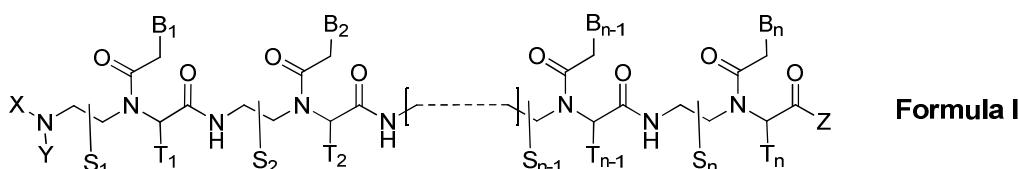


CLAIMS

1. A peptide nucleic acid derivative represented by **Formula I**, or a pharmaceutically acceptable salt thereof:



wherein,

n is an integer between 10 and 25;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence, or partially complementary to the target pre-mRNA sequence with one or two mismatches;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1},$ and T_n independently represent deuterido [D], hydrido [H], substituted or non-substituted alkyl, or substituted or non-substituted aryl radical;

X is hydrido radical;

Y represents aminocarbonyl [$\text{NH}_2\text{-C(=O)-}$], aminothiocarbonyl [$\text{NH}_2\text{-C(=S)-}$], substituted or non-substituted alkyloxycarbonyl, substituted or non-substituted aryloxycarbonyl, substituted or non-substituted alkylaminocarbonyl, substituted or non-substituted arylaminocarbonyl, substituted or non-substituted alkylaminothiocarbonyl, substituted or non-substituted arylaminothiocarbonyl, substituted or non-substituted alkyloxythiocarbonyl, substituted or non-substituted aryloxythiocarbonyl, substituted or non-substituted alkylphosphonyl, or substituted or non-substituted arylphosphonyl radical;

Z represents hydrido, hydroxy, substituted or non-substituted alkyloxy, substituted or non-substituted aryloxy, non-substituted amino [$-\text{NH}_2$], substituted or non-substituted alkylamino, substituted or non-substituted arylamino, substituted or non-substituted alkyl, or substituted or non-substituted aryl radical;

$B_1, B_2, \dots, B_{n-1},$ and B_n are independently selected from natural nucleobases including adenine, thymine, guanine, cytosine and uracil, and unnatural nucleobases; and

at least four of $B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from unnatural nucleobases with a substituted or non-substituted amino radical covalently linked to the nucleobase moiety;

and wherein the target splice site sequence is not [(5' $\rightarrow$ 3') UUGCCUGGUAAGGA] within the human androgen receptor pre-mRNA.

2. The peptide nucleic acid derivative according to claim 1, or a pharmaceutically acceptable salt thereof:

wherein,

n is an integer between 10 and 25;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence, or partially complementary to the target pre-mRNA sequence with one or two mismatches;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1}$, and T_n independently represent deuterido, hydrido, substituted or non-substituted alkyl, or substituted or non-substituted aryl radical;

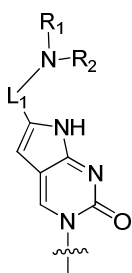
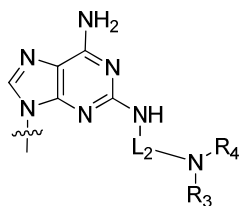
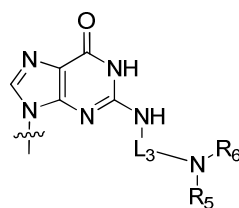
X is hydrido radical;

Y represents aminocarbonyl, aminothiocarbonyl, substituted or non-substituted alkyloxycarbonyl, substituted or non-substituted aryloxycarbonyl, substituted or non-substituted alkylaminocarbonyl, substituted or non-substituted arylaminocarbonyl, substituted or non-substituted alkylaminothiocarbonyl, substituted or non-substituted arylaminothiocarbonyl, substituted or non-substituted alkyloxythiocarbonyl, substituted or non-substituted aryloxythiocarbonyl, substituted or non-substituted alkylphosphonyl radical, or substituted or non-substituted arylphosphonyl radical;

Z represents hydrido, hydroxy, substituted or non-substituted alkyloxy, substituted or non-substituted aryloxy, non-substituted amino, substituted or non-substituted alkylamino, substituted or non-substituted arylamino, substituted or non-substituted alkyl, or substituted or non-substituted aryl radical;

$B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from natural nucleobases including adenine, thymine, guanine, cytosine and uracil, and unnatural nucleobases;

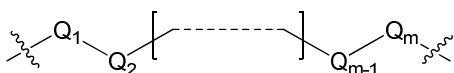
at least four of $B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**:

**Formula II****Formula III****Formula IV**

wherein,

R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are independently selected from hydrido, and substituted or non-substituted alkyl radical;

L_1 , L_2 and L_3 are a covalent linker represented by **Formula V** covalently linking the basic amino group to the nucleobase moiety:

**Formula V**

wherein,

Q_1 and Q_m are substituted or non-substituted methylene ($-\text{CH}_2-$) radical, and Q_m is directly linked to the basic amino group;

Q_2 , Q_3 , ..., and Q_{m-1} are independently selected from substituted or non-substituted methylene, oxygen ($-\text{O}-$), sulfur ($-\text{S}-$), and substituted or non-substituted amino radical [$-\text{N}(\text{H})-$, or $-\text{N}(\text{substituent})-$]; and

m is an integer between 1 and 15.

