Microsynth

GalNAc Conjugates for Antisense and siRNA Applications

3'-GalNAc functionalized ASOs and siRNAs (sense strand)

Trivalent GalNAc funtionalized oligonucleotides for increased uptake in hepatocytes

Introduction

Conjugation of N-acetylgalactosamine has become a major clinical strategy for delivery of oligonucleotides to hepatocytes. Such conjugates are efficiently internalized by binding to the asialoglycoprotein receptor (ASGR, see ***Figure 1***), which exhibits high affinity for N-acetyl galactosamine (GalNAc) terminated oligosaccharides. [1] The functional ASGR clears N-acetyl galactosamine from serum by receptor mediated endocytosis. The ASGR is abundantly expressed on hepatocytes (ca. 500,000 copies/cell) and it is conserved across all mammals. [2]

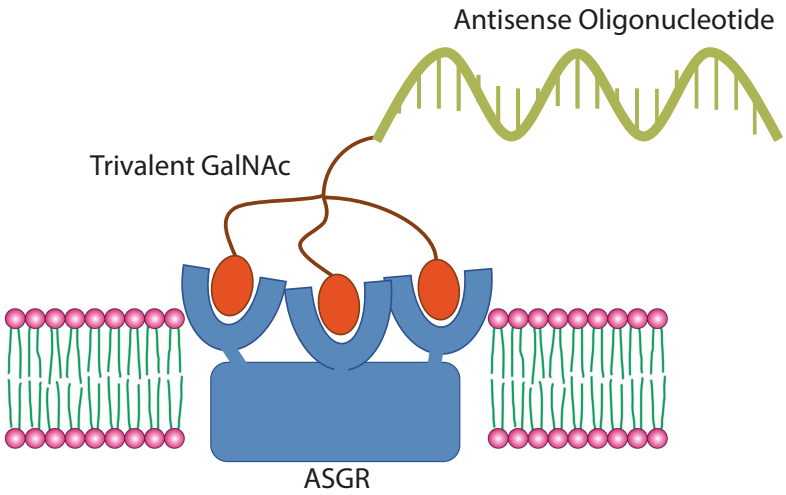

Figure 1: *Scheme of ASO-GalNAc conjugate binding to ASGR.*

Antisense Oligonucleotides

GalNAc-conjugated ASOs represent an advanced therapeutic platform for liver-targeted delivery. The improved potency of GalNAc-conjugated ASOs in animals is a direct result of enhanced delivery of the modified ASOs to hepatocytes via binding to ASGR. For efficient delivery the ASO is conjugated to a trivalent GalNAc moiety. [3]

siRNA

Similarly, GalNAc-conjugated siRNA represent a novel class of RNAi therapeutics with demonstrated preclinical efficacy in vivo. Optimal design of multivalent GalNAc-conjugated siRNAs can elicit robust RNAi-mediated gene silencing in hepatocytes in vitro and in vivo without the aid of drug delivery agents. Suitably stabilized siRNAs were found to inhibit target gene expression in mice with single-dose ED50 values of 1 mg/kg. Importantly, the delivery approach shows improved tissue-specific delivery and efficacy after SC dosing relative to IV administration. [4]

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GalNAc-Oligonucleotide Conjugates for Therapeutic Applications

Microsynth provides GalNAc-conjugated ASOs containing a trivalent GalNAc cluster attached to the 3'-end of the oligonucleotide (see ***Figure 2***). These conjugates are available for DNA, 2'-OMe, 2'-MOE-oligonucleotides including the options of phosphodiester or phosphorothioate linkages. To complete our ASO portfolio we also provide LNA- or MOE-gapmers as GalNAc-conjugates. For gene silencing applications using siRNA we offer GalNAc-conjugated siRNAs where the trivalent GalNAc cluster is attached to the 3'-end of the sense strand.

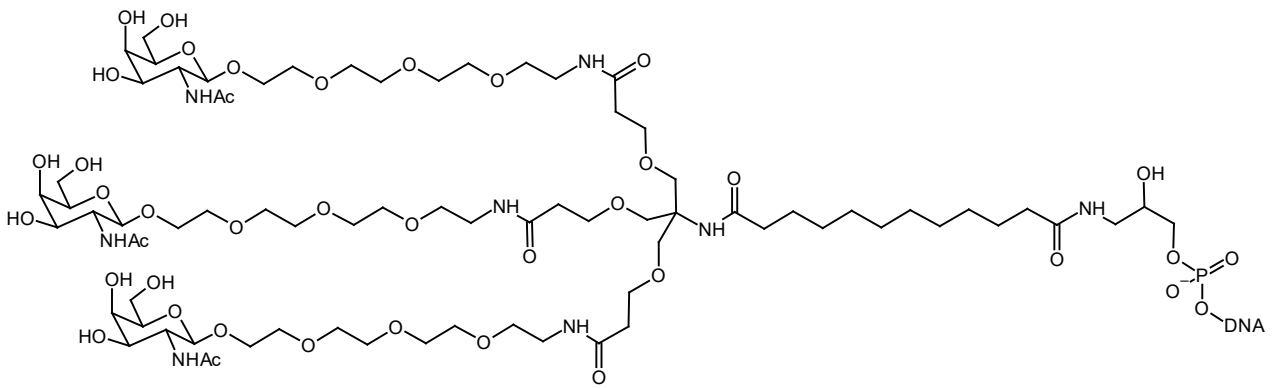

Figure 2: *Chemical structure of trivalent GalNAc cluster.*

References

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