In one aspect, the disclosure provides for an oligomeric compound of 8 – 35 nucleotides in length, comprising three regions:

i) a first region (region A), which is an antisense oligomer consisting of 7 – 25 contiguous nucleotides complementary to a nucleic acid target, wherein the first region comprises at least one nucleoside analog and wherein the internucleoside linkages of the first region are internucleoside linkage other than phosphodiester;

ii) a second region (region B) covalently linked to the 5' or 3' nucleotide of the first region via a phosphodiester linkage, wherein region B consists of between 1 – 4 phosphodiester linked DNA or RNA nucleotides; and

iii) a third region which comprises a conjugate moiety, a targeting moiety, or a blocking moiety, wherein the third region is covalently linked to the second region.

In some embodiments, region A and region B form a single contiguous nucleotide sequence of 8 – 35 nucleotides in length.

c) a step of [sequential] oligonucleotide synthesis of a first region (A) and a second region (B), wherein the synthesis step is followed by

d) a step of adding a third region [phosphoramidite comprising]

i) optionally a linker group (-Y-)

ii) a group X comprising a group selected from the group consisting of a conjugate, a targeting group, a blocking group, a reactive group [e.g. an amine or an alcohol] or an activation group (X-) or optionally an -Y – X group

followed by

a) the cleavage of the oligomeric compound from the [solid phase] support

wherein, optionally said method further comprises a further step selected from:

b) wherein the third group is an activation group, the step of activating the activation group to produce a reactive group, followed by adding a conjugate, a blocking, or targeting group to the reactive group, optionally via a linker group (Y);

c) wherein the third region is a reactive group, the step of adding a conjugate, a blocking, or targeting group to the reactive group, optionally via a linker group (Y).

d) wherein the third region is a linker group (Y), the step of adding a conjugate, a blocking, or targeting group to the linker group (Y)

wherein steps f), g) or h) are performed either prior to or subsequent to cleavage of the oligomeric compound from the oligonucleotide synthesis support.

In some embodiments, the method may be performed using standard phosphoramidite chemistry, and as such the region X and/or region X or region X and Y may be provided, prior to incorporation into the oligomer, as a phosphoramidite. Please see figures 5 – 10 which illustrate non-limiting aspects of the method of the disclosure.

The disclosure provides for a method of synthesizing (or manufacture) of an oligomeric compound, such as the oligomeric compound of the disclosure, said method comprising a step of [sequential] oligonucleotide synthesis of a first region (A) and optionally a second region (B), wherein the synthesis step is followed by a step of adding a third region [phosphoramidite comprising] region X (also referred to as region C), or Y such as a region comprising a group selected from the group consisting of a conjugate, a targeting group, a blocking group, a functional group, a reactive group [e.g. an amine or an alcohol] or an activation group (X), or an -Y – X group followed by the cleavage of the oligomeric compound from the [solid phase] support.

CLAIMS

1. An oligomeric compound of 8 – 35 nucleotides in length, comprising three regions:
   i) a first region (region A), which is an antisense oligomer consisting of 7 – 25 contiguous nucleotides complementary to a nucleic acid target, wherein the first region comprises at least one nucleoside analog and wherein the internucleoside linkages of the first region are internucleoside linkage other than phosphodiester;
   ii) a second region (region B) covalently linked to the 5' or 3' nucleotide of the first region via a phosphodiester linkage, wherein region B consists of between 1 – 4 phosphodiester linked DNA or RNA nucleotides; and
   iii) a third region which comprises a conjugate moiety, a targeting moiety, or a blocking moiety, wherein the third region is covalently linked to the second region.

2. The oligomeric compound according to claim 1, wherein the internucleoside linkages other than phosphodiester are selected from the group consisting of phosphorothioate, phosphorodithioate and boranophosphate.

3. The oligomeric compound according to claim 1 or 2, wherein the nucleic acid target is selected from the group consisting of a microRNA, a mRNA, a lncRNA (long non-coding RNA), a snRNA, snoRNA, and a viral RNA.

4. The oligomeric compound according to any one of claims 1 - 3, wherein the first region of the oligomeric compound is a gapmer, a mixmer, or a totalmer.

5. The oligomeric compound according to any one of claims 1 - 4, wherein the first region of the oligomeric compound comprises at least one bicyclic nucleotide analogue (LNA).

6. The oligomeric compound according to any one of claims 1 –5, wherein the first region and the second region form a contiguous nucleotide sequence.

7. The oligomeric compound according to any one of claims 1 – 6, wherein the second region is 5' to the first region.

8. The oligomeric compound according to any one of claims 1 – 6, wherein the second region is 3' to the first region.

9. The oligomeric compound according to any one of claims 1 – 8, wherein the second region comprises at least two consecutive DNA or RNA units, which are linked by phosphodiester linkages.

