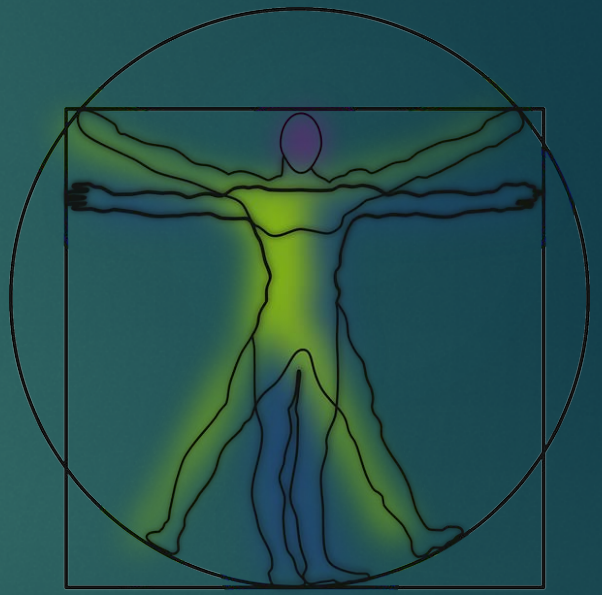
INCRESCENT®

MULTIMERIC OLIGONUCLEOTIDES FOR ENHANCED POTENCY AND PRECISION

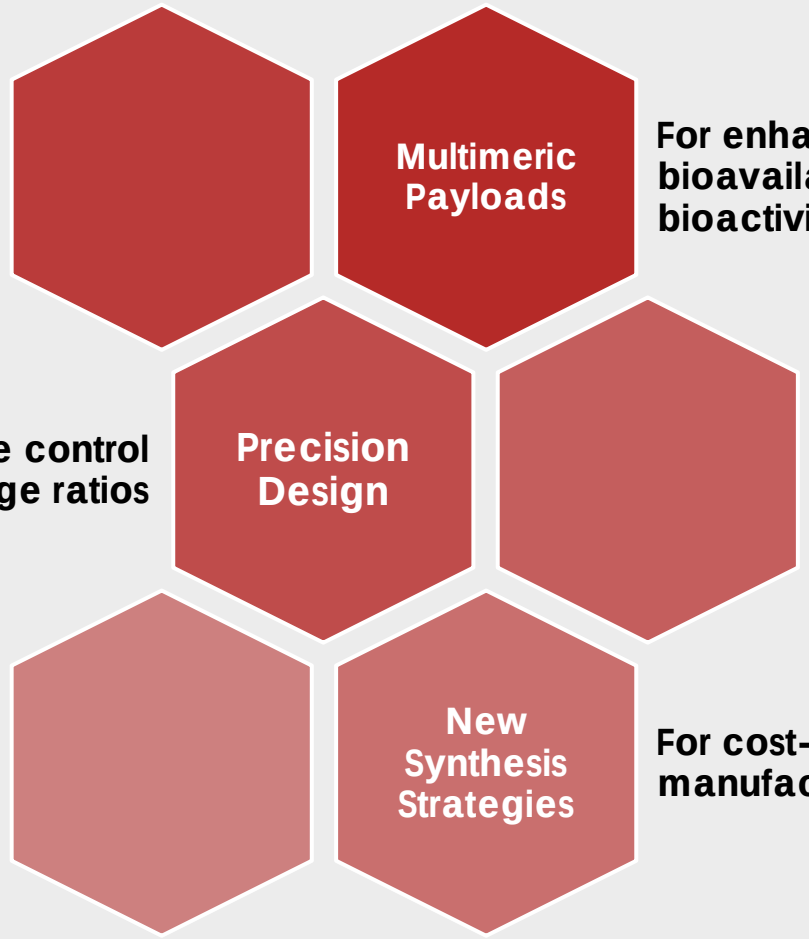
MPEGLA® The Standard for Standards®

Increscent® Breaks Through Prior Limitations

- The field of oligonucleotide therapeutics has been slow to progress beyond genetic targets in the liver because the necessary tools did not exist
- Now, with the Increscent® platform, drug developers can reach previously inaccessible cells and tissues with targeted oligonucleotide conjugates
- Increscent® multimeric conjugates
  - Remain in circulation far longer than traditional conjugates
  - Deliver significantly more active agent to target cells per binding event
  - Can be fine-tuned to delivery precise quantities of multiple agents in a single molecule



