fibrin. In contrast, u-PA has a low binding specificity to fibrin and administration of u-PA promotes systemic fibrinolysis. Because of this, there is a concern for the risk that a hemorrhagic complication may develop. For the reason, t-PA is more preferably used for treating thrombosis rather than u-PA.

[0004]

Antibodies binding to fibrin with a stronger affinity than to fibrinogen have been developed (Patent Literatures 1 and 2). These Patent Literatures disclose that the antibodies are used for treating cancer.

Citation List

Patent Literatures

[0005]

Patent Literature 1: WO2014/133093

Patent Literature 2: WO2018/203517

Summary of Invention

[0006]

The present ~~invention~~ disclosure provides a fusion protein suitable for dissolving a fibrin clot and a pharmaceutical composition containing the fusion protein.

[0006a] In one aspect, the present disclosure provides a fusion protein comprising an antibody that binds to insoluble fibrin or an antigen-binding fragment thereof and a catalytic domain of prourokinase, wherein the

antibody or the antigen-binding fragment thereof and the catalytic domain of prourokinase are linked directly or via a linker to each other.

[0006b] In another aspect, the present disclosure provides a pharmaceutical composition comprising the fusion protein according to the disclosure.

[0006c] In another aspect, the present disclosure provides a use of the pharmaceutical composition according to the disclosure, in the manufacture of a medicament for dissolving a fibrin clot.

[0006d] In another aspect, the present disclosure provides a use of the pharmaceutical composition according to the disclosure in the manufacture of a medicament for treating a disease selected from cerebrovascular disorder and myocardial infarction.

[0007]

According to the present ~~invention~~disclosure, the following ~~invention~~disclosures are provided.

Claims

[Claim 1]

A fusion protein comprising an antibody that binds to insoluble fibrin or an antigen-binding fragment thereof and a catalytic domain of prourokinase, wherein the antibody or the antigen-binding fragment thereof and the catalytic domain of prourokinase are linked directly or via a linker to each other.

[Claim 2]

The fusion protein according to claim 1, wherein the linker is a non-cleavable linker.

[Claim 3]

The fusion protein according to claim 1 or 2, wherein the linker is a peptide linker.

[Claim 4]

The fusion protein according to any one of claims 1 to 3, further comprising a kringle domain, wherein the kringle domain and the catalytic domain are linked to each other in this order.

[Claim 5]

The fusion protein according to any one of claims 1 to 4, wherein an amino acid sequence of a plasmin cleavage site in the kringle domain is modified such that the cleavage site is more resistant to plasmin cleavage.

[Claim 6]

The fusion protein according to claim 4 or 5, further comprising an EGF-like domain, wherein the EGF-like domain, the kringle domain and the catalytic domain are linked to each other in this order.

[Claim 7]

The fusion protein according to any one of claims 1 to 6, wherein a prourokinase mutant has an amino acid sequence having a sequence identity of 90% or more to the amino acid sequence represented by SEQ ID NO:2.

[Claim 8]

The fusion protein according to any one of claims 1 to 7, wherein the antibody that binds to insoluble fibrin or the antigen-binding fragment thereof binds to a peptide consisting of the amino acid sequence represented by SEQ ID NO:17 or 18 and insoluble fibrin.

[Claim 9]

The fusion protein according to any one of claims 1 to 8, wherein the insoluble fibrin antibody or the antigen-binding fragment thereof comprises:

a heavy chain variable region containing heavy chain CDR1 having the amino acid sequence represented by SEQ ID NO:11, heavy chain CDR2 having the amino acid sequence represented by SEQ ID NO:12 and heavy chain CDR3 having the amino acid sequence represented by SEQ ID NO:13; and

a light chain variable region containing light chain CDR1 having the amino acid sequence represented by SEQ ID NO:14, light chain CDR2 having the amino acid sequence

represented by SEQ ID NO:15 and light chain CDR3 having the amino acid sequence represented by SEQ ID NO:16.

[Claim 10]

A pharmaceutical composition comprising the fusion protein according to any one of claims 1 to 9.

[Claim 11]

~~The~~ Use of the pharmaceutical composition according to claim 10, in the manufacture of a medicament for ~~for use in~~ dissolving a fibrin clot.

[Claim 12]

The pharmaceutical composition according to claim 10 or the use according to claim 11, which is a thrombolytic agent or a fibrinolytic enzyme agent.

[Claim 13]

Use of the ~~The~~ pharmaceutical composition according to any one of claims 10 to 12~~,~~ in the manufacture of a medicament for ~~for use in~~ treating a disease selected from cerebrovascular disorder and myocardial infarction.