nucleosides linked by a phosphodiester linkages. In some embodiments, Region B may be further extended by further phosphodiester DNA/RNA (such as DNA nucleosides). The conjugate group (Marked X, otherwise region C herein) is illustrated on the left side of each compound (e.g. Cholesterol, GalNAc, Conj1 – 4, 1a – 4a, and 5 or 6), and may, optionally be covalently attached to the terminal nucleoside of region B via a phosphorus nucleoside linkage group, such as phosphodiester, phosphorothioate, phosphorodithioate, boranophosphate or methylphosphonate, or may be linked via an alternative linkage, e.g. a triazol linkage (see L in compounds d), e), and f

Figure 13. Non-limiting Illustration of compounds of the invention, where the compounds comprise the optional linker (Y) between the third (conjugate) region (X) and the second region (region B). Same nomenclature as Figure 12. Suitable linkers are disclosed herein, and include, for example alkyl linkers, for example C6 linkers. In compounds a), b) and c), the linker between X and region B is attached to region B via a phosphorus nucleoside linkage group, such as phosphodiester, phosphorothioate, phosphorodithioate, boranophosphate or methylphosphonate, or may be linked via an alternative linkage eg. a triazol linkage (Li). In these compounds Lii represents the internucleoside linkage between the first (A) and second regions (B). Compounds d), e), & f) further comprise a linker (Y) between region B and the conjugate group, and region Y may be linked to region B via, for example, a phosphorus nucleoside linkage group, such as phosphodiester, phosphorothioate, phosphorodithioate, boranophosphate or methylphosphonate, or in some embodiments a triazole linkage. In addition, or alternatively X may be an activation group or a reactive group. X may be covalently attached to region B via a phosphorus nucleoside linkage group, such as phosphodiester, phosphorothioate, phosphorodithioate, boranophosphate or methylphosphonate, or may be linked via an alternative linkage, e.g. a triazol linkage.

Figure 14. Silencing of PCSK9 mRNA with cholesterol-conjugates *in vivo*. Mice were injected with a single dose of 10 mg/kg unconjugated LNA-antisense oligonucleotide (#40) or equimolar amounts of LNA antisense oligonucleotides conjugated to Cholesterol with different linkers and sacrificed at days 1, 3, 7 and 10 after dosing. RNA was isolated from liver and kidney and subjected to PCSK9 specific RT-qPCR. A) Quantification of PCSK9 mRNA from liver samples normalized to BACT and shown as percentage of the average of equivalent saline controls; B) Quantification of PCSK9 mRNA from kidney samples normalized to BACT and shown as percentage of the average of equivalent saline controls.

Figure 15. Kim-1 expression from rat safety study (see Example 5).

Figure 16: Serum PCSK9 and LDL cholesterol in samples from cynomolgus monkeys injected four times (one injection/week) with 0.5 or 1.5 mg/kg/week of SEQ ID 2 and 18.

Figure 17. Serum PCSK9 and LDL cholesterol in samples from cynomolgus monkeys injected four times (one injection/week) with 0.5 or 1.5 mg/kg/week of SEQ ID 3 and 19.