The Increscent® Advantage



Multimeric Payloads

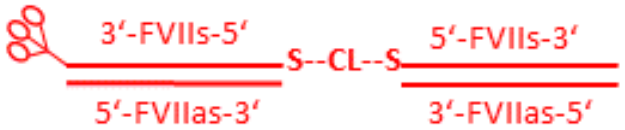
Featuring multiple therapeutic agents joined together by covalent linkers and conjugated to a cell targeting ligand

- Oligonucleotide agents may be
  - Single-stranded, double-stranded, or combinations
  - siRNA, ASO, miRNA, etc.
- Compatible with a variety of
  - Chemical modifications
  - Linkers
  - Cell-targeting ligands

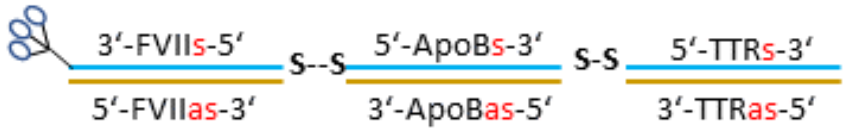
Multimeric Payloads

Examples Using siRNA

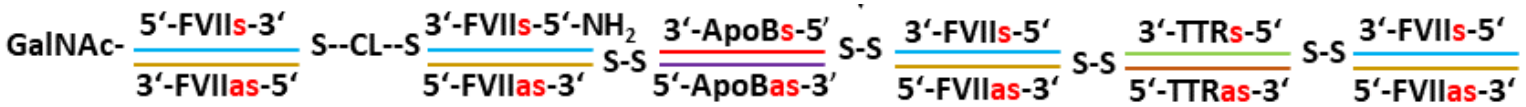
- **Homodimer**



- **Heterotrimer**



- **Heterohexamer**



Legend

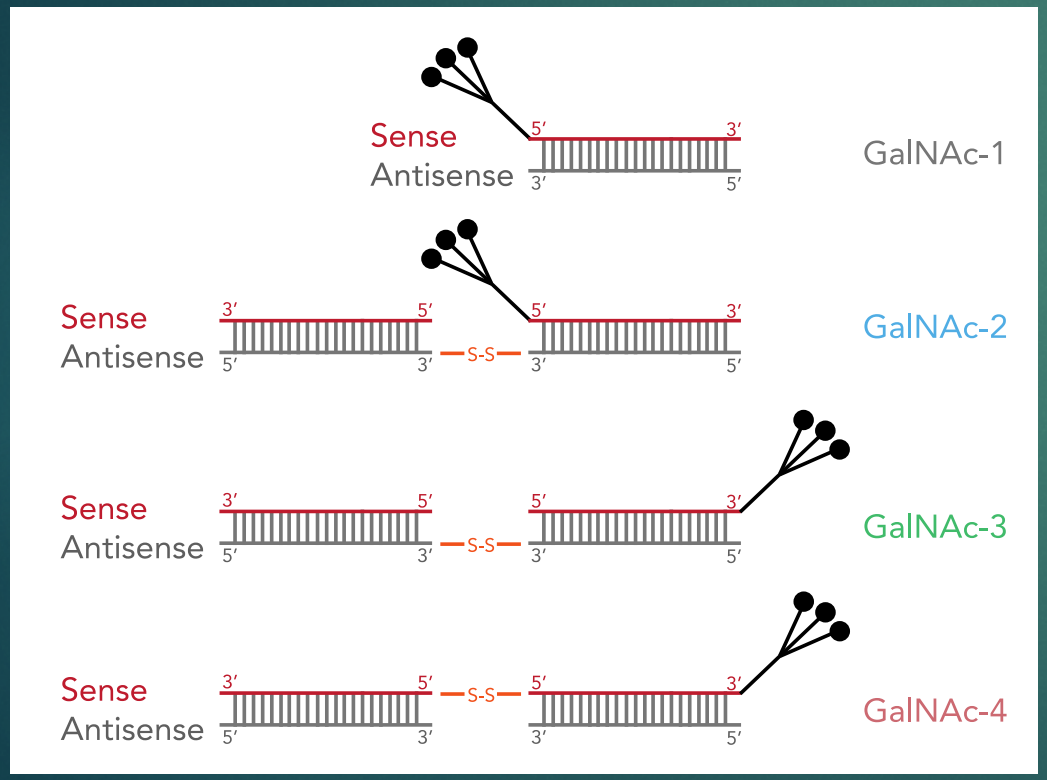
S-CL-S Cleavable linker ("CL" represents a cleavable moiety)

