CLAIMS

1. A composition comprising the following (1) and (2):
(1) a universal influenza vaccine antigen; and
(2) a vaccine adjuvant,
wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

2. The composition according to Claim 1, wherein the universal influenza vaccine antigen is an influenza HA split vaccine antigen which produces an antibody that binds to a LAH of a HA stem region.

3. The composition according to Claim 2, wherein the influenza HA split vaccine antigen has a HA stem region exposed outside.

4. The composition according to Claim 1, wherein the universal influenza vaccine antigen is an influenza HA split vaccine antigen wherein the HA stem region, which is exposed outside, enhances the antigenicity of the LAH of the HA stem region, and the influenza HA split vaccine is capable of producing an antibody that binds to the LAH of the HA stem region.

5. The composition according to any one of Claims 1 to 4, wherein the acidic treatment is performed at a pH of 3.0 to 6.5.

6. The composition according to any one of Claims 1 to 5, wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine which has not undergone a formalin treatment to an acidic treatment.

7. The composition according to any one of Claims 1 to 6, wherein the universal influenza vaccine antigen is produced by a production process including: subjecting an influenza HA split vaccine to an acidic treatment; and thereafter, subjecting the influenza HA split vaccine to a formalin treatment.

8. The composition according to any one of Claims 1 to 7, wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine of a single HA subtype to an acidic treatment.

9. The composition of according to any one of Claims 1 to 7, wherein the universal influenza vaccine antigen is a vaccine antigen comprising two or more kinds of influenza HA split vaccine antigens each of which is produced by subjecting an influenza HA split vaccine of a single HA subtype to an acidic treatment.

10. The composition according to any one of Claims 1 to 9, wherein the acidic treatment is performed at a pH of 4.0 to 6.0.

11. The composition according to any one of Claims 1 to 10, wherein the acidic treatment is performed at a pH of 4.4 to 5.8.

12. The composition of any one of Claims 1 to 11, wherein the vaccine adjuvant is a substance which enhances the physiological activity of TLR.

13. The composition of any one of Claims 1 to 12, wherein the vaccine adjuvant is a substance which enhances the physiological activity of one or more TLRs selected from the group consisting of TLR7, TLR8, and TLR9.

14. The composition of any one of Claims 1 to 13, wherein the vaccine adjuvant is a substance which enhances the physiological activity of at least TLR7.

15. The composition of any one of Claims 1 to 14, wherein the vaccine adjuvant is a substance which enhances the physiological activity of at least TLR8.

16. The composition of any one of Claims 1 to 15, wherein the vaccine adjuvant is a substance which enhances the physiological activity of at least TLR9.

17. The composition according to Claims 13 or 14, wherein the substance which enhances the physiological activity of TLR7 is a low molecular weight compound which enhances the physiological activity of TLR7, or a conjugated compound in which a low molecular weight compound which enhances the physiological activity of TLR7 and a lipid are chemically linked via a spacer.

18. The composition of claim 17, wherein the low molecular weight compound which enhances the physiological activity of TLR7 or the low molecular weight compound which enhances the physiological activity of TLR7 comprised in the conjugated compound has a molecular weight of 200 to 600 and has an adenine skeleton, a pyrimidine skeleton, an imidazoquinoline skeleton, an imidazopyridine skeleton, or a quinazoline skeleton.

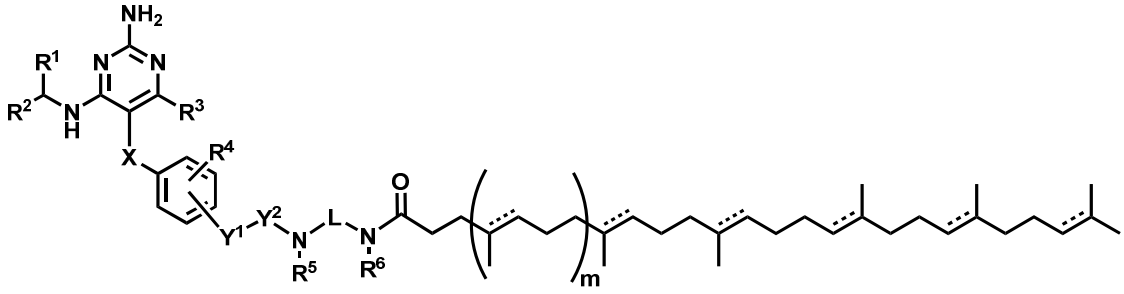
19. The composition of claim 18, wherein the low molecular weight compound which enhances the physiological activity of TLR7 or the low molecular weight compound which enhances the physiological activity of TLR7 comprised in the conjugated compound has a pyrimidine skeleton, an adenine skeleton, or an imidazoquinoline skeleton.

