

CLAIMS

1. An apparatus for the controlled delivery of an HBV vaccine to a predetermined tissue site within a subject in need thereof, comprising:

a cartridge assembly comprising an outer cartridge, an inner cartridge, a reservoir containing the HBV vaccine, wherein a reservoir containment volume is contained within the outer cartridge and configured to receive the reservoir;

an applicator comprising a cartridge assembly receiving volume, a needle hub, and an insertion detector, wherein the insertion detector senses loading of the reservoir in the reservoir containment volume;

at least one interlock, wherein the interlock facilitates proper execution of the HBV vaccine administration procedure;

at least one injection orifice through which the HBV vaccine is administered;

a plurality of penetrating electrodes arranged with a predetermined spatial relationship relative to the orifice;

an electrical field generator for generating an electrical signal operatively connected to the electrodes; and

a controlled source of energy sufficient to transfer a predetermined amount of the HBV vaccine at a predetermined rate from the reservoir through the orifice to the predetermined site within the subject,

wherein the HBV vaccine comprises:

a first nucleic acid molecule comprising a first polynucleotide encoding an HBV polymerase antigen, wherein the HBV polymerase antigen comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 4 and wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity;

a second nucleic acid molecule comprising a second polynucleotide encoding a truncated HBV core antigen consisting of the amino acid sequence of SEQ ID NO: 2; and

a pharmaceutically acceptable carrier,

wherein the first nucleic acid molecule and the second nucleic acid molecule are present in the same nucleic acid molecule or in two different nucleic acid molecules.

2. A kit for the controlled delivery of an HBV vaccine to a predetermined tissue site within a subject in need thereof, comprising:

(i) the HBV vaccine comprising:

a first nucleic acid molecule comprising a first polynucleotide encoding an HBV polymerase antigen, wherein the HBV polymerase antigen comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 4 and wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity; and

a second nucleic acid molecule comprising a second polynucleotide encoding a truncated HBV core antigen consisting of the amino acid sequence of SEQ ID NO: 2; and

a pharmaceutically acceptable carrier,

wherein the first nucleic acid molecule and the second nucleic acid molecule are present in the same nucleic acid molecule or in two different nucleic acid molecules;

(ii) an apparatus, comprising:

a cartridge assembly comprising an outer cartridge, an inner cartridge, a reservoir for the HBV vaccine, wherein a reservoir containment volume is contained within the outer cartridge and configured to receive the reservoir;

an applicator comprising a cartridge assembly receiving volume, a needle hub, and an insertion detector, wherein the insertion detector senses loading of the reservoir in the reservoir containment volume;

at least one interlock, wherein the interlock facilitates proper execution of the HBV vaccine administration procedure;

at least one injection orifice through which the HBV vaccine is administered;

a plurality of penetrating electrodes arranged with a predetermined spatial relationship relative to the orifice;

an electrical field generator for generating an electrical signal operatively connected to the electrodes; and

a controlled source of energy sufficient to transfer a predetermined amount of the HBV vaccine at a predetermined rate from the reservoir through the orifice to the predetermined site within the subject.

3. The apparatus of claim 1 or the kit of claim 2, wherein the electrodes are a plurality of elongate electrodes.
4. The apparatus of claim 1 or the kit of claim 2, wherein the interlock prevents inadvertent actuation of cartridge function.
5. The apparatus of any one of claims 1, 3 and 4, or the kit of any one of claims 2 to 4 wherein at least one interlock is selected from the group consisting of a mechanical interlock, a light emitter/collector, a cartridge breech, a force interlock, an alignment guide and a splay shield, a trigger lock, and a safety switch.
6. The apparatus of any one of claims 1 and 3 to 5, or the kit of any one of claims 2 to 5, wherein the apparatus comprises at least two sets of interlocks, wherein a first interlock is a mechanical interlock, and a second interlock is selected from the group consisting of a light emitter/collector, a cartridge breech, a force interlock, an alignment guide and a splay shield, a trigger lock, and a safety switch.
7. The apparatus or kit of any one of claims 5 to 6, wherein the mechanical interlock is a reservoir interlock.
8. The apparatus or kit of claim 7, wherein the reservoir interlock further comprises at least one reservoir lockout hole.
9. The apparatus or kit of any one of claims 5 to 8, wherein the cartridge breech provides an optical line of sight through at least one reservoir lockout hole.
10. The apparatus or kit of any one of claims 7 to 9, wherein the reservoir interlock further comprises a tab extending from one or more of the cartridge surface, wherein the tab ensures that reservoir is properly inserted into the cartridge.

