C122S replacement).*

See also, for example, page 74, lines 21-26, which recite:

Provided herein are modified Urokinase-type plasminogen activator (u-PA) polypeptides that are modified so that they cleave inhibitory sequences in C3, such that activation of C3 into C3a and C3b fragments is inhibited. The activity/specificity of the modified u-PA polypeptides provided herein is such that they cleave C3 with greater activity and/or specificity or kcat/km compared to the unmodified u-PA polypeptide, particularly of any of SEQ ID NOs: 1-6.

Basis for the amendment also can be found, for example, at section C., beginning at page 84, line 25, which details C3 as a target of the modified u-PA polypeptides, and the role of C3 in inhibiting complement activation.

Claim 1 also is amended to incorporate a limitation of claim 8 to recite that the modified u-PA polypeptide has at least 85% sequence identity with the unmodified modified u-PA polypeptide of any of SEQ ID NOs.1-6.

Claim 1 is further amended to replace the word “replacements” with “modifications”. Basis for the amendments can be found, for example, in the specification at page 99, lines 25 to page 100, line 4, which recites (**emphasis added**):

*The modified u-PA polypeptides provided herein contain one or more amino acid modifications such that they cleave complement protein C3 in a manner that results in inactivation or inhibition of complement. **The modifications can be a single amino acid modification, such as single amino acid replacements (substitutions), insertions or deletions, or multiple amino acid modifications, such as multiple amino acid replacements, insertions or deletions.** Exemplary modifications are amino acid replacements, including single or multiple amino acid replacements. The amino acid replacement can be a conservative substitution, such as set forth in Table 3, or a non-conservative substitution, such as any described herein. Modified u-PA polypeptides provided herein can contain at least or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more modified positions compared to the u-PA polypeptide not containing the modification.*

Basis for this amendment can also be found, for example, at page 101, line 17 to page 102, line 8. Moreover, further basis for this amendment also can be found at page 103, lines 27-32, which recites:

Provided herein are modified u-PA polypeptides that contain one or more, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and more amino acid modifications in a u-PA polypeptide and that cleave complement protein C3 such that complement is inhibited or inactivated. Modifications are in the primary amino acid sequence, and include replacements, deletions and insertions of amino acid residues.

Claim 2 has also been amended to refer to “modifications” and to remove the V41L modification.

Claim 4 has been removed. Subsequent claims are renumbered consecutively and amended to depend on renumbered claims.

The remaining claims and their dependencies have been amended for consistency, including to update claim numbers and dependencies, to recite consistent claim language throughout and to correct minor typographical or grammatical errors. Specifically, claims 145, 155 and 233 are amended to correct claim dependencies. Further, claims 123, 151, and 212 are amended to reference the correct antecedent. Claims 1, 70, 88, 104, 137, 138, 165, 183, 196, 224 and 240 are amended to correct obvious grammatical or typographical errors. Claims 1, 2, 26, and 240-244 are amended to address objections set forth in the Written Opinion.

Unless otherwise indicated, claims are referenced by numbering before amendment throughout this submission.

No matter has been added by these amendments.

2 Arguments

The Written Opinion of the International Search Authority cites:

- D1** UniProt Accession No. A0A2R9BBQ2 (Plasminogen activator, urokinase)
- D2** U.S. Publication No. 2006/142195
- D3** Tsuji et al., "The effects of amino-acid mutations on specific interactions between urokinase-type plasminogen activator and its receptor: Ab initio molecular orbital calculations," Journal of Molecular Graphics and Modelling 29:975-984 (2011)
- D4** U.S. Patent No. 5,728,564
- D5** European Publication No. 0336508
- D6** European Publication No. 0387380
- D7** U.S. Patent No. 5,472,692
- D8** European Publication No. 0266032

The Written Opinion acknowledges that original claims 1 to 244 possess industrial applicability and that claims 3-7, 10, 12-24, 29-56, 64-110 and 112-244 are novel and inventive, but alleges that claims 1, 2, 8, 9, 11, 25-28, 57-63 and 111 lack novelty and

inventive step over D1 and/or D2. Applicant traverses these characterizations of the prior art for at least the following reasons.

2.1 Novelty

Claims 1, 2, 8, 9, 11, 25-28, 57-63, and 111 are rejected as lacking novelty over reference **D1** because the Written Opinion alleges that **D1** discloses a database entry disclosing a sequence that is allegedly fully identical to SEQ ID NO 2 except for one mutation that allegedly corresponds to V41L. The Written Opinion concludes that “a simple deletion of said not new mutant from the scope of the claims would restore novelty.”

D1 is the UniProt entry for the mature form of wild-type pygmy chimpanzee (*Bonobo*) u-PA. The protease domain portion appears to be almost 100% identical to SEQ ID NO:2 (protease domain of human uPA), except that **D1** contains L at residue 41.

Without prejudice, claims 1 and 2 are amended to delete the modification V41L. Thus, as amended none of the claims recite a modified u-PA polypeptide that contains only the V41L replacement.

The claims are novel over **D1** and any other reference of which Applicant is aware.

2.2 Inventive Step

Claims 1, 2, 8, 9, 11, 25-28, 57-63, and 111 also are alleged to lack inventive step.

The Written Opinion states that the closest prior art is **D2**, which teaches urokinase variants that result in increased enzymatic activity in the presence of fibrin (modifications at V420, T421, D422, S423), reduce the stability of the catalytic active conformation in the absence of fibrin (at position 194), and also teaches a point mutation that prevents plasmin catalysis (at I275). The Written Opinion states that the difference between **D2** and the presently-claimed subject matter resides in the positions of the present substitutions, and that this distinguishing technical feature is directly associated with the technical effect of increasing activity/specificity for complement protein C3.

All of documents **D2-D8** are cited under the category of “A” which indicates a document defining the general state of the art which is not considered to be of particular relevance. None of **D2-D8** teaches or suggests a modified u-PA containing any of the modifications recited in claim 1 that has increased activity/specificity for C3.

Neither **D1** nor **D2**, nor any of additional references **D3-D8**, teaches a modified u-PA that has any of the recited modifications and increased activity/specificity for a complement protein that is C3, compared to the unmodified u-PA polypeptide set forth in any of SEQ ID NOs: 1-6 or a catalytically active fragment that does not contain the modifications.

Claim 1 has been amended to incorporate the limitation of claim 4, i.e., to recite that the complement protein is C3. Thus, the claims are amended to recite modified u-PA polypeptides that are deemed inventive by the ISA.

At least for these reasons, Applicant respectfully submits that the amended claims possess an inventive step over the cited art and requests withdrawal of this objection.

2.3 Response to additional observations (Item VIII)

2.3.1 The modifications in claim 1 are not limited to replacements

Claim 1 is allegedly unclear because the Written Opinion objects to the recitation that the modifications can be replacements, insertions, and deletions, but the first paragraph in the claim recites that the modifications are replacements.

The modifications called out in claim 1 are replacements, but the modifications in u-PA are not limited to replacements (see, *e.g.*, dependent claim 8). For clarity, claim 1 is amended to replace the word “replacements” with “modifications” in the first paragraph of claim 1. Claim 2 also is amended to recite modifications. Thus, the claims clearly refer to a modified u-PA containing modifications selected from among replacements, insertions, and deletions.

