

CLAIMS

1. An *in vitro* method for the diagnostic, prognostic or monitoring of a flaviviral infection or associated disease, comprising detecting the presence or level of a complex formed by a flaviviral non-structural protein 1 (NS1) and plasma lipoprotein particles in a biological sample obtained from a subject.
2. The *in vitro* method according to claim 1, comprising :
 - a. Contacting the biological sample with an antibody specific for the flaviviral NS1 or an antibody specific for plasma lipoproteins to form an immunoreaction product;
 - b. detecting the presence of the immunoreaction product, and
 - c. quantitating the complex formed by NS1 and plasma lipoprotein particles.
3. The *in vitro* method according to claim 2, which comprises :
 - a. Contacting the biological sample with an antibody specific for the flaviviral NS1 to form a first immunoreaction product;
 - b. Contacting said first immunoreaction product with an antibody specific for plasma lipoproteins to form a second immunoreaction product;
 - c. detecting the presence of the second immunoreaction product, and
 - d. quantitating the complex formed by NS1 and plasma lipoprotein particles.
4. The *in vitro* method according to any one of claims 2 to 3, wherein the quantity of the complex is determined by capture ELISA using the antibody specific for the flaviviral NS1 coated on a solid support and the antibody specific for plasma lipoproteins as detection antibodies.
5. The *in vitro* method according to any one of claims 2 to 4, wherein a third antibody raised against antibody specific for plasma lipoproteins and conjugated to a suitable label is used for detecting the presence of the second immunoreaction product.
6. The *in vitro* method according to any one of claims 1 to 5, wherein the plasma lipoprotein particles are High Density Lipoprotein (HDL) particles, preferably Apolipoprotein A1 (ApoA1) positive lipoprotein particles.

7. The in vitro method according to any one of claims 2 to 6, wherein the antibody specific for plasma lipoproteins is an antibody specific for Apolipoprotein A1 (ApoA1).
8. The in vitro method according to any one of claims 1 to 5, wherein the plasma lipoprotein particles are Low Density Lipoprotein (LDL) particles, preferably Apolipoprotein B positive lipoprotein particles.
9. The in vitro method according to any one of claims 2 to 5 and 8, wherein the antibody specific for plasma lipoproteins is an antibody specific for Apolipoprotein B (ApoB).
10. The in vitro method according to any one of claims 2 to 6 and 8, wherein the antibody specific for plasma lipoproteins is an antibody specific for Apolipoprotein E (ApoE).
11. The in vitro prognostic method according to any one of claims 1 to 10, which is for the prognostic of a severe form of a flaviviral infection in a subject infected with a flavivirus, wherein the more the level of complex, the less the risk to develop severe form of flaviviral infection.
12. The in vitro prognostic method according to claim 11, which is performed in a biological sample obtained during primary or acute infection.
13. The in vitro prognostic method according to any one of claim 11 or 12, wherein the complex is formed by a flaviviral non-structural protein 1 (NS1) and plasma High Density Lipoprotein (HDL) particles, preferably Apolipoprotein A1 (ApoA1) positive lipoprotein particles.
14. The in vitro monitoring method according to any one of claims 1 to 10, which is carried out on biological samples obtained from said subject at different times during the disease.
15. The in vitro diagnostic method according to any one of claims 1 to 10, wherein the presence of complex formed by flaviviral NS1 and plasma lipoprotein particles in said sample is indicative of a flaviviral infection.

16. The in vitro diagnostic method according to claim 15, wherein complex formed by flaviviral NS1 and HDL particles are quantitated, preferably complex composed by flaviviral NS1 and ApoA1 positive lipoprotein particles.
- 5 17. The in vitro diagnostic method according to claim 15 or 16, which is repeatedly carried out on a biological sample obtained from said subject to quantitate complex of flaviviral NS1-HDL particles and/or complex of flaviviral NS1-LDL particles and/or complex of flaviviral NS1-other plasma lipoprotein particles, preferably complex of flaviviral NS1-Apo1 positive lipoprotein particles, complex of flaviviral NS1-ApoE positive lipoprotein
10 particles, and/or complex of flaviviral NS1-ApoB positive lipoprotein particles.
18. A biomarker for the diagnostic, prognostic or monitoring of a flaviviral infection or associated disease, comprising a complex formed by a flaviviral non-structural protein 1 (NS1) and plasma lipoprotein particles as defined in any one of claims 1, 6 and 8.
- 15 19. Use of the presence or level of the biomarker according to claim 18 in a biological sample obtained from a subject for the diagnostic, prognostic or monitoring of a flaviviral infection or associated disease.
- 20 20. A method of treating a flaviviral infection or associated disease in a subject in need thereof, comprising:
- diagnosing a flavivirus infection in the individual by detecting the presence or level of a complex formed by the flaviviral non-structural protein 1 (NS1) and plasma lipoprotein particles in a biological sample obtained from the subject according to
25 the method of any one of claims 1 to 10 and 15-17, wherein the presence or level of the complex is indicative of a flaviviral infection in the subject; and
 - administering an appropriate treatment if the individual is diagnosed with a flaviviral infection.
- 30 21. A kit to detect a complex formed by a flaviviral NS1 and plasma lipoprotein particles in a biological sample obtained from a subject, comprising:
- a. An antibody specific for the flaviviral NS1;
 - b. An antibody specific for specific for plasma lipoproteins, preferably specific for HDL, and more preferably for ApoA1; and preferably further comprising
35 an antibody specific for ApoB and/or ApoE;

- c. Means for detecting the production of an immunoreaction product between said two antibodies and the complex formed by the flaviviral NS1 and plasma lipoprotein particles.
- 5 22. An in vitro method for quantitating a complex formed by the flaviviral non-structural protein 1 (NS1) and plasma lipoprotein particles in a biological sample obtained from a subject, comprising:
- 10 a. Contacting the biological sample with an antibody specific for the flaviviral NS1 or an antibody specific for plasma lipoproteins to form an immunoreaction product;
- b. detecting the presence of the immunoreaction product, and
- c. quantitating the complex formed by NS1 and plasma lipoprotein particles ,according to the method of any one of claims 2 to 10.
- 15 23. The kit according to claim 21, the in vitro method according to any one of claims 1 to 17 and 22, the biomarker or use thereof according to claim 18 or 19 or the method of treatment according to claim 20, wherein the flaviviral NS1 is the NS1 from Dengue virus and/or the flaviviral infection is a Dengue virus infection.
- 20 24. The kit according to any one of claims 21 or 23, the in vitro method according to any one of claims 1 to 17 and 22, the biomarker or use thereof according to claim 18 or 19 or the method of treatment according to claim 20, wherein the biological sample is blood, plasma or serum.
- 25 25. The kit according to any one of claims 21 and 23 to 24, the in vitro method according to any one of claims 1 to 17 and 22, the biomarker or use thereof according to claim 18 or 19 or the method of treatment according to claim 20, wherein the subject is a human being.