S-S Cleavable disulfide linker

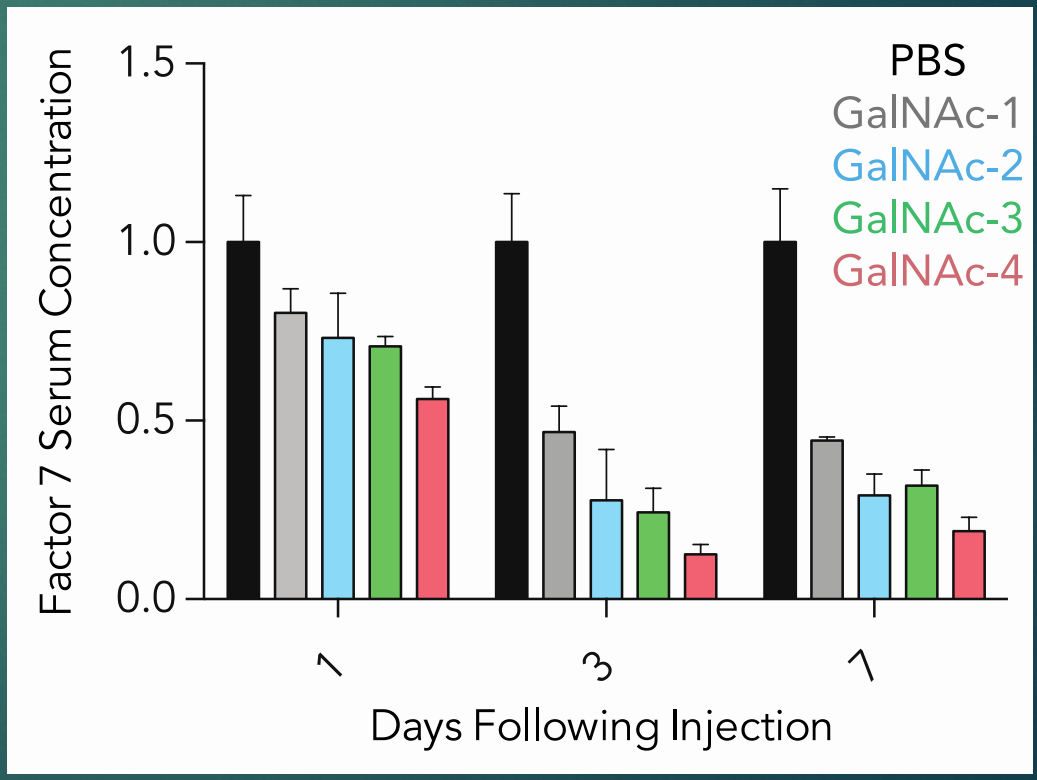
Triantennary GalNAc ligand

Homodimers of siFVII Deliver Twice the Activity per Unit of Ligand

