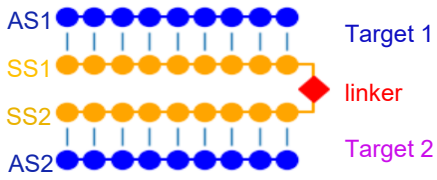
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# Integrated Discovery of Dual-targeting siRNAs

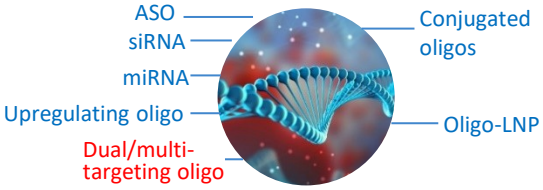
## *Dual-targeting Oligo*




**Dual-targeting Oligo:**

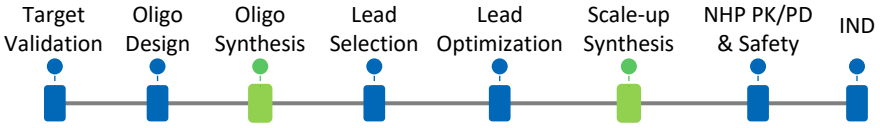
- ✓ **Identical PK & Co-delivery:** Enables synchronized delivery and uptake of both siRNAs into the same target cell.
- ✓ **Simplified Development Path:** May streamline development as a single drug candidate compared with combination therapy.
- ✓ **Synergy in Polygenic Diseases:** Effectively treats complex diseases (e.g., CNS, cardiometabolic) by simultaneously silencing two distinct disease-causing transcripts.

## Oligo Discovery Platform Highlights




| | |
|---|---|
| **300+** Clients | **250+** Targets |
| **1000+** Projects | **60+** IND Projects |

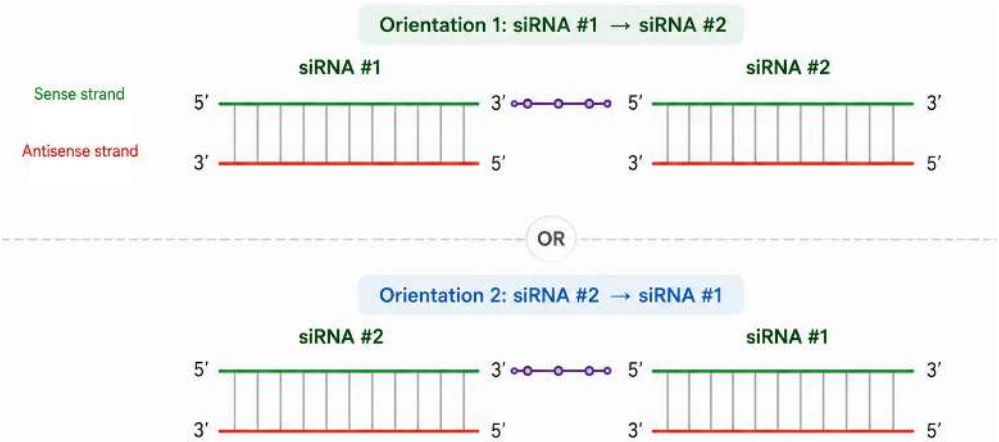
## One-stop Service with Flexible Entry Points




| | |
|---|---|
| Target Validation | Chemical Modification Exploration |
| Sequence Design | Off-target, *In Vitro* Tox, Stability |
| *In Vitro* Screening on mRNA | Delivery Tool Discovery & Optimization |
| *In Vitro* Functional Assays | *In Vivo* PK/PD/Disease Models in Rodents & NHPs |

## *Different Dual-targeting siRNA Designs*

| Therapy | Target | Mechanism | Key Effects |
|---|---|---|---|
| **siRNA #1 (Oligo1)** | **Target 1** | siRNA → ⬇ Target1 mRNA → ⬆ lipoprotein lipase (LPL) activity | ⬇ LDL-C, ⬇ TG, ⬇ ApoB |
| **siRNA #2 (Oligo2)** | **Target 2** | siRNA → ⬇ Target2 mRNA → ⬆ LDL receptors | ⬇ LDL-C |




**Linkers**

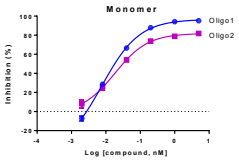
- PEG
- Alkyl
- Nucleotide
- GalNAc
- Disulfide

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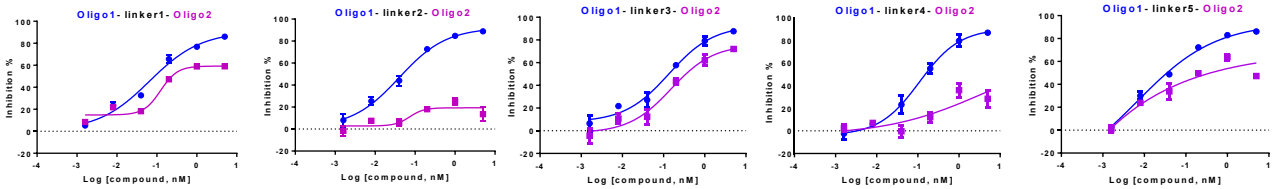
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# In Vitro and In Vivo Evaluation of Different Dual-targeting siRNAs

