CLAIMS

It is claimed:

1. A therapeutic combination for use in treating a hepatitis B virus (HBV) infection in a subject in need thereof, comprising:

i) at least one of:

a) a truncated HBV core antigen consisting of an amino acid sequence that is at least 95% identical to SEQ ID NO: 2, and

b) a first non-naturally occurring nucleic acid molecule comprising a first polynucleotide sequence encoding the truncated HBV core antigen.

c) an HBV polymerase antigen having an amino acid sequence that is at least 90% identical to SEQ ID NO: 7, wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity, and

d) a second non-naturally occurring nucleic acid molecule comprising a second polynucleotide sequence encoding the HBV polymerase antigen; and

ii) an RNAi agent for inhibiting the expression of an HBV gene, preferably, the RNAi agent is selected from the group consisting of:

1) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 2;

2) an RNAi agent having the sense strand sequence and antisense strand sequence shown in Table 3;

3) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 4, preferably the RNAi having the modified sense strand sequence and antisense strand sequence shown in Table 4;

4) an RNAi agent targeting a target sequence shown in Table 5;

5) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 6;

6) an RNAi agent having a core antisense sequence shown in Table 7 and a core sense strand sequence shown in Table 8, preferably the RNAi having

the modified sense strand sequence shown in Table 7 and the modified antisense strand sequence shown in Table 8; and

7) an RNAi agent having a duplex of an antisense strand and a sense strand shown in Table 9, preferably the RNAi agent comprises the duplex shown in Table 9.

2. The therapeutic combination of claim 1, comprising at least one of the HBV polymerase antigen and the truncated HBV core antigen.

3. The therapeutic combination of claim 2, comprising the HBV polymerase antigen and the truncated HBV core antigen.

4. The therapeutic combination of claim 1, comprising at least one of the first non-naturally occurring nucleic acid molecule comprising the first polynucleotide sequence encoding the truncated HBV core antigen and the second non-naturally occurring nucleic acid molecule comprising the second polynucleotide sequence encoding the HBV polymerase antigen.

5. A therapeutic combination for use in treating a hepatitis B virus (HBV) infection in a subject in need thereof, comprising

i) a first non-naturally occurring nucleic acid molecule comprising a first polynucleotide sequence encoding a truncated HBV core antigen consisting of an amino acid sequence that is at least 95% identical to SEQ ID NO: 2; and

ii) a second non-naturally occurring nucleic acid molecule comprising a second polynucleotide sequence encoding an HBV polymerase antigen having an amino acid sequence that is at least 90% identical to SEQ ID NO: 7, wherein the HBV polymerase antigen does not have reverse transcriptase activity and RNase H activity; and

iii) an RNAi agent for inhibiting the expression of an HBV gene, wherein. the RNAi agent is selected from the group consisting of:

1) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 2;

2) an RNAi agent having the sense strand sequence and antisense strand sequence shown in Table 3;

3) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 4, preferably the RNAi having the modified sense strand sequence and antisense strand sequence shown in Table 4;
4) an RNAi agent targeting a target sequence shown in Table 5;
5) an RNAi agent having the core sense strand sequence and antisense strand sequence shown in Table 6;
6) an RNAi agent having a core antisense sequence shown in Table 7 and a core sense strand sequence shown in Table 8, preferably the RNAi having the modified sense strand sequence shown in Table 7 and the modified antisense strand sequence shown in Table 8; and
7) an RNAi agent having a duplex of an antisense strand and a sense strand shown in Table 9, preferably the RNAi agent comprises the duplex shown in Table 9, more preferably, the RNAi agent is conjugated to a targeting ligand.

6. The therapeutic combination of claim 4 or 5, wherein the first non-naturally occurring nucleic acid molecule further comprises a polynucleotide sequence encoding a signal sequence operably linked to the N-terminus of the truncated HBV core antigen, and the second non-naturally occurring nucleic acid molecule further comprises a polynucleotide sequence encoding a signal sequence operably linked to the N-terminus of the HBV polymerase antigen, preferably, the signal sequence independently comprises the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 15, preferably the signal sequence is independently encoded by the polynucleotide sequence of SEQ ID NO: 8 or SEQ ID NO: 14.
7. The therapeutic combination of any one of claims 1-6, wherein
a) the truncated HBV core antigen consists of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; and
b) the HBV polymerase antigen comprises the amino acid sequence of SEQ ID NO: 7.
8. The therapeutic combination of any one of claims 1-7, wherein each of the first, and second non-naturally occurring nucleic acid molecules is a DNA molecule, preferably the DNA molecule is present on a plasmid or a viral vector.

9. The therapeutic combination of any one of claims 4 to 8, comprising the first non-naturally occurring nucleic acid molecule and the second non-naturally occurring nucleic acid molecule in the same non-naturally nucleic acid molecule.
10. The therapeutic combination of any one of claims 4 to 8, comprising the first non-naturally occurring nucleic acid molecule and the second non-naturally occurring nucleic acid molecule in two different non-naturally occurring nucleic acid molecules.
11. The therapeutic combination of any one of claims 4 to 10, wherein the first polynucleotide sequence comprises a polynucleotide sequence having at least 90% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 3.
12. The therapeutic combination of claim 11, wherein the first polynucleotide sequence comprises the polynucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3.
13. The therapeutic combination of any one of claims 4 to 12, wherein the second polynucleotide sequence comprises a polynucleotide sequence having at least 90% sequence identity to SEQ ID NO: 5 or SEQ ID NO: 6.
14. The therapeutic combination of claim 13, wherein the second polynucleotide sequence comprises the polynucleotide sequence of SEQ ID NO: 5 or SEQ ID NO: 6.
15. The therapeutic combination of any one of claims 1-14, wherein the RNAi agent has the duplex structure of AD04580; AD04585; AD04776; AD04872; AD04962; AD04963; AD04982; or AD05070 shown in Table 9, preferably the RNAi agent is conjugated to a targeting ligand (NAG13), (NAG13)s, (NAG18), (NAG18)s, (NAG24), (NAG24)s, (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), or (NAG39) depicted in Table 10..A kit comprising the therapeutic combination of any one of claims 1-15, and instructions for using the therapeutic combination in treating a hepatitis B virus (HBV) infection in a subject in need thereof.

16. The therapeutic combination of any one of claims 1 to 15 for use in treating a hepatitis B virus (HBV) infection in a subject in need thereof.