GalNAc-Homodimer Conjugates and Monomer Control



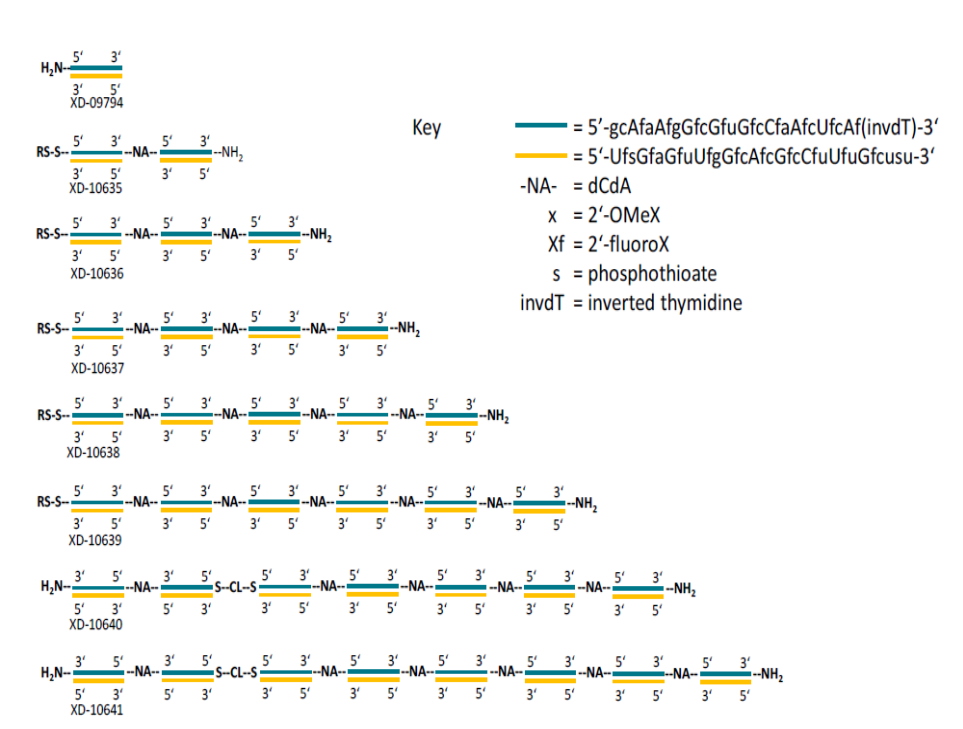
Doubling the payload per GalNAc ligand improves *in vivo* gene silencing