11. The apparatus or kit of claim 6, wherein the apparatus further comprise a third interlock.
12. The apparatus or kit of claim 11, wherein the third interlock is a force interlock.
13. The apparatus or kit of claim 12, wherein the force interlock senses a force applied against the predetermined tissue site of the subject and prevents administration of the HBV vaccine to the subject when insufficient force is provided.
14. The apparatus or kit of any one of claims 12 to 13, wherein the force interlock further forms an electrical lock within the applicator.
15. The apparatus of any one of claims 1 and 3 to 14, or the kit of any one of claims 2 to 14, wherein the apparatus further comprises a key to the reservoir, wherein the key slides over the barrel of the reservoir to ensure appropriate mating within the cartridge assembly.
16. The apparatus or kit of any one of claims 5 to 6 wherein the splay shield comprises at least one rib and at least one edge to engage with the predetermined tissue site of the subject and place the apparatus into tension perpendicular to the direction of the needle deployment for administration of the HBV vaccine.
17. The apparatus of claim 1 or kit of claim 2, wherein the cartridge assembly further comprises a stick shield.
18. The apparatus or kit of any one of claims 5, 6, and 16, wherein the splay shield comprises at least one hole for slidable movement of the stick shield.
19. The apparatus of any one of claims 1 and 3 to 18, or the kit of any one of claims 2 to 18, wherein upon loading of the cartridge assembly into the applicator, the reservoir moves forward to mate with the needle hub and contacts the cartridge to an injection needle at the time of administration of the HBV vaccine.

20. The apparatus of any one of claims 1 and 3 to 19, or the kit of any one of claims 2 to 19, wherein the inner cartridge moves in a slidable manner in relationship to the outer cartridge.
21. The apparatus of any one of claims 1 and 3 to 20, or the kit of any one of claims 2 to 20, wherein the inner cartridge engages with an inner cartridge cap at a distal end, wherein the inner cartridge cap locks the electrodes in place and provides a bearing surface for the stick shield.
22. The apparatus of claim 1 or the kit of claim 2, wherein the apparatus further comprises at least one sensor.
23. The apparatus or kit of claim 22, wherein the sensor is selected from the group consisting of a cartridge loading sensor, a cartridge loaded sensor, a cartridge force sensor, an insertion mechanism position sensor, an insertion detector, an optical detector, and an electrical sensor.
24. The apparatus or kit of claim 23, wherein the cartridge loading sensor and the cartridge loaded sensor form a portion of a loading drive subassembly.
25. The apparatus or kit of claim 24, wherein the loading drive subassembly further includes at least one cartridge guide rail and a loading motor.
26. The apparatus or kit of any one of claims 24 to 25, wherein the loading drive subassembly further has a connection to a pinion gear assembly pulling the cartridge assembly into the cartridge assembly receiving volume via at least one rack on the base of the outer cartridge.
27. The apparatus or kit of claim 26, wherein the pinion gear assembly engages the rack on the outer cartridge.