2.3.2 Claim 1 clearly indicates that the function of modified u-PA is higher, and thus associated with greater inhibition or reduction of complement activation

Claim 1 also is objected to because the “third paragraph compares a function to that of the unmodified u-PA. This is without indicating equal, higher or lower.”

Applicant respectfully disagrees. Claim 1 recites that the “modified u-PA polypeptide cleaves a complement protein to thereby **inhibit or reduce** complement activation compared to the unmodified u-PA polypeptide,” (emphasis added). Thus, it is clear that the modified u-PA polypeptide reduces complement activation compared to the unmodified u-PA polypeptide.

2.3.3 Chymotrypsin numbering is clear to the person skilled in the art

Claim 1 is objected to because the use of chymotrypsin numbering is allegedly unclear. The Written Opinion states that u-PA (SEQ ID NO:2) allegedly does not align with the mature chymotrypsin polypeptide (SEQ ID NO:76).

Applicant respectfully requests reconsideration of the rejection. Alignment of a protease domain of another protease, such as the protease domain of u-PA, can be made with chymotrypsin. This is standard nomenclature that is described and defined in the application and is understood by the person skilled in the art.

Specifically, the catalytically essential residues S195, H57, N102 in chymotrypsin, which are invariant in all serine proteases, are aligned with u-PA to define the corresponding residue number; the amino acids of u-PA polypeptide that correspond to amino acids of chymotrypsin are then given the numbering of the chymotrypsin amino acids. Despite a low overall sequence identity with chymotrypsin, alignment with these required residues allows for a consistent, conventionally used numbering system. Chymotrypsin numbering is consistent among all forms of u-PA (pro-peptides, mature, and protease domain). Using numbering other than chymotrypsin numbering would be confusing, since the claims encompass the various forms of modified u-PA.

Chymotrypsin numbering is the standard numbering scheme used by a person skilled in the art of serine proteases. As is known to those skilled in the art, chymotrypsin numbering was developed by Bode *et al.* (The EMBO Journal (1989) 8:3467-3475),

where the numbering of residues of the serine protease thrombin was “obtained on the basis of topological equivalences with bovine chymotrypsinogen.” Thus, chymotrypsin numbering is determined from a structure-based alignment based on the topological equivalence of a sequence to bovine chymotrypsinogen. The numbering scheme has been adapted by those skilled in the art as a common numbering scheme for all serine proteases of the chymotrypsin family. In the numbering scheme, a suffix is used to denote an insertion of an amino acid in a serine protease relative to the chymotrypsinogen reference sequence.

Chymotrypsin numbering permits consistent numbering of residues among all forms of a proteases (precursors, zymogen, and mature activated forms). Furthermore, the application as filed in fact includes a Table 1 (p. 40-41 of the application as filed) that clearly and unambiguously states the equivalence between numbering of mature u-PA residues relative to chymotrypsin numbering.

A person skilled in the protease field will readily understand the chymotrypsin numbering; changing to a different numbering scheme would on the other hand cause confusion. Chymotrypsin numbering of u-PA by alignment of u-PA with chymotrypsin is well-known, and used throughout the literature (see *e.g.*, Spraggon *et al.* (1995) *Structure* 3:681-691; Hartley, B.S., (1974) *Symp. Soc. Gen. Microbiol.* 24: 151-182 (attached)). One of skill in the art readily can align the u-PA protease domain with the chymotrypsin protease domain to identify corresponding amino acids.

The application presents the mutations of hundreds of mutants based on chymotrypsin numbering, and is defined and described in the application as filed (Table 1, p. 40-41 of the application as filed). Chymotrypsin numbering and alignment of proteases with chymotrypsin are detailed in the application as filed, for example, at page 39, line 6 to page 40, line 2, which recite:

As used herein, chymotrypsin numbering refers to the amino acid numbering of a mature chymotrypsin polypeptide of SEQ ID NO:76. Alignment of a protease domain of another protease, such as, for example, the protease domain of u-PA, can be made with chymotrypsin. In such an instance, the amino acids of u-PA polypeptide that correspond to amino acids of chymotrypsin are given the numbering of the chymotrypsin amino acids. Corresponding positions can be determined by such alignment by one of skill in the art using manual alignments or by

using the numerous alignment programs available (for example, BLASTP). Corresponding positions also can be based on structural alignments, for example by using computer simulated alignments of protein structure. Recitation that amino acids of a polypeptide correspond to amino acids in a disclosed sequence refers to amino acids identified upon alignment of the polypeptide with the disclosed sequence to maximize identity or homology (where conserved amino acids are aligned) using a standard alignment algorithm, such as the GAP algorithm. The corresponding chymotrypsin numbers of amino acid positions 159-411 of the u-PA polypeptide set forth in SEQ ID NO:3 are provided in Table 1. The amino acid positions relative to the sequence set forth in SEQ ID NO:3 are in normal font, the amino acid residues at those positions are in bold, and the corresponding chymotrypsin numbers are in italics. For example, upon alignment of the serine protease domain of u-PA (SEQ ID NO:2) with mature chymotrypsin, the isoleucine (I) at position 159 in u-PA is given the chymotrypsin numbering of I16. Subsequent amino acids are numbered accordingly. In one example, a phenylalanine (F) at amino acid position 173 of mature u-PA (SEQ ID NO:3) corresponds to amino acid position F30 based on chymotrypsin numbering. Where a residue exists in a protease, but is not present in chymotrypsin, the amino acid residue is given a letter notation. For example, residues in chymotrypsin that are part of a loop with amino acid 60 based on chymotrypsin numbering, but are inserted in the u-PA sequence compared to chymotrypsin, are referred to for example as D60a, Y60b or P60c. These residues correspond to D208, Y209 and P210, respectively, by numbering relative to the mature u-PA sequence set forth in SEQ ID NO:3.

Therefore, using chymotrypsin numbering in the claim is consistent with the understanding of those of skill in the art, and with the disclosure and description in the application as filed.

2.3.4 Dependent claims 8 and 9 are not broader than claim1

Claims 8 and 9 are objected to as unclear because they allegedly refer to u-PA polypeptides of broader scope than claim 1. The Written Opinion objects to claim 8 because “claim 1 is restricted to 6 ‘start’-sequences to which at maximum 9 modifications can be made, these claims refer to an end result having 85% identity to

any of said 'start'-sequences." Thus, the maximum number of replacements will allegedly differ based on the length of the 'start sequence,' from 38 replacements to 64 replacements, which, the Written Opinion claims, are both more than claim 1 allows. The Written Opinion also objects to claim 9, which allegedly recites a maximum of 15 replacements, as exceeding the scope allowed in claim 1. Claim 22 is similarly objected to.