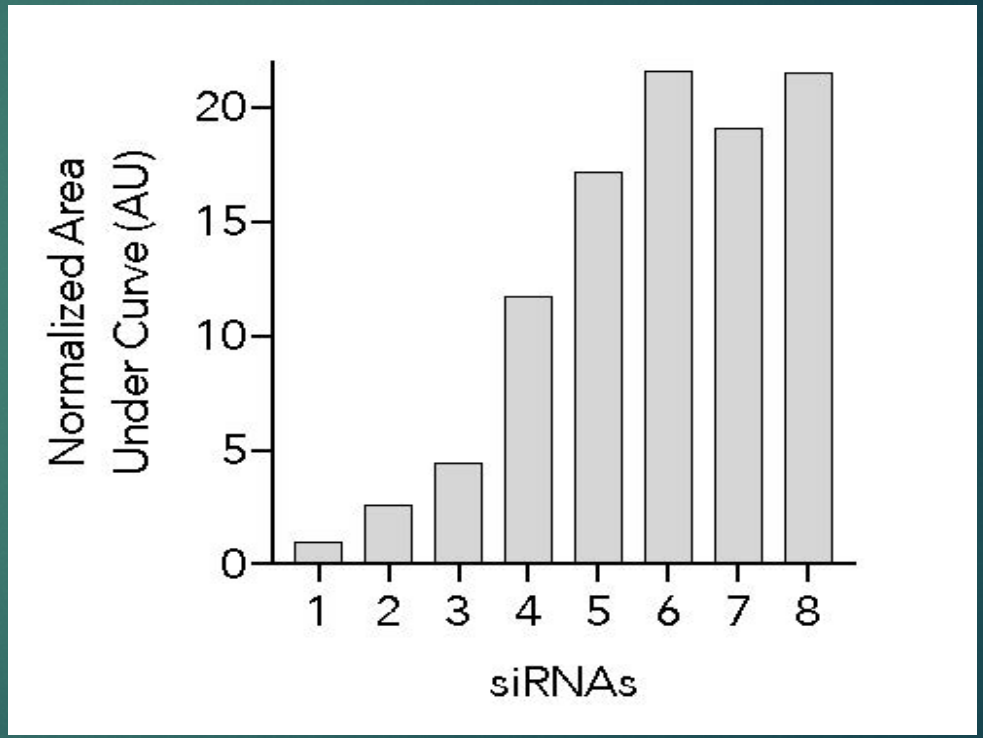
- Activity normalized to GalNAc

Multimeric Payloads Improve Bioavailability

Synthesis of a series of multimers (1-mer to 8-mer without targeting ligands)



