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Potent knock down of lncRNAs in vitro and in vivo with antisense LNA™ GapmeRs

While long non-coding RNAs (IncRNAs) are believed to exceed protein coding RNAs in numbers, only very few have been characterized in any detail. One of the most basic yet powerful approaches to study lncRNAs is loss of function analysis, but since many lncRNAs are nuclear retained or have long residence time in the nucleus, these are hard to target by RNAi based methods

We have developed single stranded LNA™-enhanced antisense oligonucleotides (ASOs, also known as LNA™ GapmeRs) that catalyze RNaseH dependent degradation of both mRNAs and lncRNA. Since RNaseH is almost exclusively present in the nucleus, all RNAs are potentially sensitive to LNA™ GapmeR knock down. The LNA™ GapmeRs are designed by our empirically derived algorithm to provide ASOs that achieve potent target knockdown with a high hit-rate.

Off-targets are a relevant concern for all antisense strategies. To address potential off targets located in either exons or introns, our LNA™ GapmeR design algorithm searches both spliced and unspliced transcriptomes in the Ensembl database, to provide maximal target specificity.

LNA™ GapmeRs applied to knock down multiple different RNA targets in vitro demonstrates that both mRNA and lncRNA targets residing in either cytoplasmic or nuclear compartments are equally efficiently silenced irrespective of the type of RNA target and its subcellular localization. We also report highly efficient and long lasting knockdown of a nuclear retained lncRNA in a broad range of tissues in mice subjected to systemic administration of a LNA™ GapmeR. LNA™ GapmeRs are therefore excellent tools for IncRNA loss of function analysis in vitro and in vivo and provide an excellent platform for therapeutic targeting of lncRNA.

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