Applicant respectfully disagrees. The number of modifications does depend on the length of the unmodified polypeptide; that does not render the claims unclear. Claim 1 recites that the modified u-PA polypeptide comprises any of one or more of the 9 recited replacements; this is open, non-limiting language. There is no limitation in claim 1 that the modified u-PA polypeptide contains only the recited replacements, the modified polypeptide can comprise any other replacements, so long as it comprises one or more of the replacements recited in claim 1, and, as amended, has at least 85% sequence identity to the unmodified u-PA polypeptide of any of SEQ ID NOs.1-6. Claims 8 and 9 are properly dependent because they recite a limitation on the number of replacements.

Nevertheless, claim 1 is amended to incorporate the limitation of claim 8 to recite that the modified polypeptide has at least 85% sequence identity with the unmodified polypeptide of any of SEQ ID NOs. 1-6. SEQ ID NOs. 1-6 set forth the sequences of WT full-length u-PA, WT protease domain u-PA, WT mature u-PA, full-length u-PA with C122S, protease domain u-PA with C122S, and mature u-PA with C122S, respectively. The number of replacements does depend upon the form of the polypeptide. The claims encompass precursor, mature, and other forms of modified u-PA polypeptides. As shown in the application as filed, different forms of u-PA are described and provided.

2.3.5 Claim 26 recites that the modifications recited in Table 14 are in the u-PA protease domain

Claim 26 is objected to because the Written Opinion alleges that table 14, referenced in the claim, discloses mutation strings, and not protease domains, as recited in the claim. Claim 26 (renumbered as claim 25) is amended to recite that the modifications recited in table 14 are in the u-PA protease domain, for clarity.

2.3.6 Claims 59 and 60 might be amended in the regional phase

Claims 59 and 60 are objected to because the claims refer to an incubation test that indicates a time for incubation, but does not indicate a temperature, which the Written Opinion considers an essential feature of the claim. **Claims 121, and 235-244** are objected to as unclear because the Written Opinion objects to the phrasing “for use for treating.”

Applicant respectfully disagrees that the claims are unclear. Because this is an international application which will be filed in numerous jurisdictions that have different standards for clarity and support, resolution of this issue is deferred to the national/regional stage. The claims will be amended, if necessary, upon national/regional stage entry.

2.3.7 Claims 240-244 are directed to pharmaceutical compositions

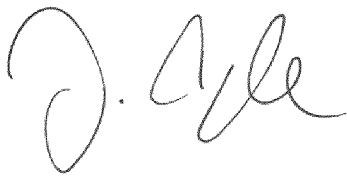
Claims 240-244 are objected to because the claims refer to the “method” of claim 239 and 235, when claims 239 and 235 are directed to pharmaceutical compositions. Claims 240-244 are amended to correct this inadvertent obvious typographical error in each claim.

The claims fulfil the requirements of clarity.

3 Conclusion

The international application complies with the requirements of the PCT and its Regulations. We request a positive international preliminary examination report to be issued.

However, if the Examiner is of the view that any objections remain outstanding, we request that the representative be informed as soon as possible. We would of course be pleased to discuss any outstanding issues with the Examiner by telephone. Alternatively, we request that a further communication be issued.

A handwritten signature in black ink, appearing to read 'J. Ogle'. The signature is fluid and cursive, with the first letter 'J' being large and prominent.

OGLE, James Matthew, PhD
European Patent Attorney
Hoffmann Eitle PartmbB
Association No. 151

Encl.: Amended set of claims (clean and marked-up)
Electronic debit order for the payment of official fees
Bode *et al.* (1989)
Hartley (1974)
Spraggon *et al.* (1995)

Amended Claims (Chapter II)

1. A modified urokinase-type plasminogen activator (u-PA) polypeptide, comprising one or more amino acid modifications selected from among modifications corresponding to R35Q, H37Y, V41R, Y40Q, D60aP, L97bA, T97aI and H99Q, and conservative amino acid modifications thereof, whereby the modified u-PA polypeptide has increased activity/specificity for a complement protein compared to the unmodified active form of the u-PA polypeptide, wherein:

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, which set forth wild-type (WT) full-length u-PA, WT protease domain u-PA, WT mature u-PA, full-length u-PA with C122S, by chymotrypsin numbering, protease domain u-PA with C122S, mature u-PA with C122S, or a catalytically active fragment thereof that includes the amino acid modification position(s);

the modified u-PA polypeptide has at least 85% sequence identity with a polypeptide of any of SEQ ID Nos. 1-6; and

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 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.

4. The modified u-PA polypeptide of any of claims 1-3 that has increased activity for cleavage of C3 that is least 3-fold greater than the unmodified u-PA polypeptide comprising the protease domain of SEQ ID NO:5, or a corresponding form of u-PA set forth in any of SEQ ID Nos. 1-4 and 6.

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

6. The modified u-PA polypeptide of any of claims 1-5, wherein the unmodified u-PA polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:2 or SEQ ID NO:5.

7. The modified u-PA polypeptide of any of claims 1-4 and 6, wherein the modified u-PA polypeptide has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with the polypeptides of any of SEQ ID NOs. 1-6 (WT full-length u-PA, WT protease domain u-PA, WT mature u-PA, full-length u-PA with C122S, protease domain u-PA with C122S, mature u-PA with C122S) or a catalytically active fragment thereof.

8. The modified u-PA polypeptide of any of claims 1-4 and 6, 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.

9. The modified u-PA polypeptide of any of claims 1-8, comprising the replacement V41R.

10. The modified u-PA polypeptide of any of claims 1-8, comprising the replacement V41L.

11. The modified u-PA polypeptide of claim 9 or claim 10, further comprising the replacement V38E.

12. The modified u-PA polypeptide of any of claims 1-11, comprising the replacement H37Y.

13. The modified u-PA polypeptide of any of claims 1-11, comprising the replacements H37Y/V38E.

14. The modified u-PA polypeptide of any of claims 1-11, comprising the replacements R35Y/H37K or R35Q/H37K.

15. The modified u-PA polypeptide of any of claims 1-11, comprising the replacements R35Y/H37K/V38E or R35Q/H37K/V38E.

16. The modified u-PA polypeptide of any of claims 1-11, comprising the replacement L97bA.

17. The modified u-PA polypeptide of any of claims 1-11, comprising R35Q.

18. The modified u-PA polypeptide of any of claims 1-11, comprising H99Q.

19. The modified u-PA polypeptide of any of claims 1-11, comprising D60aP.
20. The modified u-PA polypeptide of any of claims 1-11, comprising T97aI.
21. The modified u-PA polypeptide of any of claims 1-20, further comprising the amino acid replacement corresponding to T39Y, T39W, T39F or conservative replacements selected from T39M or T39L.
22. The modified u-PA polypeptide of any of claims 1-21, further comprising the amino acid replacement T39Y.
23. The modified u-PA polypeptide of any of claims 1-22, further comprising the amino acid replacements R35Q/H37Y or V38E/V41R/Y149R or R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aT/Y60bT/T97aI/L97bA/H99Q/C122S/Y149R.
24. The modified u-PA polypeptide of any of claims 1-23, wherein the modified u-PA polypeptide has ED₅₀ for inactivation cleavage of C3 of less than or 100 nM, or 50 nM or 30 nM or 25 nM in an in vitro assay.
25. The modified u-PA polypeptide of claim 24, wherein:
the polypeptide comprises the modifications in the protease domain set forth in Table 14; and
has an ED₅₀ of 100 nM or less, has an ED₅₀ less of 50 nM or less, or has an ED₅₀ less than 30 nM, or has an ED₅₀ less than 25 nM.
26. The modified u-PA polypeptide of claim 24 or claim 25, wherein the assay comprises incubation of the substrate complement protein human C3 with various concentrations of each modified protease for 1 hour at 37 °C to determine the ED₅₀.
27. The modified u-PA polypeptide of any of claims 1-26 that cleaves C3 with an ED₅₀ of 50 nM or less.
28. The modified u-PA polypeptide of claim 27, comprising the modification V41R.
29. The modified u-PA polypeptide of claim 27, comprising the modifications V38E/V41R.
30. The modified u-PA polypeptide of claim 28, further comprising a replacement at one or more of positions R35, H37 and V38.
31. The modified u-PA polypeptide of claim 30, wherein the replacement at V38 is E.