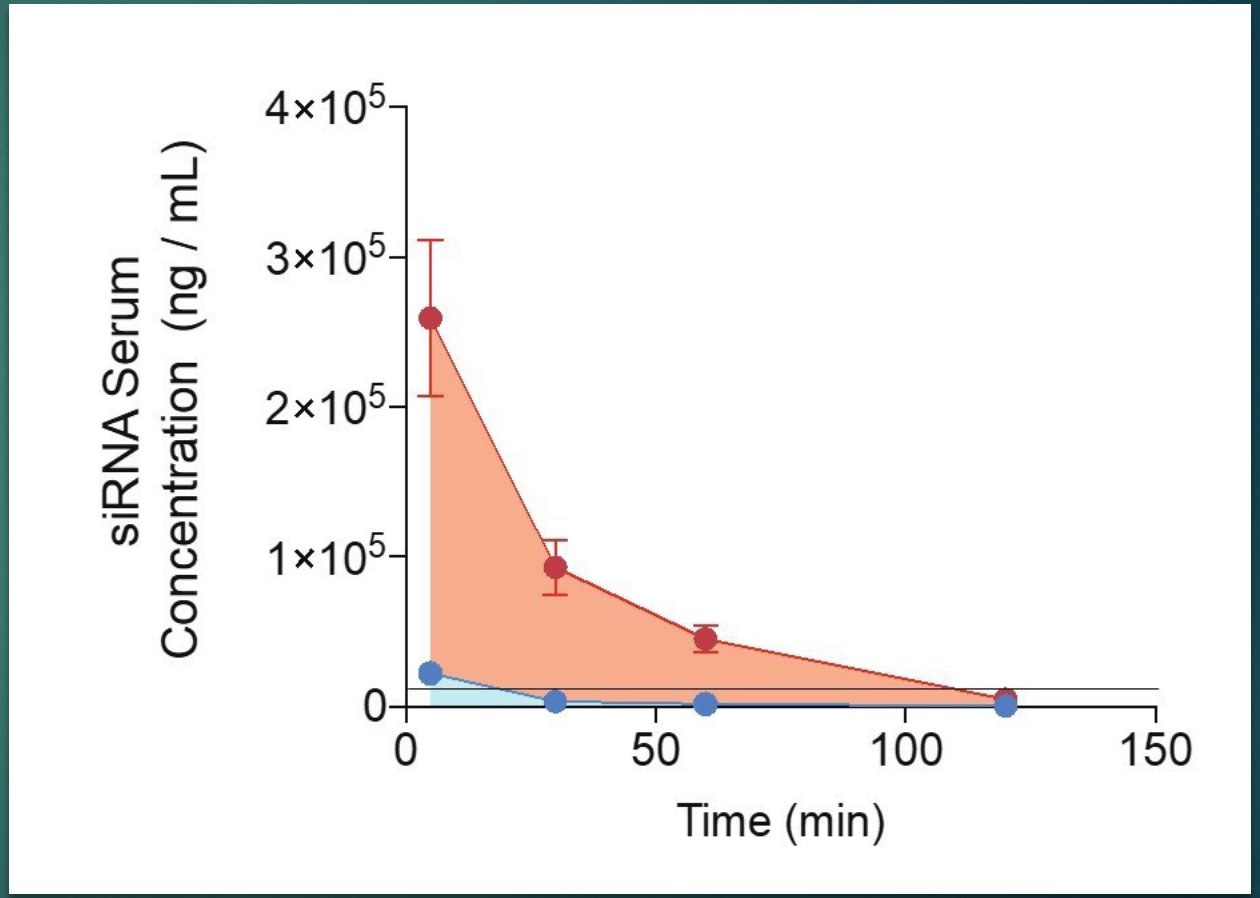
Serum half-life measured after IV bolus administration to mice at 20 mg/kg. Samples taken at 5, 30, 60, 12, 360 minutes and at day 7