20. The composition of any one of Claims 17 to 19, wherein the lipid is a lipid derived from squalene or squalane.

21. The composition according to any one of Claims 17 to 20, wherein the compound which enhances the physiological activity of TLR7 is a conjugated compound in which a low molecular weight compound having an adenine skeleton and a lipid derived from squalene or squalane are chemically linked via a spacer or a pharmaceutically acceptable salt thereof.

22. The composition according to any one of Claims 17 to 20, wherein the compound which enhances the physiological activity of TLR7 is a conjugated compound in which a low molecular weight compound having a pyrimidine skeleton and a lipid derived from squalene or squalane are chemically linked via a spacer or a pharmaceutically acceptable salt thereof.

23. The composition according to any one of Claims 17 to 20 and 22, wherein the compound which enhances the physiological activity of TLR7 is a compound represented by Formula (1) or a pharmaceutically acceptable salt thereof:



(1)

wherein

X represents methylene,

R^1 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms which may be substituted with hydroxy group,

R^2 represents a hydrogen atom or an alkyl group having 1 to 6 carbon atoms,

R^3 represents an alkyl group having 1 to 3 carbon atoms,

R^4 represents a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group having 1 to 3 carbon atoms, or an alkoxy group having 1 to 3 carbon atoms,

Y^1 represents a single bond or methylene,

Y^2 represents a single bond or –C(O)–,

L represents a straight chain alkylene having 2 or 3 carbon atoms,

R^5 and R^6 independently represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or R^5 and R^6 are taken together to form a substituted or unsubstituted 5– to 8–membered nitrogen–containing saturated heterocycle, provided that when the 5– to 8–membered nitrogen–containing saturated heterocycle is substituted, it is substituted with the same or different 1 to 4 substituents selected from hydroxy group and halogen atom, and

m represents 0 or 1,

------ are all double bonds.

24. The composition according to any one of Claims 17 to 20, 22 and 23, wherein the conjugated compound is:

(4E,8E,12E,16E,20E)–N–{2–[{4–[(2–amino–4–{[(3S)–1–hydroxyhexan–3–yl]amino}–6–methylpyrimidin–5–yl)methyl]benzyl}(methyl)amino]ethyl}–4,8,12,17,21,25–hexamethylhexacosa–4,8,12,16,20,24–hexaenamide;

(4E,8E,12E,16E,20E)–1–(4–{4–[(2–amino–4–{[(2S)–1–hydroxypentan–2–yl]amino}–6–methylpyrimidin–5–yl)methyl]–3–methoxybenzyl}piperazin–1–yl)–4,8,12,17,21,25–hexamethylhexacosa–4,8,12,16,20,24–hexaen–1–one;

(4E,8E,12E,16E,20E)–1–(4–{4–[(2–amino–4–{[(2S)–1–hydroxypentan–2–yl]amino}–6–methylpyrimidin–5–yl)methyl]–3–methoxybenzoyl}piperazin–1–yl)–4,8,12,17,21,25–hexamethylhexacosa–4,8,12,16,20,24–hexaen–1–one;

4-[(2-amino-4-{[(2S)-1-hydroxypentan-2-yl]amino}-6-methylpyrimidin-5-yl)methyl]-N-(2-{[(4E,8E,12E,16E,20E)-4,8,12,17,21,25-hexamethylhexacosa-4,8,12,16,20,24-hexaenoyl]amino}ethyl)-3-methoxybenzamide;

4-[(2-amino-4-{[(2S)-1-hydroxypentan-2-yl]amino}-6-methylpyrimidin-5-yl)methyl]-N-(2-{[(4E,8E,12E,16E,20E)-4,8,12,17,21,25-hexamethylhexacosa-4,8,12,16,20,24-hexaenoyl](methyl)amino}ethyl)-3-methoxybenzamide;or
a pharmaceutically acceptable salt thereof.