32. The modified u-PA polypeptide of any of claims 1-31, comprising R35Y/H37S/V38E/V41R.

33. The modified u-PA polypeptide of any of claims 1-32, 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;

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V38D/T39Y/Y40L/V41R/L97bI/H99E/C122S/R217E;

F30Y/R36H/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/M157K/T158A;

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F30Y/R35I/R36H/H37D/V38E/T39F/Y40F/V41R/T97aI/L97bA/H99Q/C122S/Y149R/M157K;

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 Q192A;
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 V38D/V41R/L97bG/H99Q/C122S/Y151L/R217A;
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 F30Y/V38D/Y40H/V41R/L97bA/H99Q/C122S/M157K;
 F30Y/R36H/V38E/Y40H/V41R/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 R35A/R37aE/V38E/Y40Q/V41L/L97bA/H99Q/C122S/Y149R;
 V38D/V41L/L97bG/H99Q/C122S/Y151L/R217Q;
 F30H/R35Q/H37W/V38D/V41R/D60aE/L97bA/H99Q/C122S/Y149L/Y151L/M157K/R217D;
 F30Y/R35F/R36H/H37G/V38E/T39Y/Y40H/V41R/Y60bS/T97aD/L97bA/H99Q/C122S/Y149R/M157K;
 T39Y/V41R/L97bG/H99Q/C122S;
 F30Y/R35I/R36H/H37E/V38E/T39Y/Y40H/V41R/Y60bS/T97aV/L97bA/H99Q/C122S/Y149L/M157K;
 R35S/R37aD/V38E/Y40Q/V41L/L97bA/H99Q/C122S/Y149R;
 Y40H/V41Q/L97bG/H99Q/C122S/R217T;
 R35W/H37D/V38D/T39Y/V41R/Y60bS/L97bA/H99Q/C122S/Y149R;

V38D/T39F/Y40L/V41R/T97aW/L97bA/H99Q/C122S;
 V38D/T39Y/Y40L/V41R/T97aE/L97bA/H99Q/C122S;
 F30Y/R35Q/R36H/H37G/R37aE/V38E/T39F/Y40F/V41R/D60aP/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 V38D/T39L/Y40L/V41R/T97aI/L97bA/H99Q/C122S;
 V38D/T39Y/Y40L/V41R/T97aW/L97bA/H99Q/C122S;
 F30Y/R36H/V38D/Y40H/V41R/L97bA/H99L/C122S/F141L/M157K/T158A;
 F30Y/R35Q/R36H/H37G/R37aE/V38E/T39Y/Y40F/V41R/D60aA/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 F30Y/R35Q/R36H/H37G/R37aE/V38E/T39Y/Y40F/V41R/D60aP/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 T39Y/V41R/Y60bP/L97bG/H99Q/C122S;
 F30H/R36H/V38D/V41R/T56A/L97bA/H99Q/C122S/Y151L/M157K;
 F30Y/R35E/R36H/H37D/R37aN/V38E/T39Y/Y40F/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 V38E/Y40Q/V41L/D60aP/Y60bL/L97bA/H99Q/C122S/Y149W;
 F30Y/R36H/V38E/Y40H/V41R/T97aI/L97bA/H99Q/C122S/M157K;
 F30H/R35Q/H37W/V38D/V41R/D60aE/Y60bS/L97bA/H99Q/C122S/Y149L/Y151L/M157K;
 R35Q/H37G/R37aE/V38E/T39Y/V41R/D60aP/Y60bT/T97aI/L97bA/H99Q/C122S/Y149R;
 F30Y/R35W/R36H/H37S/V38E/T39Y/Y40H/V41R/Y60bN/T97aE/L97bA/H99Q/C122S/Y149R/Y151P/M157K/Q192H;
 F30Y/R35M/R36H/H37D/R37aD/V38E/T39Y/Y40F/V41R/D60aP/Y60bS/T97aE/L97bA/H99Q/C122S/Y149R/M157K;
 F30Y/R35W/R36H/H37D/V38E/T39Y/Y40H/V41R/Y60bT/T97aD/L97bA/H99Q/C122S/Y149R/M157K;
 V38D/T39L/Y40L/V41R/T97aV/L97bA/H99Q/C122S;
 V38D/V41R/Y60bS/T97aI/L97bR/H99E/C122S/Y151L/E175D/Q192F/R217E/K224R;
 T39Y/V41R/Y60bP/L97bA/H99Q/C122S;
 R36H/V38D/Y40F/V41R/D97E/A98G/T97adel/H99L/L97bdel/C122S/Y151L/Q192E/R217D;
 R35M/H37G/R37aD/V38E/T39W/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R;
 ;
 F30Y/V38D/Y40L/V41R/L97bA/H99Q/C122S/Y151L/M157K/Q192H;
 F30H/V38D/Y40F/V41R/L97bA/H99Q/C122S/Y151L/M157F;
 H37M/R37aD/V38E/T39A/V41R/D60aP/Y60bS/T97aI/L97bA/H99Q/C122S/Y149R;
 F30H/V38D/V41R/L97bA/H99Q/Y151L/M157K;
 T22I/F30Y/R35S/V38D/Y40H/V41R/L97bA/H99Q/C122S/I138V/M157K;

R35L/H37D/R37aS/V38E/T39Y/V41R/D60aP/Y60bD/T97aI/L97bA/H99Q/C122S/Y149R;
 F30Y/R35L/V38D/Y40H/V41R/N76S/L97bA/H99Q/C122S/M157K/K187E;
 F30H/V38D/V41R/L97bA/H99Q/C122S/Y151L/M157S;
 R35W/H37D/V38D/T39Y/V41R/Y60bH/L97bA/H99Q/C122S/Y149R;
 F30Y/R36H/H37G/V38E/T39W/Y40H/V41R/Y60bA/T97aE/L97bA/H99Q/C122S/Y149Q/
 M157K;
 R35Q/H37G/R37aE/V38W/T39Y/V41R/Y60bK/T97aS/L97bR/H99E/C122S/Y151L/E175D/
 Q192T/R217E/K224R;
 H37G/R37aD/G37bD/V38F/T39H/V41R/Y60bK/L97bR/H99E/C122S/Y151L/E175D/Q192
 T/R217E/K224R;
 V38D/T39Y/Y40M/V41R/T97aE/L97bA/H99Q/C122S;
 R35Q/H37N/V38D/T39Y/V41R/Y60bP/L97bA/H99Q/C122S;
 F30Y/R35W/R36H/H37D/V38E/T39Y/Y40F/V41R/Y60bS/T97aE/L97bA/H99Q/C122S/Y1
 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;
 Y40H/V41T/L97bG/H99Q/C122S/R217T; and
 any of these polypeptides in which C122S is C122C, by chymotrypsin numbering.