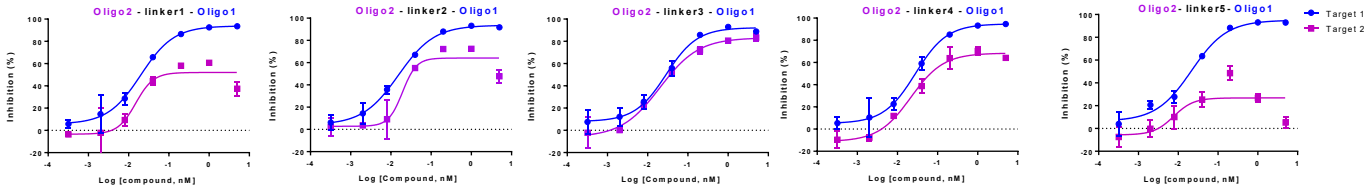
## In Vitro Evaluation




**Orientation 1: 5' Oligo1 sense 3' – linker – 5' Oligo2 sense 3' – GalNAc (LC96)**

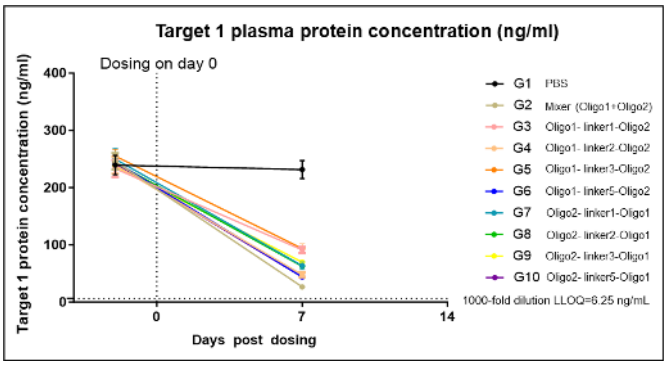


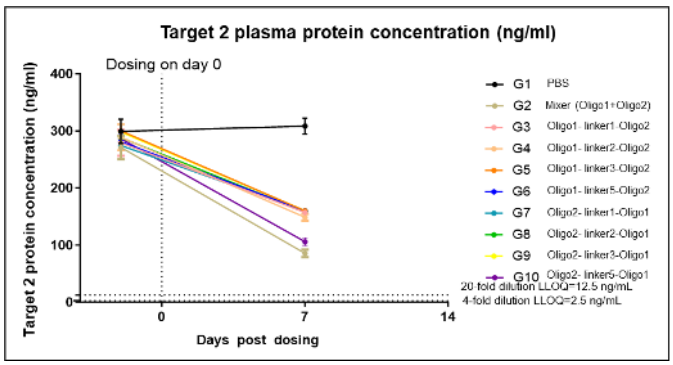

**Orientation 2: 5' Oligo2 sense 3' – linker – 5' Oligo1 sense 3' – GalNAc (LC96)**




✓ ***Target 2 KD was affected by linker type and Oligo orientation, whereas Target 1 was less affected***

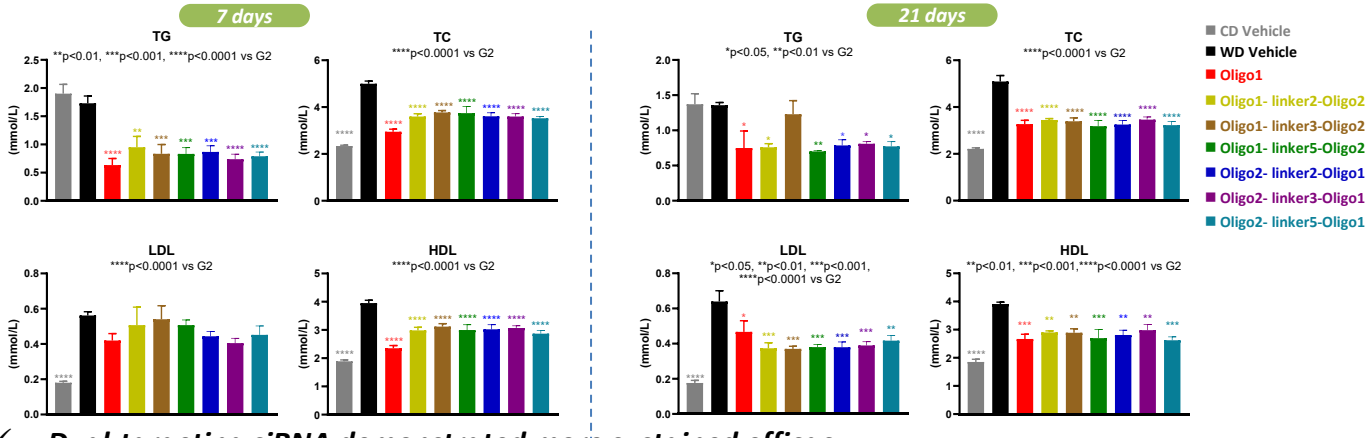
## Pharmacodynamic Evaluation




✓ ***The dual-targeting siRNA showed comparable pharmacodynamics (PD) to the mono siRNA mix.***

## Evaluation of therapeutic efficacy in the WD model




✓ ***Dual-targeting siRNA demonstrated more sustained efficacy.***


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