10. The oligomeric compound according to any one of claims 1 –9 wherein the second region consists of a dinucleotide of sequence AA, AT, AC, AG, TA, TT, TC, TG, CA, CT, CC, CG, GA, GT, GC, or GG.

11. The oligomeric compound according to any one of claims 1–9, wherein the second region consists of a trinucleotide of sequence AAA, AAT, AAC, AAG, ATA, ATT, ATC, ATG, ACA, ACT, ACC, ACG, AGA, AGT, AGC, AGG, TAA, TAT, TAC, TAG, TTA, TTT, TTC, TAG, TCA, TCT, TCC, TCG, TGA, TGT, TGC, TGG, CAA, CAT, CAC, CAG, CTA, CTG, CTC, CTT, CCA, CCT, CCC, CCG, CGA, CGT, CGC, CGG, GAA, GAT, GAC, CAG, GTA, GTT, GTC, GTG, GCA, GCT, GCC, GCG, GGA, GGT, GGC, or GGG.

12.The oligomeric compound according to any one of claims 1 – 11, wherein the second region is covalently linked to the third region at the terminal nucleoside of the second region (i.e. the 3' or 5' terminus, depending on the position of the first region).

13. The oligomeric compound according to any one of claims 1 – 12, wherein the third region is a conjugate group comprising a non-nucleotide moiety selected from the group consisting of: a carbohydrate, a lipophilic group, a protein, a peptide, an antibody or fragment thereof, a polymer, a reporter group, a dye, a receptor ligand, a small molecule drug, a prodrug, and a vitamin.

14. The oligomeric compound according to claim 13, wherein the conjugate group is selected from sterol, fatty acid, cholesterol, GalNAc or a GalNAc cluster.

15. The oligomeric compound according to any one of claims 1 – 12, wherein the third region is a blocker group.

16. The oligomeric compound according to any one of claims 1 – 12, wherein the third region comprises a targeting group.

17. The oligomeric compound according to any one of claims 1 – 16, wherein the second and third regions are covalently joined by a linker group.

18. The oligomeric compound according to claim 17, wherein the linker group between the second and third regions comprises a group selected from phosphodiester, a phosphorothioate, and phosphorodithioate or a boranophosphate group, such as a phosphodiester group.

19. A pharmaceutical composition comprising the oligomeric compound of any one of claims 1-18, and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

20. The oligomeric compound according to any one of claims 1-18 for use in the inhibition of a nucleic acid target in a cell.

21. The oligomeric compound according to any one of claims 1-18 for use in medicine.

22. The oligomeric compound according to any one of claims 1-18 for use in the treatment of a medical disease or disorder.

23. The use of the oligomeric compound according to any one of claims 1-18 for the preparation of a medicament for the treatment of a disease or disorder selected from the group consisting of alpha-1 antitrypsin liver disease (AAT-LivD), alcohol dependence, anemia or inflammation/chronic kidney disease (CKD), atherosclerosis, atherosclerosis/high lipoprotein (a) (Lp(a)), cancer, liver cancer, cardiometabolic diseases, viral disease, hepatitis C virus (HCV), polycythemia, hepatitis B, BKV, human immunodeficiency virus (HIV), rare diseases (or genetic disorder), hemochromatosis, hemophilia A, B, hypertriglyceridemia, hyperlipidemia, high/low density lipoprotein (HDL/LDL) cholesterol imbalance, dyslipidemias, nonalcoholic steatohepatitis (NASH), porphyria, rare bleeding disorders, serum amyloid A (SAA)-amyloidosis, thrombosis, acromegaly, hypercholesterolemia, inflammatory disorders, obesity, transthyretin (TTR) amyloidosis, diabetes (type I and/or II), cushing's syndrome, glucose homeostasis, chronic heart failure, cardiovascular disease or disorder, myocardial

infarction (MI), blood clotting disorder, fibrosis, liver fibrosis, cardiac fibrosis, local fibrosis, disease or disorder that results (or is associated with) bone-lose, liver disease or disorder, metabolic disorder, metabolic syndrome, familial combined hyperlipidemia (FCHL), acquired hyperlipidemia, statin-resistant, vascular disease, peripheral arterial disease, heart disease, ischemia, acute coronary syndrome (ACS), coronary artery disease (CAD), coronary heart disease (CHD).

24. An oligomeric compound according to any one of claims 1-18 for use in inhibiting the expression of a target gene in a cell, wherein said cell expresses said target gene, and wherein said oligomeric compound is to be administered in an amount effective to reduce the expression of the target gene in said cell.