34. The modified u-PA polypeptide of any of claims 1-33, further comprising one
 or more of the amino acid modifications R35Q, Y60bQ and Y149R.

35. The modified u-PA polypeptide of any of claims 1-34, further comprising the amino acid modification R37aE or R37aS.

36. The modified u-PA polypeptide of any of claims 1-35, comprising the replacements R35Q/H37Y/T39Y/V41R or R35Q/H37Y/T39Y/V41R/C122S.

37. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications R35Q/H37Y/T39Y/V41R/L97bA/H99Q/C122S or R35Q/H37Y/T39Y/V41R/L97bA/H99Q.

38. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications T39Y/V41R/Y60bQ/L97bA/H99Q or T39Y/V41R/Y60bQ/L97bA/H99Q/C122S.

39. The modified u-PA polypeptide of any of claims 1-35, comprising the replacements T39Y/V41R/D60aP/L97bA/H99Q/C122S or T39Y/V41R/D60aP/L97bA/H99Q.

40. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications corresponding to Y40Q/V41L/L97bA/C122S or Y40Q/V41R/L97bA/C122S or Y40Q/V41L/L97bA or Y40Q/V41R/L97bA.

41. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications corresponding to R37aS/V41R/L97bG/H99Q or R37aS/V41R/L97bG/H99Q/C122S.

42. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications corresponding to T39Y/V41L/L97bA/H99Q/C122S or T39Y/V41R/L97bA/H99Q/C122S or T39Y/V41L/L97bA/H99Q or T39Y/V41R/L97bA/H99Q.

43. The modified u-PA polypeptide of claim 40, further comprising the replacement corresponding to H99Q.

44. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications corresponding to 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.

45. The modified u-PA polypeptide of claim 44, wherein the unmodified polypeptide consists of the polypeptide of SEQ ID NO:2 or SEQ ID NO:5, the protease domain.

46. The modified u-PA polypeptide of claim 44, wherein the unmodified polypeptide consists of the mature u-PA of SEQ ID NO:3 or SEQ ID NO:6.

47. The modified u-PA polypeptide of claim 44, wherein the unmodified polypeptide consists of the pro-peptide of SEQ ID NO:1 or SEQ ID NO:4.

48. The modified u-PA polypeptide of any of claims 1-35, comprising the amino acid modifications:

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 each with no replacement at C122.

49. The modified u-PA polypeptide of any of claims 1-35 comprising the amino acid modifications corresponding to
 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 protease domain set forth in SEQ ID NO:2 or SEQ ID NO:5.

50. The modified u-PA polypeptide of any of claims 1-49, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 8-44.

51. The modified u-PA polypeptide of any of claims 1-50, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:21 or 987.

52. The modified u-PA polypeptide of any of claims 1-50, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:18.

53. The modified u-PA polypeptide of any of claims 1-52, wherein the unmodified u-PA polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO:5.

54. The modified u-PA polypeptide of claim 48, wherein the unmodified u-PA polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO:2 or SEQ ID NO:5.

55. The modified u-PA polypeptide of claim 49, wherein the unmodified u-PA polypeptide consists of the sequence of amino acid residues set forth in SEQ ID NO:5.

56. The modified u-PA polypeptide of any of claims 1-55 that cleaves within residues QHARASHLG (residues 737-745) of human C3 (SEQ ID NO:47).

57. The modified u-PA polypeptide of claim 56, wherein P1-P1' is RA.

58. The modified u-PA polypeptide of any of claims 1-57 that has stability of greater than 50% after incubation in PBS, or a body fluid for 7 days.

59. The modified u-PA polypeptide of any of claims 1-58 that has stability of greater than 80% after incubation in PBS, or a body fluid for 7 days.

60. The modified u-PA polypeptide of claim 58 or claim 59, wherein incubation is effected in a body fluid.

61. The modified u-PA polypeptide of claim 60, wherein the body fluid is aqueous humor.

62. The modified u-PA polypeptide of any of claims 1-61, wherein the modified u-PA polypeptide, when in active form, has at least 100-fold decreased activity on plasmin compared to a corresponding form of unmodified u-PA polypeptide.

63. The modified u-PA polypeptide of any of claims 1-62 that is conjugated to another moiety or polymer either directly or via a linker.

64. The modified u-PA polypeptide of claim 63 that is a fusion protein.

65. The modified u-PA polypeptide of claim 63 or claim 64 that is PEGylated.

66. The modified u-PA polypeptide of any of claims 1-65 that comprises a polymer that increases serum half-life and/or to reduces immunogenicity or both.

67. The modified u-PA polypeptide of claim 66, wherein the polymer comprises a polypeptide.

68. The modified u-PA polypeptide of any of claims 63-67 that is linked directly or indirectly to serum albumin.

69. The modified u-PA polypeptide of claim 68, wherein the serum albumin is a human serum albumin (HSA).

70. The modified u-PA polypeptide of claim 68 or claim 69, wherein 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 thereto.

71. The modified u-PA polypeptide of claim 63, wherein the polymer is an Fc domain.

72. The modified u-PA polypeptide of claim 71, wherein the Fc domain comprises the sequence set forth in SEQ ID NO: 50 or SEQ ID NO:992 or a form that has at least 90% or at least 95% sequence identity thereto.

73. The modified u-PA polypeptide of any of claims 63-72, wherein the polymer is linked directly to the modified u-PA polypeptide.

74. The modified u-PA polypeptide of any of claims 63-73 wherein the polypeptide or polymer is linked via a peptide linker to the modified u-PA polypeptide.

75. The modified u-PA polypeptide of claim 74, wherein the linker comprises Gly and/or Ser.

76. The modified u-PA polypeptide of claim 74 or 75, wherein the linker contains up to 20, 30, 40, or 50 amino acid residues.

77. The modified u-PA polypeptide of claim 74, 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 S, G, E and K.

78. The modified u-PA of claim 77, comprising the sequence of amino acid residues set forth in any of SEQ ID Nos: 1001-1003, 1024-1029 and multimers thereof and sequences having at least 99% sequence identity thereto.

79. A fusion protein, comprising a modified u-PA polypeptide or a catalytically active portion of a modified u-PA polypeptide of any of claims 1-78 that is fused to a non-protease polypeptide or a portion thereof.

80. The fusion protein of claim 79, wherein the non-protease polypeptide is a multimerization domain or a protein transduction domain (PTD).

81. The fusion protein of claim 79, wherein the non-protease polypeptide is a multimerization domain that is an Fc domain.