3. The peptide nucleic acid derivative according to claim 2, or a pharmaceutically acceptable salt thereof:

wherein,

n is an integer between 11 and 23;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence, or partially complementary to the target pre-mRNA sequence with one or two mismatches;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1},$ and T_n are hydrido radical;

X is hydrido radical;

Y represents aminocarbonyl, substituted or non-substituted alkyloxycarbonyl, or substituted or non-substituted alkylaminocarbonyl;

Z represents non-substituted amino, or substituted or non-substituted alkylamino radical;

$B_1, B_2, \dots, B_{n-1},$ and B_n are independently selected from natural nucleobases including adenine, thymine, guanine, cytosine and uracil, and unnatural nucleobases;

at least four of $B_1, B_2, \dots, B_{n-1},$ and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**;

R_1, R_2, R_3, R_4, R_5 and R_6 are independently selected from hydrido, and substituted or non-substituted alkyl radical;

Q_1 and Q_m are substituted or non-substituted methylene radical, and Q_m is directly linked to the basic amino group;

$Q_2, Q_3, \dots,$ and Q_{m-1} are independently selected from substituted or non-substituted methylene, oxygen, and amino radical; and

m is an integer between 1 and 11.

4. The peptide nucleic acid derivative according to claim 2, or a pharmaceutically acceptable salt thereof:

wherein,

n is an integer between 11 and 21;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence, or partially complementary to the target pre-mRNA sequence with one or two mismatches;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1},$ and T_n are hydrido radical;

X is hydrido radical;

Y represents substituted or non-substituted alkyloxycarbonyl, or substituted or non-substituted alkylaminocarbonyl;

Z represents non-substituted amino, or substituted or non-substituted alkylamino radical;

$B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from natural nucleobases including adenine, thymine, guanine, cytosine and uracil, and unnatural nucleobases;

at least four of $B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**;

R_1, R_2, R_3, R_4, R_5 and R_6 are independently selected from hydrido, and substituted or non-substituted alkyl radical;

Q_1 and Q_m are methylene radical, and Q_m is directly linked to the basic amino group;

$Q_2, Q_3, \dots$, and Q_{m-1} are independently selected from methylene, oxygen, and amino radical; and

m is an integer between 1 and 11.

5. The peptide nucleic acid derivative according to claim 2, or a pharmaceutically acceptable salt thereof:

wherein,

n is an integer between 11 and 19;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1}$, and T_n are hydrido radical;

X is hydrido radical;

Y represents substituted or non-substituted alkyloxycarbonyl, or substituted or non-substituted alkylaminocarbonyl;

Z represents non-substituted amino, or substituted or non-substituted alkylamino radical;

$B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from natural nucleobases including adenine, thymine, guanine, cytosine and uracil, and unnatural nucleobases;

at least four of $B_1, B_2, \dots, B_{n-1}$, and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**;

R_1 , R_3 , and R_5 are hydrido radical, and R_2 , R_4 , and R_6 independently represent hydrido, or substituted or non-substituted alkyl radical;

Q_1 and Q_m are methylene radical, and Q_m is directly linked to the basic amino group;

Q_2 , Q_3 , ..., and Q_{m-1} are independently selected from methylene and oxygen radical;

and

m is an integer between 1 and 9.

6. The peptide nucleic acid derivative according to claim 2, or a pharmaceutically acceptable salt thereof:

wherein,

n is an integer between 12 and 19;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence;

S_1 , S_2 , ..., S_{n-1} , S_n , T_1 , T_2 , ..., T_{n-1} , and T_n are hydrido radical;

X is hydrido radical;

Y represents substituted or non-substituted alkyloxycarbonyl radical;

Z represents non-substituted amino, or substituted or non-substituted alkylamino radical;

B_1 , B_2 , ..., B_{n-1} , and B_n are independently selected from adenine, thymine, guanine, cytosine, and unnatural nucleobases;

at least five of B_1 , B_2 , ..., B_{n-1} , and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**;

R_1 , R_2 , R_3 , R_4 , R_5 , and R_6 are hydrido radical;

Q_1 and Q_m are methylene radical, and Q_m is directly linked to the basic amino group;

Q_2 , Q_3 , ..., and Q_{m-1} are independently selected from methylene and oxygen radical;

and

m is an integer between 1 and 9.

