Summary ~~of the invention~~

It is an object of the present ~~invention~~disclosure to provide a method of producing viral vaccines with a reduced number of steps requiring the handling of infectious material, while producing viral antigens of decreased reactivity.

In one aspect, there is provided a method for the manufacture of a preparation comprising virus antigens comprising a) inoculation of cells with infectious enveloped virus in a fluid, wherein said cells are primary cells or a cultured cell line, b) propagation of said virus in said cells, wherein said cells are in form of a cell culture, c) collecting said propagated virus, d) completely inactivating said collected virus directly after collection of the virus prior to any purification step and wherein the virus containing fluid or its non-viral constituents is (are) not further concentrated before said inactivating step, and e) treating said inactivated virus with detergent to produce a split virus vaccine, resulting in a preparation comprising viral antigens.

In one aspect, there is provided a method for the manufacture of a preparation comprising viral antigens comprising a) obtaining a fluid comprising infectious enveloped virus, inoculated in cells, wherein said cells are primary cells or a cultured cell line, b) inactivating said collected virus from step (a), prior to any purification step of the virus and wherein the virus containing fluid or its non-viral constituents is (are) not further concentrated before said inactivating step, c) treating said inactivated virus with detergent to produce a split virus vaccine, and d) purifying said inactivated virus resulting in a preparation comprising viral antigens.

Therefore the present ~~invention~~disclosure provides a method for the manufacture of a preparation comprising virus antigens comprising

a) inoculation of cells with infectious virus in a fluid,

b) propagation of said virus in said cells,

c) collecting said propagated virus in the cell culture supernatant ,

d) inactivating said collected virus, and

e) treating said inactivated virus with a detergent,

resulting in a preparation comprising viral antigens.

In one ~~a second aspect~~embodiment a method for the manufacture of a preparation is provided comprising viral antigens comprising

a) obtaining a fluid comprising infectious virus,

b) completely inactivating said collected virus,

c) treating said inactivated virus with a detergent, and

d) purifying said inactivated virus resulting in a preparation comprising viral antigens.

Other ~~aspects~~embodiments of the ~~invention~~disclosure provide vaccine preparations

prepared from the viral antigens produced according to the methods of the ~~invention~~disclosure.

In another ~~aspect~~embodiment the present ~~invention~~disclosure provides the method of increasing the resistance to a viral infection in a subject comprising manufacturing a preparation comprising viral antigens and administering said preparation to a subject.

Brief description of the drawings

Fig. 1a shows a flow chart of the inventive procedure from virus collection after propagation to the inactivated harvest.

Fig. 1b shows a continuation of the flow chard of the inventive procedure from inactivated harvest to a monvalent bulk preparation.

Claims:

1. A method for the manufacture of a preparation comprising virus antigens comprising
a) inoculation of cells with infectious enveloped virus in a fluid, wherein said cells are primary cells or a cultured cell line,
b) propagation of said virus in said cells, wherein said cells are in form of a cell culture,
c) collecting said propagated virus,
d) completely inactivating said collected virus directly after collection of the virus prior to any purification step and wherein the virus containing fluid or its non-viral constituents is (are) not further concentrated before said inactivating step, and
e) treating said inactivated virus with detergent to produce a split virus vaccine, resulting in a preparation comprising viral antigens.

2. The method of claim 1, wherein the step of collecting said propagated virus comprises separating the virus from cells and/or cell debris of said cells after infection.

3. The method of claim 1, wherein said inactivation is performed by addition of formaldehyde, or performed by UV irradiation.

4. The method of claim 1, wherein said propagated virus is released into said fluid.

5. The method of claim 1, wherein after the collection the collected fluid is treated with a nuclease.

6. The method of claim 1, wherein said cells are mammalian or avian cells.

7. The method of claim 1, wherein said cells are epithelial cells.

8. The method of claim 1, wherein said virus is an influenza virus.

9. The method of claim 1, wherein the concentration of non-viral protein during said inactivation is below 350 µg/ml.

10. A method for the manufacture of a preparation comprising viral antigens comprising
a) obtaining a fluid comprising infectious enveloped virus, inoculated in cells, wherein said cells are primary cells or a cultured cell line,
b) inactivating said collected virus from step (a), prior to any purification step of the virus and wherein the virus containing fluid or its non-viral constituents is (are) not further concentrated before said inactivating step,
c) treating said inactivated virus with detergent to produce a split virus vaccine, and
d) purifying said inactivated virus resulting in a preparation comprising viral antigens.

11. The method of claim 10, wherein said fluid is obtained from a cell culture.

12. The method of claim 11, further comprising the step of stabilizing said viral antigens.

Claims:

1. A method for the manufacture of a preparation comprising virus antigens comprising

a) inoculation of cells with infectious virus in a fluid,

b) propagation of said virus in said cells,

c) collecting said propagated virus,

d) completely inactivating said collected virus, and

e) treating said inactivated virus with detergent,

resulting in a preparation comprising viral antigens.

2. The method of claim 1, wherein the step of collecting said propagated virus comprises separating the virus from said cells and/or cell debris of said cells after infection.

3. The method of 1, wherein said inactivation is performed by addition of formaldehyde.

4. The method of 1, wherein said inactivation is performed by UV irradiation.

5. The method of 1, wherein said propagated virus is released into said fluid.

6. The method of 1, wherein after the collection the collected fluid is treated with a nuclease.

7. The method of 6, wherein said nuclease is benzonase.

8. The method of claim 1, wherein said cells are in form of a cell culture during said virus propagation.

9. The method of claim 1, wherein said cells are mammalian or avian cells.

10. The method of claim 1, wherein said cells are epithelial cells.

11. The method of claim 8, wherein said cells are Vero cells.

12. The method of claim 1, wherein said virus is an enveloped virus

13. The method of claim 12, wherein said virus is an orthomyxo virus

14. The method of claim 13, wherein said virus is an influenza virus.

15. The method of claim 1, wherein the concentration of non-viral protein during said inactivation is below 350 µg/ml.

16. The method of claim 1, wherein said manufacture is on industrial scale amounts.

17. The method of claim 16, wherein said inactivation is performed on at least 1l virus containing fluid.

18. A method for the manufacture of a preparation comprising viral antigens comprising

a) obtaining a fluid comprising infectious virus,

b) inactivating said collected virus,

c) treating said inactivated virus with detergent, and

d) purifying said inactivated virus resulting in a preparation comprising viral antigens.

19. The method of claim 18, wherein said fluid is obtained from a cell culture.

20. The method of claim 19 further comprising the step of stabilizing said viral antigens.

21. The method of claim 20, wherein said viral antigens are stabilized by addition of an effective amount of Tween 80.

22. The method of claim 21, wherein Tween 80 is in an amount of about 0.125 %.

23. A method of increasing the resistance to a viral infection in a subject comprising manufacturing a preparation comprising

viral antigens by administering a preparation obtained by any one of the methods of claims 1-22 to a subject.