82. The fusion protein of claim 79 that comprises a furin activation site.

83. The fusion protein of claim 82, wherein the furin activation site comprises QSGQKTLRRRK (SEQ ID NO:996) or QCGQKTLRRRK (SEQ ID NO:995) or

QSGQKTLRRKR (SEQ ID NO: 1044) or a furin activation site having at least 98% sequence identity thereto.

84. A fusion protein, comprising a modified u-PA polypeptide or catalytically active portion thereof of any of claims 1-78, wherein the fusion protein comprises a signal sequence and the modified u-PA polypeptide or catalytically active portion thereof.

85. The fusion protein of claim 84, wherein the signal sequence is from Il-2, u-PA, or IgGκ.

86. A fusion protein of any of claims 79-85, comprising a fusion partner.

87. The fusion protein of claim 86, wherein the fusion partner is a multimerization domain.

88. The fusion protein of claim 86, 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).

89. The fusion protein of claim 88, wherein the fusion partner is a HABD that is Tumor Necrosis factor-Stimulated Gene-6 (TSG-6).

90. The fusion protein of claim 88, wherein the fusion partner is HSA.

91. The fusion protein of claim 88, wherein the fusion partner is IgG Fc.

92. The fusion protein of claim 88, wherein the fusion partner is an anti-type II collagen antibody scFv fragment or an anti-VEGFR antibody or fragment thereof.

93. The fusion protein of any of claims 79-92, comprising an activation sequence.

94. The fusion protein of claim 93, 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.

95. The fusion protein of claim 93, wherein the activation sequence is a u-PA activation sequence or a furin activation sequence.

96. The fusion protein of claim 95, 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.

97. The fusion protein of any of claims 79-96, comprising an activation sequence, a modified u-PA polypeptide, and HSA.

98. A fusion protein of claim 79, comprising the sequence of amino acids set forth in any of SEQ ID NOs: 1006, 1007, 1009, and 1010.

99. A fusion protein of claim 79, comprising the sequence of amino acids set forth in any of SEQ ID Nos: 1004-1019 and 1034-1040.

100. The fusion protein of claim 79, comprising the sequence of amino acids set forth in SEQ ID NO:1015 or 1019.

101. The fusion protein of any of claims 79-100 that does not have a signal sequence or from which the signal sequence has been removed upon expression.

102. A fusion of any of claims 79-101 that is a two-chain activated form containing an A chain and a B chain.

103. The fusion protein of claim 102, wherein the B chain starts at residues IIGG of the modified u-PA polypeptide and ends at the C-terminus of the fusion protein.

104. A fusion protein of claim 102, comprising a modified u-PA polypeptide and HSA.

105. The fusion protein of claim 102 or claim 103, 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.

106. The fusion protein of claim 105, 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.

107. The fusion protein of any of claims 79-106 that is a two chain activated fusion protein, 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; and the A and B chains are linked via a disulfide bridge between C168 and C299 of SEQ ID NO:1015.

108. The fusion protein of claim 87 that is a dimer via interaction of complementary multimerization domains.

109. The fusion protein of claim 108, wherein the multimerization domain is an Fc domain.

110. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified u-PA polypeptide or fusion protein of any of claims 1-109.

111. A vector, comprising the nucleic acid molecule of claim 110.

112. The vector of claim 111 that is a prokaryotic vector.

113. The vector of claim 111 that is a eukaryotic vector.

114. The vector of claim 111 that is a viral vector.

115. The vector of claim 111 that is a yeast vector.

116. The vector of any of claims 111-115 that is a herpes virus simplex vector, or a vaccinia virus vector, or an adenoviral vector, or an adeno-associated viral vector, or a retroviral vector, or an insect vector.

117. The vector of any of claims 111-116 that is an expression vector.
118. The vector of any of claims 111-116 that is a gene therapy vector.
119. Use of the nucleic acid of claim 110 or the vector of any of claims 111-118 for gene therapy 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.
120. The vector of any of claims 111-118 for use for treating a complement mediated disease by inhibiting complement activation.
121. A method of treating a disease or condition mediated by or involving complement activation, comprising administering the nucleic acid molecule of claim 110 or the vector of any of claims 111-118.
122. The method of claim 121, wherein the complement-mediated disease or condition is selected from among inflammatory diseases and conditions, 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.
123. The method of claim 121, wherein the disease or condition is an ocular or ophthalmic disease or is rejection or inflammation due to a transplanted organ.
124. The method of claim 121, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.
125. The method of claim 121, wherein the disease or condition is a macular degeneration.
126. The method of claim 124, wherein the macular degeneration is age-related macular degeneration (AMD).
127. The method of claim 121, wherein the disease or condition is delayed renal graft function (DGF).
128. The method of claim 121, wherein the disease or condition is atypical hemolytic uremic syndrome (aHUS).
129. The method of claim 121, wherein the disease or condition is Complement 3 Glomerulopathy (C3G).

130. The use of claim 119, wherein the complement-mediated disease or condition is selected from among inflammatory diseases and conditions, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), sepsis, Rheumatoid arthritis (RA), an ocular disease, 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), and Ischemia-reperfusion injury.

131. The use of claim 119, wherein the disease or condition is an ophthalmic or ocular disease or is rejection or inflammation due to a transplanted organ.

132. The use of claim 119, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

133. The use of claim 119, wherein the disease or condition is a macular degeneration.

134. The use of claim 132, wherein the macular degeneration is age-related macular degeneration (AMD).

135. The use of claim 119, wherein the disease or condition is delayed renal graft function (DGF).

136. The use of claim 119, wherein the disease or condition is atypical hemolytic uremic syndrome (aHUS).

137. The use of claim 119, wherein the disease or condition is Complement 3 Glomerulopathy (C3G).

138. An isolated cell or a cell culture, comprising the nucleic acid molecule of claim 110 or the vector of any of claims 111-118.

139. A non-human cell, comprising the nucleic acid molecule of claim 110 or the vector of any of claims 111-118.

140. An isolated cell, comprising the nucleic acid molecule of claim 110 or the vector of any of claims 111-118, wherein the isolated cell is not a human zygote.

141. A method of inhibiting complement activation, comprising contacting a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109, in active form, with complement protein C3, whereby complement protein C3 is cleaved such that complement activation is reduced or inhibited.

142. The method of claim 141, wherein contacting the modified u-PA polypeptide with complement protein C3 is effected in vitro.

143. The method of claim 11, wherein contacting the modified u-PA polypeptide with complement protein C3 is effected in vivo.

144. The method of any of claims 141-143, wherein the inhibition of complement activation leads to a reduction of inflammatory symptoms associated with a complement-mediated disease or disorder selected from among an inflammatory disorder, a neurodegenerative disorder, and a cardiovascular disorder.

145. The method of claim 144, wherein the complement-mediated disease or disorder is selected from among inflammatory diseases and conditions, sepsis, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), Rheumatoid arthritis (RA), ocular 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), and ischemia-reperfusion injury.

146. The method claim 145, wherein the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

147. The method of any of claims 141-146, wherein the complement mediated disease or disorder results from treatment of a subject.