28. The apparatus or kit of any one of claims 26 to 27, wherein the rack comprises at least one rack teeth.
29. The apparatus or kit of any one of claims 26 to 28, wherein a first rack teeth provides a tactile sensation when the cartridge assembly is inserted into the cartridge assembly receiving volume.
30. The apparatus or kit of any one of claims 26 to 29, wherein the rack teeth provide torsional stability.
31. The apparatus or kit of any one of claims 23 to 26, wherein the cartridge loading sensor detects an initiating flag on the cartridge assembly to initiate loading.
32. The apparatus or kit of any one of claims 23 to 26, wherein the cartridge loaded sensor detects an initiating flag on the cartridge assembly to cease loading.
33. The apparatus of any one of claims 1 and 3 to 32, or the kit of any one of claims 2 to 32, wherein the apparatus further comprises a continuing flag for the cartridge loading to continue.
34. The apparatus or kit of claim 23, wherein the insertion detector is a light emitter / collector IR sensor.
35. The apparatus or kit of any one of claims 22 to 34, wherein the sensor detects a reservoir label and verifies the HBV vaccine.
36. An apparatus for the controlled delivery of an HBV vaccine to a predetermined tissue site within a subject comprising:
a cartridge assembly comprising a housing, a reservoir containing the HBV vaccine, wherein a reservoir containment volume is contained within the housing and configured to receive the reservoir;

an applicator comprising a cartridge assembly receiving volume, a needle hub, and an insertion detector, wherein the insertion detector senses loading of the reservoir in the reservoir containment volume; at least one injection orifice through which the HBV vaccine is administered;

a plurality of penetrating electrodes arranged with a predetermined spatial relationship relative to the orifice;

an electrode support structure comprising a hole and a wall, wherein the electrode support structure prevents inadvertent perpendicular motion of the electrodes;

an electrical field generator for generating an electrical signal operatively connected to the electrodes; and

a controlled source of energy sufficient to transfer a predetermined amount of the HBV vaccine at a predetermined rate from the reservoir through the orifice to the predetermined site within the subject,

wherein the HBV vaccine comprises:

a first nucleic acid molecule comprising a first polynucleotide encoding an HBV polymerase antigen, wherein the HBV polymerase antigen comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 4 and wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity;

a second nucleic acid molecule comprising a second polynucleotide encoding a truncated HBV core antigen consisting of the amino acid sequence of SEQ ID NO: 2; and

a pharmaceutically acceptable carrier, and

wherein the first nucleic acid molecule and the second nucleic acid molecule are present in the same nucleic acid molecule or in two different nucleic acid molecules.

37. A kit comprising:

(i) an HBV vaccine comprising

a first nucleic acid molecule comprising a first polynucleotide encoding an HBV polymerase antigen, wherein the HBV polymerase antigen comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 4 and wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity;

a second nucleic acid molecule comprising a second polynucleotide encoding a truncated HBV core antigen consisting of the amino acid sequence of SEQ ID NO: 2; and
a pharmaceutically acceptable carrier, and
wherein the first nucleic acid molecule and the second nucleic acid molecule are present in the same nucleic acid molecule or in two different nucleic acid molecules; and

(ii) an apparatus comprising:

a cartridge assembly comprising a housing, a reservoir for the HBV vaccine, wherein a reservoir containment volume is contained within the housing and configured to receive the reservoir;

an applicator comprising a cartridge assembly receiving volume, a needle hub, and an insertion detector, wherein the insertion detector senses loading of the reservoir in the reservoir containment volume;

at least one injection orifice through which the HBV vaccine is administered;

a plurality of penetrating electrodes arranged with a predetermined spatial relationship relative to the orifice;

an electrode support structure comprising a hole and a wall, wherein the electrode support structure prevents inadvertent perpendicular motion of the electrodes;

an electrical field generator for generating an electrical signal operatively connected to the electrodes; and

a controlled source of energy sufficient to transfer a predetermined amount of the HBV vaccine at a predetermined rate from the reservoir through the orifice to the predetermined site within the subject.

38. The apparatus of claim 36 or the kit of claim 37, wherein the electrode support structure provides an operative connection between a conductive contact region located on the distal region of the electrodes and the controlled source of energy when the electrodes are deployed into the predetermined tissue site within the subject.

39. The apparatus of claim 36 or 38, or the kit of claim 37 or 38, wherein the electrode support structure comprises at least one hole for passage of the electrodes and a hole for passage of an injection needle.

