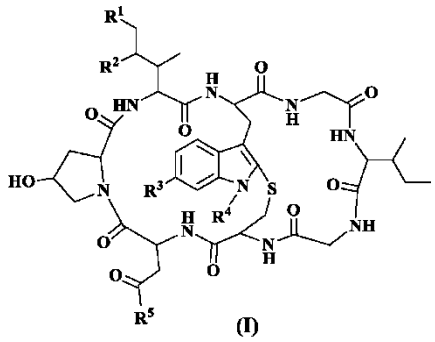
Claims

1. A non-natural amatoxin-antibody conjugate, comprising a toxin moiety having a structural formula (I) or a pharmaceutically acceptable salt thereof, and a biomacromolecule moiety A having a binding affinity to a target,



(I)

wherein:

R^1 is H, -OH or -O-L-A;

R^2 is H or -OH;

R^3 is OC_{1-6} alkyl;

R^4 is H or -L-A;

R^5 is $-NH_2$, -OH, -NH-L-A or -O-L-A;

wherein O is an oxygen atom, N is a nitrogen atom and H is a hydrogen atom.

2. The non-natural amatoxin-antibody conjugate of claim 1, wherein L comprises the following structure:

$$-L_1-[L_2]_m-[AA]_n-L_3-$$

wherein: L_1 is a linker connecting to the biomacromolecule moiety A; L_2 is a spacer connecting L_1 to AA; m is an integer selected from 1-6; L_3 is a structural fragment connecting to the toxin moiety; AA is a structural fragment consisting of 1 to 6 amino acids, and n is 0 or 1.

3. The non-natural amatoxin-antibody conjugate of claim 1 or claim 2, wherein A comprises an antibody or its antigen-binding fragment thereof, an antibody-like protein or a nucleic acid aptamer.

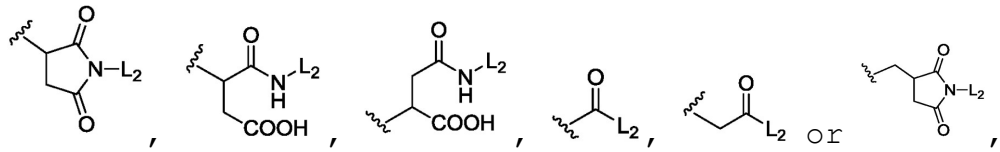
4. The non-natural amatoxin-antibody conjugate of claim

3, wherein the antibody or its antigen-binding fragment thereof comprises a chimeric antibody, a deimmunized antibody, a humanized antibody, a human antibody, a bispecific antibody, a tetra-specific antibody, a nanobody or their antigen-binding fragments thereof.

5. The non-natural amatoxin-antibody conjugate of claim 3 or 4, wherein the antigen-binding fragment is selected from the group consisting of Fab, F(ab'), Fd, Fv, a single-chain Fv or a disulfide-linked Fv(dsFv).

6. The non-natural amatoxin-antibody conjugate of claim 1 or 2, wherein only one of R^1, R^4 and R^5 comprises a -L-A structure.

7. The non-natural amatoxin-antibody conjugate of claim 2, wherein L_1 is a linker connecting to A, and wherein L_1 is selected from:



wherein a wavy line represents the connection to A.

8. The non-natural amatoxin-antibody conjugate of claim 2, wherein L_2 is a substituted or unsubstituted C1-C6 alkyl, a substituted or unsubstituted C3-C20 cycloalkyl, a substituted or unsubstituted C3-C20 heterocycloalkyl, a substituted or unsubstituted C5-C20 aryl, a substituted or unsubstituted C5-C20 heteroaryl, or $-(CH_2CH_2O)a-$, wherein a is an integer selected from 1 to 20.

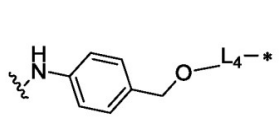
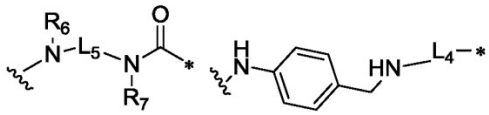
9. The non-natural amatoxin-antibody conjugate of claim 8, wherein the substituted comprises a substitution with a hydroxyl group, a sulfydryl group, halogen, a carboxyl group, an amino group, a phosphate group, a nitro group, a cyano group, a sulfo group, or a further substituted or unsubstituted C1-C6 alkyl.

10. The non-natural amatoxin-antibody conjugate of claim 9, wherein the further substituted comprises a substitution with a hydroxyl group, a sulfydryl group, halogen, a carboxyl group, an amino group, a phosphate group, a nitro group, a cyano group, or a sulfo group.

11. The non-natural amatoxin-antibody conjugate of claim 2, wherein the amino acids are L- amino acids selected from glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, tryptophan, serine, tyrosine, cysteine, methionine, asparagine, glutamine, threonine, aspartate, glutamate, lysine, arginine or histidine.

12. The non-natural amatoxin-antibody conjugate of claim 11, wherein the amino acids are selected from phenylalanine, citrulline, valine, lysine, serine, glutamate, aspartate or glycine.

13. The non-natural amatoxin-antibody conjugate of claim 2, wherein L_3 comprises


,  or any linking group that connects to the toxin moiety;

wherein a wavy line represents the connection to AA and an asterisk represents the connection to the toxin moiety.

14. The non-natural amatoxin-antibody conjugate of claim 13, wherein L4 is a carbonyl group or a single bond.

15. The non-natural amatoxin-antibody conjugate of claim 13 or claim 14, wherein R6 and R7 are each independently selected from hydrogen or C1-C6 alkyl.

16. The non-natural amatoxin-antibody conjugate of claim 13 or claim 14, wherein L5 is C2-C12 alkyl.

17. A pharmaceutical composition comprising the

non-natural amatoxin-type antibody conjugate as claimed in any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition is an anti-lung cancer drug, an anti-renal cancer drug, an anti-urethral cancer drug, an anti-colorectal cancer drug, an anti-prostate cancer drug, an anti-glioblastoma drug, an anti-ovarian cancer drug, an anti-pancreatic cancer drug, an anti-breast cancer drug, an anti-melanoma drug, an anti-liver cancer drug, an anti-bladder cancer drug, an anti-malignant lymphoma drug, an anti-leukemia drug, an anti-gastric cancer drugs or an anti-esophageal cancer drug.

19. The use of the non-natural amatoxin-type antibody conjugate as claimed in any one of claims 1 to 16 or a pharmaceutical composition of claim 17 or 18 in the preparation of a medicament for treating a tumor or cancer.