148. The method of any of claims 141-147, wherein treatment with the modified u-PA polypeptide is effected prior to treatment of a subject.

149. A method of treating a disease or condition mediated by or involving complement activation, comprising administering a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109, in active form, wherein inhibition of complement activation effects treatment or amelioration of the disease or condition.

150. The method of claim 149, wherein the complement-mediated disease or condition is selected from among inflammatory diseases and conditions, sepsis, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), Rheumatoid arthritis (RA), an ocular disease, 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), and Ischemia-reperfusion injury.

151. The method of claim 149, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

152. The method of claim 149, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

153. The method of claim 149, wherein the disease or condition is a macular degeneration.

154. The method of claim 153, wherein the macular degeneration is age-related macular degeneration (AMD).

155. The method of claim 149, wherein the disease or condition is delayed renal graft function (DGF).

156. The method of claim 149, wherein the disease or condition is atypical hemolytic uremic syndrome (aHUS).

157. The method of claim 149, wherein the disease or condition is Complement 3 Glomerulopathy (C3G).

158. The method or use of any of claims 119-137 and 141-157, wherein the modified u-PA polypeptide or encoding nucleic acid molecule or vector is administered intravenously.

159. The method or use of any of claims 119-137 and 141-157, wherein the modified u-PA polypeptide or encoding nucleic acid molecule or vector is administered subcutaneously.

160. The method or use of any of claims 119-137 and 141-157, wherein the modified u-PA polypeptide or encoding nucleic acid molecule or vector is administered to the eye.

161. The method or use of claim 160, wherein administration to the eye is effected by intravitreal or sub-retinal or intra-retinal injection.

162. The method or use of claim 160 or claim 161, wherein the modified u-PA polypeptide is linked to a transduction domain to facilitate transduction into the vitreous humor.

163. The method or use of any of claims 119-137 and 141-162, wherein the modified u-PA polypeptide is PEGylated.

164. The method or use of any of claims 119-137 and 141-162, wherein the modified u-PA polypeptide is modified by albumination, glycosylation, farnesylation, carboxylation, hydroxylation, phosphorylation, HESylation, and/or PASylation.

165. The method or use of any of claims 119-137 and 141-164, wherein a single dosage is 0.1 to 10 mg dependent upon route of administration.

166. The method or use of any of claims 119-137 and 141-165, wherein the treatment is repeated a plurality of times.

167. The method or use of any of claims 119-137 and 141-166, wherein the treatment is repeated every 2 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-monthly or monthly.

168. The method of any of claims 119-137 and 141-167, wherein treatment is repeated every two months, every three months or every four months.

169. A combination, comprising:

(a) a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109; and

(b) a second agent or agents for treating a complement-mediated disease or disorder.

170. The combination of claim 169, wherein the second agent or agents is an anti-inflammatory agent(s) or anticoagulant(s).

171. The combination of claim 169 or claim 170, wherein the second agent is an anti-inflammatory agent(s) selected from among any one or more of a nonsteroidal anti-inflammatory drug (NSAID), antimetabolite, corticosteroid, analgesic, cytotoxic agent, pro-inflammatory cytokine inhibitor, anti-inflammatory cytokine, B cell targeting agent, compound targeting T antigens, adhesion molecule blocker, chemokine receptor antagonist, kinase inhibitor, PPAR- γ (gamma) ligand, complement inhibitor, heparin, warfarin, acenocoumarol, phenindione, EDTA, citrate, oxalate, argatroban, lepirudin, bivalirudin, and ximelagatran.

172. The method, use or combination of any of claims 119-137 and 141-168, wherein the modified u-PA polypeptide comprises the modification V41R or V41L.

173. The method, use or combination of any of claims 119-137 and 141-168, wherein the modified u-PA polypeptide comprises the modification V41R.

174. The method, use or combination of any of claims 119-137 and 141-168, wherein the modified u-PA polypeptide comprises the modifications V38E/V41R.

175. The method, use or combination of any of claims 119-137 and 141-168, wherein the modified u-PA polypeptide comprises the modifications Y40Q/V41R/L97bA or Y40Q/V41L/L97bA or R37aS/V41R/L97bG/H99Q.

176. The method, use or combination of any of claims 119-137 and 141-168, wherein the modified u-PA polypeptide comprises the modifications:

R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/Y149R.

177. The method, use or combination of any of claims 172-176, wherein the unmodified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO:2 or SEQ ID NO:5

178. The modified u-PA polypeptide of any of claims 1-78 or the fusion protein of any of claims 79-109, method, use or combination of any of claims 119-137 and 141-177, wherein the modified u-PA polypeptide or fusion protein comprises the sequence of amino acid residues set forth in SEQ ID NO: 21 or 987 or in any of SEQ ID Nos: 40-44, or 40-44 without the modification at C122, by chymotrypsin numbering.

179. A method of treating DGF, comprising intravenously administering a modified u-PA polypeptide of any of claims 1-78 or the fusion protein of any of claims 79-109.

180. A method of treating atypical hemolytic uremic syndrome (aHUS), comprising administering a modified u-PA polypeptide of any of claims 1-78 or the fusion protein of any of claims 79-109.

181. A method of treating Complement 3 Glomerulopathy (C3G), comprising administering a modified u-PA polypeptide of any of claims 1-78 or the fusion protein of any of claims 79-109.

182. The method of any of claims 179-181, wherein a single dosage is 0.1 to 3 mg, or 0.1 to 2 mg, or 1 to 3 mg, or 1 to 10 mg.

183. The method of any of claims 179-181, wherein the modified u-PA polypeptide or fusion protein comprises the sequence of amino acid residues set forth in SEQ ID NO: 21 or 987 or in any of SEQ ID NOS: 40-44, or 40-44 without the modification at C122, by chymotrypsin numbering.

184. The method of any of claims 179-183, wherein the treatment is repeated a plurality of times.

185. The method of any of claims 179-184, wherein the treatment is repeated every 2 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-monthly or monthly.

186. The method of any of claims 179-185, wherein treatment is repeated every two months, every three months, or every four months.

187. The method of any of claims 101-105, wherein the modified u-PA polypeptide comprises the replacements

R35Q/H37Y/R37aE/V38E/T39Y/V41R/D60aP/Y60bQ/T97aI/L97bA/H99Q/C122S/Y149R.

188. The method of any of claims 179-187, wherein the modified u-PA polypeptide or fusion protein comprises the protease domain set forth in SEQ ID NO:21 or 987 or a catalytically active portion thereof.

189. A method of treating an ophthalmic disorder or ocular disorder, comprising administering a modified u-PA polypeptide of any of claims 1-71 or the fusion protein of any of claims 79-109 to the eye.

190. The method of claim 189, wherein the disorder is macular degeneration or diabetic retinopathy.

191. The method of claim 190, wherein the disorder is AMD.

192. The method of any of claims 189-191, wherein a single dosage is from 0.1 mg to 2 mg/ eye or 3 mg/eye.

193. The method of any of claims 189-191, wherein a single dosage is from 1 mg to 2 mg/eye.

194. The method of any of claims 189-191, wherein a single dosage is 0.1 to 1 mg.

195. The method of any of claims 179-194, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in any of SEQ ID NO: 21 or 987 or any of SEQ ID NOs: 40-44, or 40-44 without the modification at C122, by chymotrypsin numbering.