40. The apparatus of any one of claims 36 and 38 to 39, or the kit of any one of claims 37 to 39, wherein the electrode support structure is a planar support structure positioned perpendicularly relative to the elongate orientation of the electrodes.

41. The apparatus or kit of claim 40, wherein the planar support structure comprises at least one aperture configured to allow passage of the electrode through the predetermined tissue site.

42. The apparatus or kit of any one of claims 40 to 41, wherein the aperture comprises at least one tubular structure arranged perpendicularly to the planar support structure.

43. The apparatus or kit of any one of claims 40 to 42, wherein the planar support structure is oriented perpendicular to the electrodes.

44. The apparatus of any one of claims 36 and 38 to 43, or the kit of any one of claims 37 to 43, wherein the electrode support structure is an adaptive electrode support.

45. The apparatus or kit of claim 44, wherein the adaptive electrode support is a compression spring.

46. The apparatus or kit of claim 45, wherein the compression spring is made from a metal, a polymer or an elastomeric material.

47. The apparatus of any one of claims 36 and 38 to 46, or the kit of any one of claims 37 to 46, wherein the electrode support structure comprises at least one telescoping tube.

48. The apparatus of any one of claims 36 and 38 to 47, or the kit of any one of claims 37 to 47, wherein the electrode support structure further comprises a stick shield spring.

49. The apparatus of claim 36 or the kit of claim 37, wherein the electrode support structure further comprises at least one lateral support member attached to the electrodes with at least one optional hinge feature.
50. The apparatus of any one of claims 36 and 38 to 49, or the kit of any one of claims 37 to 49, wherein the electrode support structure is made from a metal, a polymer, a ceramic, a composite, or a compressible matrix material.
51. The apparatus or kit of claim 50, wherein the compressible matrix material is selected from the group consisting of a cellulose, a foamed plastic, a rubber polymer, a microcellular plastic, foamed silicon, foamed polychloroprene, and carbon foam matrix.
52. The apparatus of any one of claims 36 and 38 to 51, or the kit of any one of claims 37 to 51, wherein the electrode support structure is made from an unconductive material.
53. The apparatus of any one of claims 36 and 38 to 52, or the kit of any one of claims 37 to 52, wherein the electrode support structure is made of a thermoplastic material.
54. The apparatus or kit of claim 53, wherein the thermoplastic material is selected from the group consisting of a polycarbonate, polystyrene, polypropylene, an acrylic, and a polyethylene.
55. The apparatus of any one of claims 36 and 38 to 54, or the kit of any one of claims 37 to 54, wherein the electrode support structure supports transcutaneous deployment of the electrode and maintains at tissue depths up to 60 mm.
56. The apparatus of any one of claims 36 and 38 to 55, or the kit of any one of claims 37 to 55, wherein the electrode proximal portion is an electrode contact and is positioned on the exterior of the inner cartridge of the cartridge assembly, wherein the electrode contact is configured for power communication with corresponding connection on the applicator.

57. The apparatus or kit of claim 56, wherein the electrode contact further comprises an outer cartridge exterior contact.

58. The apparatus or kit of any one of claims 56 to 57, wherein the electrode contact provides an electrically conductive interface with corresponding electrodes while not interfering with forward travel of the electrodes mounted on the inner cartridge.

59. The apparatus of any one of claims 1, 3-36 and 38 to 58, or the kit of any one of claims 2 to 35 and 37 to 58, wherein the applicator further comprises an injection drive assembly, wherein the injection drive assembly mates with the cartridge assembly.

60. The apparatus of any one of claims 1, 3-36 and 38 to 58, or the kit of any one of claims 2 to 35 and 37 to 58, wherein the apparatus further comprises a depth selection button.

61. The apparatus or kit of claim 60, wherein the depth selection button is selected from the group consisting of a toggle, a switch, and a sliding switch.

62. The apparatus of any one of claims 1, 3-36 and 38 to 58, or the kit of any one of claims 2 to 35 and 37 to 58, wherein the apparatus further comprises a plurality of channel and a plurality of retaining post.