Steady increase from 1-3. Exponential increase from 4-5. Maximum obtained 6-8.

Hexamer Exhibits Significantly Longer *In Vivo* Serum Half-Life Over Monomer with No Observed Toxic Effects

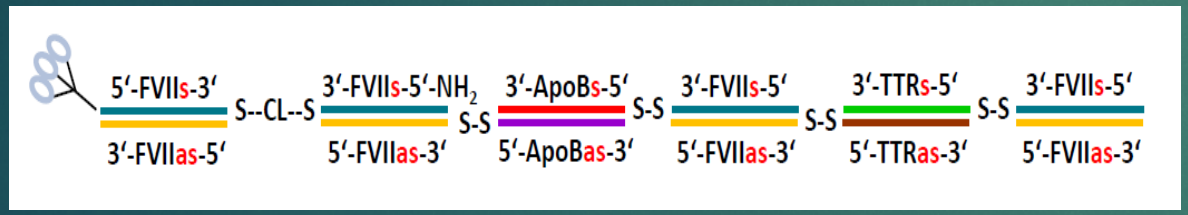
Hexamer ● and Monomer ● administered via IV bolus to mice at 20 mg/kg. Blood samples taken at 5, 30, 60 and 120 minutes



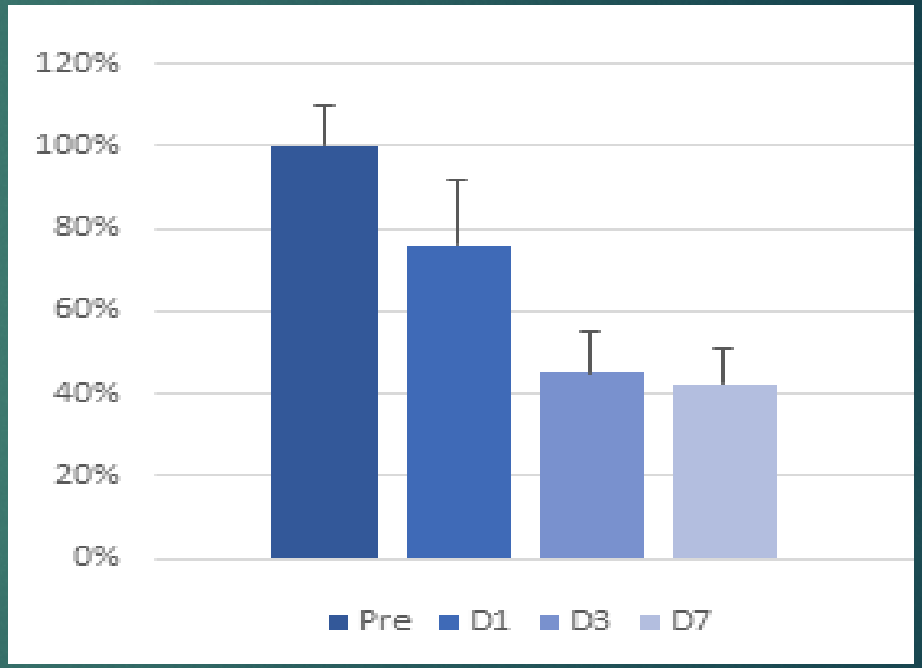
Multimeric Payloads Improve Bioactivity

We constructed a GalNac-conjugated heterohexamer having 4 units of siFVII, 1 unit of siApoB and 1 unit of siTTR.

The compound was administered to mice via IV bolus at 6 mg/kg – effectively 4 mg/kg siFVII and 1 mg/kg each of siApoB and siTTR.



TTR protein levels at days 1, 3 and 7 demonstrate effective knockdown at just 1 mg/kg effective dose:



- Performance of 1 mg/kg of siTTR delivered via IV in our GalNac-heterohexamer more than equals the performance of 1 mg/kg GalNAc-siTTR monomer delivered subcutaneously, as published in J. K. Nair, et al., J. Am. Chem. Soc., 2014, 136 (40), pp 16958-16961 (FIG 5b).

Multimeric Payloads Enable Precise Control Over Stoichiometric Ratios

- Tomorrow's oligonucleotide therapeutics will address complex diseases requiring the delivery of multiple agents for a multiplexed therapeutic effect
- For agents of varying potency requiring dosage in a precise ratio, conjugating the various agents into a single molecule locks in a stoichiometric ratio for precise drug delivery

Tetramer Examples

Oligo1•Oligo1•Oligo1•Oligo2

Oligo1•Oligo2•Oligo3•Oligo1

Oligo1•Oligo2•Oligo3•Oligo4

New Synthesis Strategies

- Multimeric oligonucleotides may be synthesized on solid support
- Solid phase synthesis, however, is
  - Inefficient for the manufacture of long multimeric oligos in large quantities
  - Incompatible with certain linkers
  - Costly
- The Increscent® synthesis strategy solves these problems and can be used alone or in conjunction with solid phase synthesis