196. The method of any of claims 179-195, wherein the treatment is repeated a plurality of times.

197. The method of any of claims 179-196, wherein the treatment is repeated every 2 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-monthly or monthly, every two months, every three months, or every four months.

198. The method of any of claims 179-197, wherein the modified u-PA polypeptide comprises the replacements
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.

199. The method of any of claims 179-198, wherein the modified u-PA polypeptide comprises the replacements Y40Q/V41L/L97bA/C122S or Y40Q/V41R/L97bA/C122S or Y40Q/V41L/L97bA or Y40Q/V41R/L97bA.

200. The method of any of claims 179-199, wherein the modified u-PA polypeptide comprises the protease domain set forth in SEQ ID NO:21 or 987 or a catalytically active portion thereof.

201. Use of a modified u-PA polypeptide for treating AMD or DGF, wherein the modified u-PA polypeptide comprises the replacements
 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 or
 Y40Q/V41L/L97bA/C122S or Y40Q/V41R/L97bA/C122S or Y40Q/V41L/L97bA or
 Y40Q/V41R/L97bA.

202. Use of a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109, in active form, for inhibiting complement activation.

203. The use of claim 202, wherein:

the modified u-PA polypeptide is contacted with complement protein C3, whereby complement protein C3 is cleaved such that complement activation is reduced or inhibited; and

contacting the modified u-PA polypeptide with complement protein C3 is effected in vitro or in a non-human animal.

204. The use of claim 202, wherein contacting the modified u-PA polypeptide with complement protein C3 is effected in vivo.

205. The use of any of claims 202-204, wherein the inhibition of complement activation leads to a reduction of inflammatory symptoms associated with a complement-mediated disease or disorder selected from among an inflammatory disorder, a neurodegenerative disorder, and a cardiovascular disorder.

206. The use of claim 205, wherein the complement-mediated disease or disorder is selected from among inflammatory diseases and conditions, sepsis, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), Rheumatoid arthritis (RA), ocular 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), and Ischemia-reperfusion injury.

207. The use of claim 206, wherein the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

208. The use of any of claims 202-207, wherein the complement mediated disease or disorder results from treatment of a subject.

209. The use of any of claims 202-208, wherein treatment with the modified u-PA polypeptide is effected prior to treatment of a subject.

210. Use of a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109, in active form, 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.

211. The use of claim 210, wherein the complement-mediated disease or condition is selected from among inflammatory diseases and conditions, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), sepsis, Rheumatoid arthritis (RA), an ocular disease, 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), and Ischemia-reperfusion injury.

212. Use of a nucleic acid encoding a modified u-PA polypeptide of any of claims 1-41 or a vector comprising the nucleic acid for gene therapy.

213. The use of any of claims 210-212, wherein the disease or condition is an ocular disease or is rejection or inflammation due to a transplanted organ.

214. The use of claim 210 or claim 212, wherein the disease or condition is a diabetic retinopathy or a macular degeneration.

215. The use of claim 210 or claim 212, wherein the disease or condition is a macular degeneration.

216. The use of claim 215, wherein the macular degeneration is age-related macular degeneration (AMD).

217. The use of claim 210 or claim 212, wherein the disease or condition is delayed renal graft function (DGF).

218. The use of claim 210 or claim 212, wherein the disease or condition is atypical hemolytic uremic syndrome (aHUS).

219. The use of claim 210 or 212, wherein the disease or condition is Complement 3 Glomerulopathy (C3G).

220. The use of any of claims 212-217 for intravitreal or intraretinal or sub-retinal injection for treatment of an ophthalmic disorder.

221. The use of claim 220, wherein a single dosage is 0.1 to 1 mg.

222. The use of claim 220, wherein a single dosage is from 0.1 mg to 2 mg/ eye or 3 mg/eye.

223. The use of claim 220, wherein a single dosage is from 1 mg to 2 mg/eye.
224. The use of any of claims 202-223, wherein the modified u-PA polypeptide comprises the sequence of amino acid residues set forth in SEQ ID NO: 21 or 987 or in any of SEQ ID NOS 40-44, or 40-44 without the modification at C122, by chymotrypsin numbering.
225. The use of any of claims 202-224, wherein the treatment is repeated a plurality of times.
226. The use of any of claims 202-225, wherein the treatment is repeated every 2 days, 3 days, 4 days, 5 days, 6 days, weekly, bi-monthly or monthly, every two months, every three months, or every four months.
227. A method of making a modified u-PA polypeptide, comprising:
introducing a nucleic acid or vector encoding a polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109 into a cell;
culturing the cell under conditions whereby the polypeptide is expressed; and
optionally, isolating the expressed polypeptide.
228. The method of claim 227, wherein the cell is a eukaryotic cell.
229. The method of claim 228, wherein the cell is a mammalian cell or a yeast cell.
230. A pharmaceutical composition, comprising a modified u-PA polypeptide of any of claims 1-78 or a fusion protein of any of claims 79-109 in a pharmaceutically acceptable vehicle.
231. The pharmaceutical composition of claim 230, wherein the modified u-PA polypeptide or fusion protein is in a two-chain activated form.
232. The pharmaceutical composition of claim 230 or claim 231, wherein the modified u-PA polypeptide or fusion protein comprises a protease domain of SEQ ID NO:21 or SEQ ID NO:987.
233. The pharmaceutical composition of any of claims 230-232, wherein the modified u-PA polypeptide or fusion protein has the sequence set forth in SEQ ID NO:1015 or 1019.
234. The pharmaceutical composition of any of claims 230-233 for use for treatment of a complement mediated disease or disorder or condition.
235. The pharmaceutical composition of claim 234, wherein the complement-mediated disease or disorder is selected from among an inflammatory disorder, a neurodegenerative disorder, and a cardiovascular disorder.

236. The pharmaceutical composition of claim 234, wherein the complement-mediated disease or disorder is selected from among inflammatory diseases and conditions, Complement 3 Glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), sepsis, Rheumatoid arthritis (RA), ocular 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), and Ischemia-reperfusion injury.

237. The pharmaceutical composition of claim 234, wherein the disease or disorder is an ocular disease or is rejection or inflammation due to a transplanted organ.

238. The pharmaceutical composition of claim 237, wherein the disease or condition is an ocular disease that is diabetic retinopathy or a macular degeneration.

239. The pharmaceutical composition of claim 238, wherein the disease or disorder or condition is a macular degeneration.

240. The pharmaceutical composition of claim 239, wherein the macular degeneration is age-related macular degeneration (AMD).

241. The pharmaceutical composition of claim 234, wherein the disease or condition is delayed renal graft function (DGF).

242. The pharmaceutical composition of claim 234, wherein the disease or condition is atypical hemolytic uremic syndrome (aHUS).

243. The pharmaceutical composition of claim 234, wherein the disease or condition is Complement 3 Glomerulopathy (C3G).