63. The apparatus of any one of claims 1, 3-36 and 38 to 58, or the kit of any one of claims 2 to 35 and 37 to 58, wherein the apparatus further comprises an insertion mechanism gear drive ring.

64. The apparatus or kit of claim 63, wherein rotation of the insertion mechanism gear ring rotates the retaining post into the channel.

65. The apparatus of any one of claims 1, 3-36 and 38 to 64, or the kit of any one of claims 2 to 35 and 37 to 64, wherein the cartridge assembly is for single use.

66. The apparatus of any one of claims 1, 3-36 and 38 to 64, or the kit of any one of claims 2 to 35 and 37 to 64, wherein the applicator is for multiple uses.
67. The apparatus of any one of claims 1, 3-36 and 38 to 66, or the kit of any one of claims 2 to 35 and 37 to 66, wherein the applicator further comprises a top housing, a side housing, an inner protective shell, a front cap, and an end cap.
68. The apparatus of any one of claims 1, 3-36 and 38 to 67, or the kit of any one of claims 2 to 35 and 37 to 67, wherein the applicator further comprises a user interface, a procedure activation trigger, a procedure countdown timer, a procedure fault indicator, or an application placement indicator.
69. The apparatus of any one of claims 1, 3-36 and 38 to 68, or the kit of any one of claims 2 to 35 and 37 to 68, wherein the apparatus further comprises a controller.
70. The apparatus of any one of claims 1, 3-36 and 38 to 69, or the kit of any one of claims 2 to 35 and 37 to 69, wherein applicator further comprises a connector for connection to the controller.
71. The apparatus or kit of any one of claims 69 to 70, wherein the controller further comprises an electrical field controller.
72. The apparatus of any one of claims 1, 3-36 and 38 to 71, or the kit of any one of claims 2 to 35 and 37 to 71, wherein the penetrating electrodes and/or the injection orifice come in contact with the predetermined tissue site with velocity of at least 50 mm/second.
73. The apparatus of any one of claims 1, 3-36 and 38 to 71, or the kit of any one of claims 2 to 35 and 37 to 71, wherein the penetrating electrodes and/or the injection orifice come in contact with the predetermined tissue site with velocity of at least 500 mm/second.

74. The apparatus of any one of claims 1, 3-36 and 38 to 73, or the kit of any one of claims 2 to 35 and 37 to 73, wherein the HBV vaccine is capable of inducing an immune response in a mammal against at least two HBV genotypes, preferably the HBV vaccine is capable of inducing a T cell response in a mammal against at least HBV genotypes B, C and D, and more preferably the HBV vaccine is capable of inducing a CD8 T cell response in a human subject against at least HBV genotypes A, B, C and D.

75. The apparatus or kit of claim 74, wherein the first non-naturally occurring nucleic acid molecule is present in a first plasmid DNA vector, and the second non-naturally occurring nucleic acid molecule is present in a second plasmid DNA vector.

76. The apparatus or kit of claim 75, wherein each of the first and second plasmid DNA vectors comprises an origin of replication, an antibiotic resistance gene, and from 5' end to 3' end, a promoter sequence, an enhancer sequence, a signal peptide coding sequence, the first polynucleotide sequence or the second polynucleotide sequence, and a polyadenylation signal sequence.

77. The apparatus or kit of claim 76, wherein the antibiotic resistance gene is a kanamycin resistance gene having a polynucleotide sequence at least 90% identical to SEQ ID NO: 12, preferably 100% identical to SEQ ID NO: 12.