25. The composition according to any one of Claims 17 to 20 and 22 to 24, wherein the compound which enhances the physiological activity of TLR7 is:

(4E,8E,12E,16E,20E)-N-{2-[{4-[(2-amino-4-{[(3S)-1-hydroxyhexan-3-yl]amino}-6-methylpyrimidin-5-yl)methyl]benzyl}(methyl)amino]ethyl}-4,8,12,17,21,25-hexamethylhexacosa-4,8,12,16,20,24-hexaenamide;

4-[(2-amino-4-{[(2S)-1-hydroxypentan-2-yl]amino}-6-methylpyrimidin-5-yl)methyl]-N-(2-{[(4E,8E,12E,16E,20E)-4,8,12,17,21,25-hexamethylhexacosa-4,8,12,16,20,24-hexaenoyl]amino}ethyl)-3-methoxybenzamide;or
a pharmaceutically acceptable salt thereof.

26. The composition according to any one of Claims 17 to 20 and 22 to 25, wherein the compound which enhances the physiological activity of TLR7 is:

(4E,8E,12E,16E,20E)-N-{2-[{4-[(2-amino-4-{[(3S)-1-hydroxyhexan-3-yl]amino}-6-methylpyrimidin-5-yl)methyl]benzyl}(methyl)amino]ethyl}-4,8,12,17,21,25-hexamethylhexacosa-4,8,12,16,20,24-hexaenamide; or
a pharmaceutically acceptable salt thereof.

27. An influenza vaccine comprising the composition according to any one of Claims 1 to 26.

28. A kit for preventing influenza comprising a universal influenza vaccine antigen, and a vaccine adjuvant,

wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

29. A composition comprising a vaccine adjuvant for use in the prevention of influenza in combination with a universal influenza vaccine antigen,

wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

30. A composition comprising a universal influenza vaccine antigen for use in the prevention of influenza in combination with a vaccine adjuvant,

wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

31. Use of a vaccine adjuvant in the manufacture of a composition for preventing influenza comprising a universal influenza vaccine antigen,

wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

32. Use of a universal influenza vaccine antigen in the manufacture of a composition for preventing influenza comprising a vaccine adjuvant,

wherein the universal influenza vaccine antigen is produced by subjecting an influenza HA split vaccine to an acidic treatment.

33. The kit according to Claim 28, the composition for use according to Claim 29, or the composition for use according

to Claim 30, wherein the universal influenza vaccine antigen and the vaccine adjuvant are to be administered simultaneously or separately.

34. The kit according to Claim 28, the composition for use according to Claim 29, or the composition for use according to Claim 30, wherein the universal influenza vaccine antigen is to be administered prior to, after, or concurrently with the administration of the vaccine adjuvant.

35. A method for producing a composition comprising an influenza HA split vaccine antigen and a vaccine adjuvant, comprising the following steps:

a) producing an influenza HA split vaccine antigen which produces an antibody that binds to a LAH of a HA stem region by subjecting an influenza HA split vaccine which has not undergone a formalin treatment to an acidic treatment; and

b) mixing the vaccine antigen obtained in step a) with the vaccine adjuvant.

36. A method for producing a composition comprising an influenza HA split vaccine antigen and a vaccine adjuvant, comprising the following steps:

a) subjecting an influenza HA split vaccine to an acidic treatment,

b) thereafter, conducting a formalin treatment to obtain an influenza HA split vaccine antigen which produces an antibody that binds to a LAH of a HA stem region; and

c) mixing the vaccine antigen obtained in step b) with the vaccine adjuvant.

37. A method for producing a kit comprising an influenza HA split vaccine antigen and a vaccine adjuvant, comprising the following steps:

a) producing an influenza HA split vaccine antigen which produces an antibody that binds to a LAH of a HA stem region

by subjecting an influenza HA split vaccine which has not undergone a formalin treatment to an acidic treatment; and

b) combining the vaccine antigen obtained in step a) with the vaccine adjuvant to form a kit.

38. A method for producing a kit comprising an influenza HA split vaccine antigen and a vaccine adjuvant, comprising the following steps:

a) subjecting an influenza HA split vaccine to an acidic treatment,

b) thereafter, conducting a formalin treatment to obtain an influenza HA split vaccine antigen which produces an antibody that binds to a LAH of a HA stem region; and

c) combining the vaccine antigen obtained in step b) with the vaccine adjuvant to form a kit.