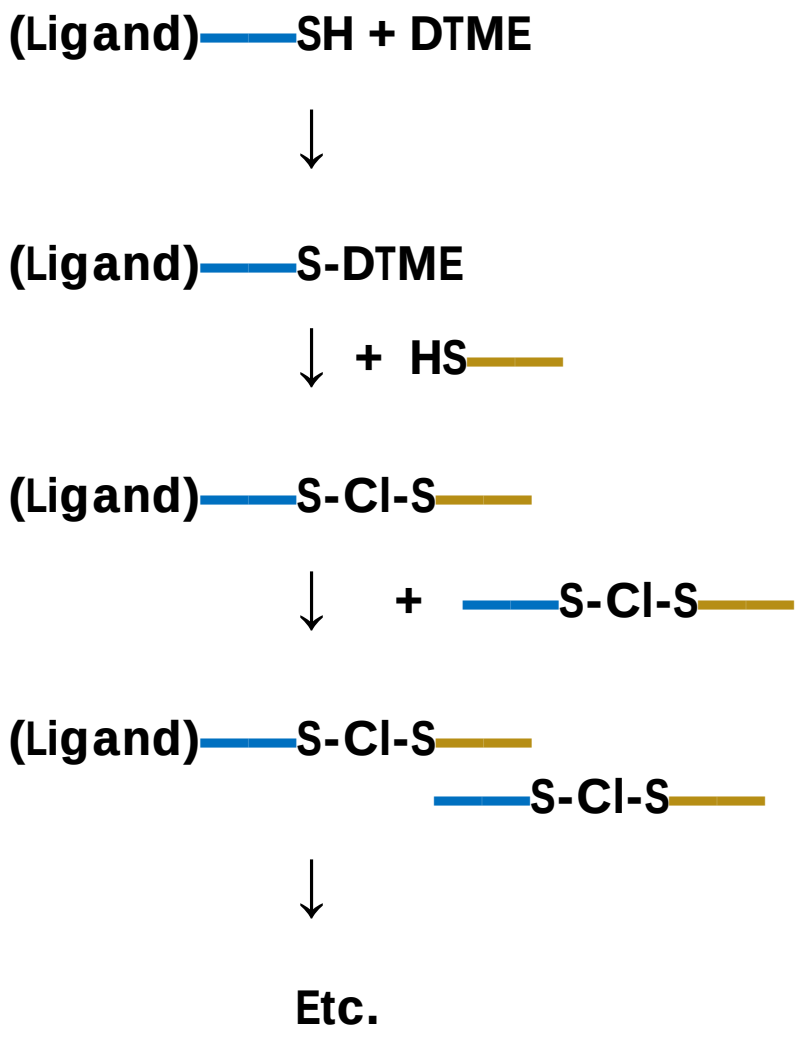
Fundamentals of the Increscent® Synthesis Strategy

This Example uses the divalent linker “DTME”, which contains within it a cleavable disulfide moiety represented as “-Cl-”

All steps are carried out in aqueous solution, at room temperature and neutral pH.

All steps achieve high yields and high purity

Other proprietary synthesis strategies are available for specific needs in the manufacture of large multimers and/or the conjugation of constituents other than GalNAc



Step 1: Mono-substitution of a functionalized single-stranded oligo with DTME. The oligo may be conjugated to a ligand (as shown); or the ligand, if desired, may be added later, at any desired location.

Yield: Mono-substituted oligo

Step 2: Add a second, functionalized oligo

Yield: Single-stranded heterodimer with a cleavable linker

Step 3: Perform annealing with another heterodimer in equimolar proportions

Yield: Intermediate construct in near quantitative yield

From here, complementary oligos — and — may be annealed to form a double-stranded trimer; or a longer multimer may be synthesized by continuing to anneal single-stranded dimers until the desired length is reached

Summary of Increscent® Attributes

Multimeric Payloads

- Deliver multiple therapeutic agents per ligand/receptor binding event
- Increase bioavailability by slowing clearance
- Together, the larger payload and increased bioavailability can result in increased bioactivity
- While we used GalNAc/ASGPr as our test system, we expect the real value of the Increscent® platform to lie in enabling ligand/receptor systems that are not as efficient as GalNAc/ASGPr

Precision Design

- The field is poised to move beyond liver-targeted monogenic therapies
- Some diseases will require multiple therapeutic agents in potentially different stoichiometric ratios
- By using the Increscent® platform, therapeutic agents can be linked together to ensure that a target cell will receive a desired ratio of individual agents

New Synthesis Strategies

- May be used alone or in conjunction with solid phase synthesis
- Compatible with a variety of therapeutic agents, chemical modifications, and linkers
- Involve simple steps carried out in aqueous solution, at room temperature and neutral pH with high yields and high purity

Increscent® Intellectual Property

- Patents pending and granted worldwide on compositions of matter, methods of synthesis, and various uses of multimeric oligonucleotides and other therapeutic agents for conjugate delivery, decreased clearance, and enhanced bioactivity
- Proprietary knowhow covering design and chemical synthesis

Contact for Licensing Opportunities

INCRESCENT®

Kristin Neuman
Executive Director
Biotechnology Licensing
MPEG LA
kneuman@mpegla.com
+1.914.588.2471