78. The apparatus or kit of claim 77, wherein the HBV vaccine comprises:

- a) a first plasmid DNA vector comprising, from 3'-end to 5'-end, the promoter sequence comprising the polynucleotide sequence of SEQ ID NO: 7, the enhancer sequence comprising the polynucleotide sequence of SEQ ID NO: 8, the signal peptide coding sequence comprising the polynucleotide sequence of SEQ ID NO: 5, the first polynucleotide sequence comprising the polynucleotide sequence of SEQ ID NO: 3, and the polyadenylation signal sequence comprising the polynucleotide sequence of SEQ ID NO: 11;
- b) a second plasmid DNA vector comprising, from 3'-end to 5'-end, the promoter sequence comprising the polynucleotide sequence of SEQ ID NO: 7, the regulatory sequence comprising the polynucleotide sequence of SEQ ID NO: 8, the signal

peptide coding sequence comprising the polynucleotide sequence of SEQ ID NO: 5, the second polynucleotide sequence comprising the polynucleotide sequence of SEQ ID NO: 1, and the polyadenylation signal sequence comprising the polynucleotide sequence of SEQ ID NO: 11; and

c) a pharmaceutically acceptable carrier,

wherein each of the first plasmid DNA vector and the second plasmid DNA vector further comprises a kanamycin resistance gene having the polynucleotide sequence of SEQ ID NO: 12, and an origin of replication having the polynucleotide sequence of SEQ ID NO: 10, and wherein the first plasmid DNA vector and the second plasmid DNA vector are in the same composition or two different compositions.

79. The apparatus or kit of claim 78, wherein the HBV vaccine does not contain a nucleic acid molecule encoding an HBV antigen selected from the group consisting of a Hepatitis B surface antigen (HBsAg), an HBV envelope (Env) antigen, and an HBV L protein antigen, nor an HBV antigen selected from the group consisting of a Hepatitis B surface antigen (HBsAg), an HBV envelope (Env) antigen, and an HBV L protein antigen.

80. A method of inducing an immune response against an HBV infection in a subject in need thereof, comprising delivering a HBV vaccine to a predetermined tissue site within the subject using the apparatus of any one of claims 1, 3-36 and 38 to 79, or the kit of any one of claims 2 to 35 and 37 to 79, wherein said subject is preferably a human suffering from a chronic HBV infection.

81. A method of treating an HBV-induced disease in a subject in need thereof, comprising delivering a HBV vaccine to a predetermined tissue site within the subject using the apparatus of any one of claims 1, 3-36 and 38 to 79, or the kit of any one of claims 2 to 35 and 37 to 79, preferably wherein said subject is a human subject and wherein the HBV-induced disease is selected from the group consisting of advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

82. The method of claim 80 or 81, wherein the predetermined tissue site is located in a skeletal muscle of the subject.

83. The method of claim 82, wherein the skeletal muscle of the subject is medial deltoid muscle.
84. The method of claim 83, wherein an injection depth at medial deltoid muscle is about 3 – 30 mm.
85. The method of claim 82, wherein the skeletal muscle of the subject is vastus lateralis muscle.
86. The method of claim 85, wherein an injection depth at vastus lateralis muscle is about 3 – 38 mm.
87. The method of any one of claims 80 to 86, wherein the electrical signal operably connected to the electrodes comprises an electrical field strength of 100 V/cm to 400 V/cm, preferably 250 V/cm.
88. The method of claim 87, wherein the electrical signal operably connected to the electrodes has a voltage of 50 to 200 V, preferably about 150 V.
89. The method of claim 88, wherein the electrical signal operably connected to the electrodes has a current of 0.5 to 5 A/sec, preferably 0.6 to 4 A/sec, more preferably 0.16 A/sec.
90. The method of claim 89, wherein the electrical signal operably connected to the electrodes has about 1 to 10 electrical pulses, preferably 6 pulses.
91. The method of claim 90, wherein the electrical signal operably connected to the electrodes has an active duration of 30 to 50 milliseconds, preferably 40.8 milliseconds, and the active duration is applied in a total duration of 200 to 500 milliseconds, preferably about 370 milliseconds.
92. The apparatus of any one of claims 1, 3-36 and 38 to 79, or the kit of any one of claims 2 to 35 and 37 to 79 for inducing an immune response against at least two HBV

genotypes, more particularly for use in the treatment of HBV-induced disease, wherein said apparatus is adapted for electroporation of the HBV vaccine in a subject in need thereof, preferably in a human.