7. The peptide nucleic acid derivative according to claim 2, or a pharmaceutical salt thereof:

wherein,

n is an integer between 12 and 18;

the compound of **Formula I** possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA;

the compound of **Formula I** is fully complementary to the target pre-mRNA sequence;

$S_1, S_2, \dots, S_{n-1}, S_n, T_1, T_2, \dots, T_{n-1},$ and T_n are hydrido radical;

X is hydrido radical;

Y represents substituted or non-substituted alkyloxycarbonyl radical;

Z represents non-substituted amino, or substituted or non-substituted alkylamino radical;

$B_1, B_2, \dots, B_{n-1},$ and B_n are independently selected from adenine, thymine, guanine, cytosine, and unnatural nucleobases;

at least five of $B_1, B_2, \dots, B_{n-1},$ and B_n are independently selected from unnatural nucleobases represented by **Formula II**, **Formula III**, or **Formula IV**;

$R_1, R_2, R_3, R_4, R_5,$ and R_6 are hydrido radical;

L_1 represents $-(CH_2)_2-O-(CH_2)_2-, -CH_2-O-(CH_2)_2-, -CH_2-O-(CH_2)_3-, -CH_2-O-(CH_2)_4-, -CH_2-O-(CH_2)_5-, -CH_2-O-(CH_2)_6-,$ or $-CH_2-O-(CH_2)_7-$ with the right end is directly linked to the basic amino group; and

L_2 and L_3 are independently selected from $-(CH_2)_2-, -(CH_2)_3-, -(CH_2)_4-, -(CH_2)_5-, -(CH_2)_6-, -(CH_2)_7-, -(CH_2)_8-, -(CH_2)_2-O-(CH_2)_2-, -(CH_2)_3-O-(CH_2)_2-,$ and $-(CH_2)_2-O-(CH_2)_3-$ with the right end is directly linked to the basic amino group.

8. A method of using the peptide nucleic acid derivative of any one of claims 1-7 to induce in cells in vitro the skipping of the target exon within the target pre-mRNA.

9. A peptide nucleic acid derivative of any one of claims 1-7, for use in inducing in a subject the skipping of the target exon within the target pre-mRNA.

10. A peptide nucleic acid derivative of any one of claims 1-7, for use in the treatment of diseases or conditions by downregulating the expression of the gene transcribing the target pre-mRNA.

11. A method of using the peptide nucleic acid derivative of any one of claims 1-7

to modulate in cells in vitro the functional activity of the gene transcribing the target pre-mRNA.

12. A peptide nucleic acid derivative of any one of claims 1-7, for use in modulating in a subject the functional activity of the gene transcribing the target pre-mRNA.

13. Use of a peptide nucleic acid derivative of any one of claims 1-7 in the manufacture of a medicament for the treatment of diseases by downregulating the expression of the gene transcribing the target pre-mRNA.

14. The use of claim 13, wherein the medicament induces in a subject the skipping of the target exon within the target pre-mRNA.

15. The use of claim 13, wherein the medicament modulates in a subject the functional activity of the gene transcribing the target pre-mRNA.

16. The peptide nucleic acid derivative of any one of claims 1-7, wherein the compound possesses at least a 10-mer complementary overlap with a 14-mer target splice site sequence that consists of 7-mer from intron and 7-mer from exon within a target pre-mRNA, wherein the target splice site sequence is not [(5' → 3') UUUUUGCGUAAGUA] within the human SCN9A pre-mRNA, [(5' → 3') UAAGUAGGAUAAGU] within the human HIF-1 α pre-mRNA, [(5' → 3') AUCCCAGGGUAACA] within the human SNAP25 pre-mRNA, [(5' → 3') UGUUUAGGUACACU] within the human SCN9A pre-mRNA, or [(5' → 3') UGUACAGAUUGUCU] within the human tyrosinase pre-mRNA.

17. The peptide nucleic acid derivative of any one of claims 1-7, wherein the compound possesses at least a 10-mer complementary overlap with a target splice site within a target pre-mRNA, wherein the target splice site sequence does not comprise [(5' → 3') UUGCCUGGUAAGGA] within the human androgen receptor pre-mRNA, [(5' → 3') UUUUUGCGUAAGUA] within the human SCN9A pre-mRNA, [(5' → 3') UAAGUAGGAUAAGU] within the human HIF-1 α pre-mRNA, [(5' → 3') AUCCCAGGGUAACA] within the human SNAP25 pre-mRNA, [(5' → 3') UGUUUAGGUACACU] within the human SCN9A pre-mRNA, or [(5' → 3') UGUACAGAUUGUCU] within the human tyrosinase pre-mRNA.