[0005]

Under such technical background, an antibody specific to insoluble fibrin and an antibody-drug conjugate (ADC) using the antibody have been proposed (Patent Literature 1).

Citation List

Patent Literature

[0006]

[Patent Literature 1]

WO 2014/133093

Summary

[0007]

The present inventors have developed an ADC of an antibody specific to insoluble fibrin and a drug, in which a linker linking the antibody and the drug has a plasmin cleavage sequence. The present inventors have found that the resulting ADC is delivered to insoluble fibrin and is cleaved by plasmin at the delivered site to release the drug at the site. Furthermore, the present inventors have found, using a tumor animal model, that the resulting ADC can target an insoluble fibrin accumulation site in the vicinity of a tumor and releases the drug at the site to show an anticancer activity against the tumor. In addition, the present inventors

(10) A pharmaceutical composition comprising the ADC according to (9); and
(11) The pharmaceutical composition according to (10), for use in treating cancer.

In one aspect, the present disclosure provides an antibody-drug conjugate (ADC), wherein the antibody is an antibody that binds to fibrin and has affinity to insoluble fibrin higher than that to fibrinogen, the drug is a cytotoxic agent, and the antibody and the drug are linked to each other through a linker having a plasmin cleavage site that allows cleavage by plasmin.

In another aspect, the present disclosure provides a use of the ADC according to the disclosure in the manufacture of a pharmaceutical composition for treating cancer.

In another aspect, the present disclosure provides an antibody that binds to fibrin, wherein the antibody has a heavy chain variable region having CDR1 set forth in SEQ ID NO: 1, CDR2 set forth in SEQ ID NO: 2, and CDR3 set forth in SEQ ID NO: 3, and a light chain variable region having CDR1 set forth in SEQ ID NO: 5, CDR2 set forth in SEQ ID NO: 6, and CDR3 set forth in SEQ ID NO: 7;
an antibody that competes with the antibody for binding to fibrin; or an antigen-binding fragment thereof.

In another aspect, the present disclosure provides an antibody that binds to fibrin, wherein the antibody has a heavy chain variable region set forth in SEQ ID NO: 4 and a light chain variable region set forth in SEQ ID NO: 8; or an antigen-binding fragment thereof.

In another aspect, the present disclosure provides an antibody that binds to fibrin, wherein the antibody has a heavy chain variable region having CDR1 set forth in SEQ ID NO: 9, CDR2 set forth in SEQ ID NO: 10, and CDR3 set forth in SEQ ID NO: 11, and a light chain variable region having CDR1 set forth in SEQ ID NO: 13, CDR2 set forth in SEQ ID NO: 14, and CDR3 set forth in SEQ ID NO: 15; an antibody that competes with the antibody for binding to fibrin; or an antigen-binding fragment thereof.

In another aspect, the present disclosure provides an antibody that binds to fibrin, wherein the antibody has a heavy chain variable region set forth in SEQ ID NO: 12 and a light chain variable region set forth in SEQ ID NO: 16; or an antigen-binding fragment thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the ADC according to the disclosure.

In another aspect, the present disclosure provides a use of the ADC according to the disclosure in the manufacture of a pharmaceutical composition for treating cancer.

In another aspect, the present disclosure provides a ADC according to the disclosure for use in therapy.

In another aspect, the present disclosure provides a pharmaceutical composition according to the disclosure for use in therapy.

Brief Description of Drawings

[0009]

[Figure 1] Figure 1 shows that antibodies obtained by the present invention are specific to insoluble fibrin.

[Figure 2] Figure 2 shows that monoclonal antibodies specific to insoluble fibrin obtained by the present invention accumulate at tumor-forming sites.

[Figure 3] Figure 3 shows especially a drug portion and a linker portion of an antibody-drug conjugate produced by the present invention.

[Figure 4] Figure 4 shows the results of verification of in vitro anticancer activity of the antibody-drug conjugate produced by the present invention.

[Figure 5] Figure 5 shows a Kaplan-Meier curve of an antibody-drug conjugate produced by the present invention for a spontaneous pancreatic cancer model.

[Figure 6A] Figure 6A shows an effect of suppressing an increase in tumor volume in tumor subcutaneous implantation mice by the antibody-drug conjugate produced by the present invention.

[Figure 6B] Figure 6B shows changes with time in weight of the mice observed in Figure 6A.

Claims

[Claim 1]

An antibody-drug conjugate (ADC), wherein

the antibody is an antibody that binds to fibrin and has affinity to insoluble fibrin higher than that to fibrinogen,

the drug is a cytotoxic agent, and

the antibody and the drug are linked to each other through a linker having a plasmin cleavage site that allows cleavage by plasmin.

[Claim 2]

The ADC according to claim 1, wherein

the linker has a valine-leucine-lysine peptide sequence as the plasmin cleavage site.

[Claim 3]

Use of the ADC according to claim 1 or 2 in the manufacture of a pharmaceutical composition for treating cancer.

[Claim 4]

The use according to claim 3, wherein the cancer is invasive cancer.

[Claim 5]

An antibody that binds to fibrin, wherein the antibody has

a heavy chain variable region having CDR1 set forth in SEQ ID NO: 1, CDR2 set forth in SEQ ID NO: 2, and CDR3 set forth in SEQ ID NO: 3, and

a light chain variable region having CDR1 set forth in SEQ ID NO: 5, CDR2 set forth in SEQ ID NO: 6, and CDR3 set forth in SEQ ID NO: 7;

an antibody that competes with the antibody for binding to fibrin; or an antigen-binding fragment thereof.

[Claim 6]

An antibody that binds to fibrin, wherein the antibody has

a heavy chain variable region set forth in SEQ ID NO: 4 and a light chain variable region set forth in SEQ ID NO: 8; or

an antigen-binding fragment thereof.

[Claim 7]

An antibody that binds to fibrin, wherein the antibody has

a heavy chain variable region having CDR1 set forth in SEQ ID NO: 9, CDR2 set forth in SEQ ID NO: 10, and CDR3 set forth in SEQ ID NO: 11, and

a light chain variable region having CDR1 set forth in SEQ ID NO: 13, CDR2 set forth in SEQ ID NO: 14, and CDR3 set forth in SEQ ID NO: 15;

an antibody that competes with the antibody for binding to fibrin; or an antigen-binding fragment thereof.

[Claim 8]

An antibody that binds to fibrin, wherein the antibody has

a heavy chain variable region set forth in SEQ ID NO: 12 and a light chain variable region set forth in SEQ ID NO: 16; or

an antigen-binding fragment thereof.

[Claim 9]

The ADC according to claim 1 or 2, wherein the antibody is the antibody according to any one of claims 5 to 8.

[Claim 10]

A pharmaceutical composition comprising the ADC according to claim 9.

[Claim 11]

Use of the ADC according to claim 9 in the manufacture of a pharmaceutical composition for treating cancer.

[Claim 12]

The ADC according to claim 1 or 2 for use in therapy.

[Claim 13]

The pharmaceutical composition according to claim 10 for use in therapy.