Defined Multimeric Oligonucleotides for Enhanced Therapeutic Effect.

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Summary

Multivalent parent oligonucleotides (POONs) with preprogrammed multivalent oligomers have the potential to improve clearance kinetics and bioavailability, but subjecting large molecules to multiple rounds of chemical conjugation is often challenging. Here we describe a defined oligonucleotide format in which a desired bioactivity is achieved by a defined sequence of defined bioactivity units. Large multimers are produced via standard oligonucleotide chemistry. The resulting molecules exhibit a multi-fold increase in serum half-life and bioactivity in vivo.

Large Multimers have Enhanced Serum Half-lives and Bioactivity wrt Monomers

Serum Half-lives: FVII Hexamer vs monomer......

Bioactivity

4:1 FVII-ApoB-TTR Hetero-hexamer

Easy Synthesis

Mono-DTME + Assymmetric Annealing

Comparison 1-8 mers: Synthesis

All Steps – high yield, high purity

Silencing per unit siRNA unchanged, per unit Ligand increased

Conclusions

The potency of a ligand-oligonucleotide therapeutic agent can be greatly enhanced by preparing the oligonucleotide in multimeric form. This has the potential to enable oligonucleotide therapeutics to be effective against hitherto intractable targets involving low receptor copy numbers and internalization rates, and/or diseases requiring multiple knockdowns or IV delivery.

Key

IV Knockdown by Hexamer exceeds SC Knockdown by Monomer

Serum Half-lives

TTR protein levels in serum

Serum Transaminase – day 7

Serum Cholesterol – day 9

Highlights:

- Defined multimeric oligonucleotides exhibit a multi-fold increase in serum half-life and bioactivity in vivo.
- Large multimers are produced via standard oligonucleotide chemistry.
- The resulting molecules exhibit a multi-fold increase in serum half-life and bioactivity in vivo.
- Bioactivity of the multimers is enhanced compared to monomers.
- The potency of a ligand-oligonucleotide therapeutic agent can be greatly enhanced by preparing the oligonucleotide in multimeric form.
- This has the potential to enable oligonucleotide therapeutics to be effective against hitherto intractable targets involving low receptor copy numbers and internalization rates, and/or diseases requiring multiple knockdowns or IV delivery.