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PH responsive endosomal release agents to enhance RNAi conjugate activity across multiple cell types and receptors

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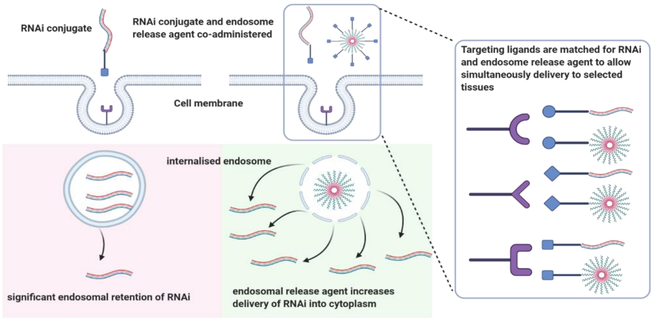
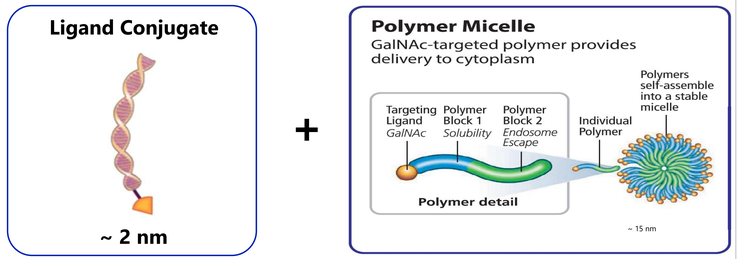
INTRODUCTION



- Despite approval of Givlaari® (givosiran) in 2019 and several late stage GalNAc conjugate programs in development, potency remains low and directing RNAi conjugates beyond hepatocytes problematic.
- The principal reason is lack of endosomal escape, as ligand conjugates are degraded before reaching the cytoplasm. This restricts potency of GalNAc systems and, for other ligand conjugates, eliminates it entirely.
- Genevant has developed a subcutaneously administered, ligand targeted, pH-responsive endosomal release agent to address this.

Genevant's RNAi 2.0 Platform

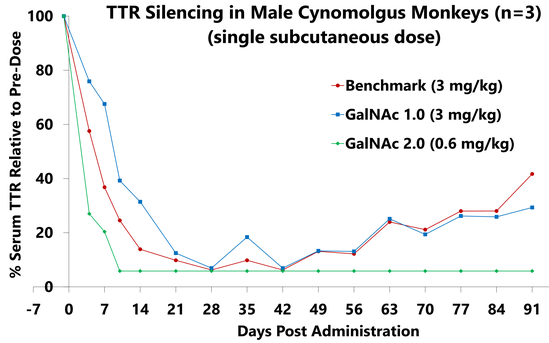
- RNAi 2.0 is a two-component system
- Ligand-siRNA conjugate and ligand-targeted endosomolytic polymer
- Both administered subcutaneously



RESULTS

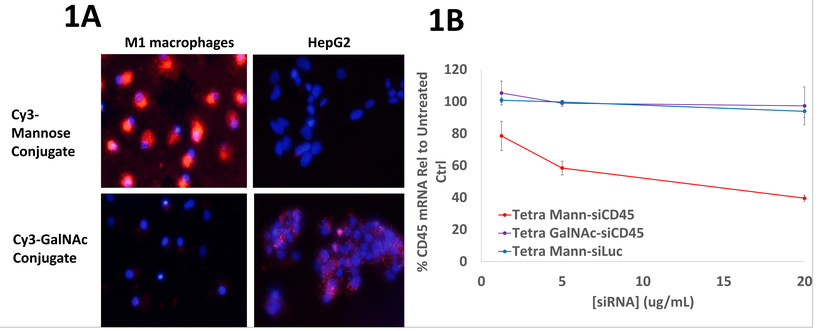
RNAi 2.0 Dramatically Enhanced Potency in NHP

- When applied to a GalNAc system in NHP, RNAi 2.0 demonstrated more rapid onset of RNAi, enhanced potency, and longer duration of effect than standard ligand conjugates, despite being administered at 1/5 the dose.
- Controls: 'Benchmark' and 'GalNAc 1.0' reflect third-party and Genevant GalNAc platforms, respectively.



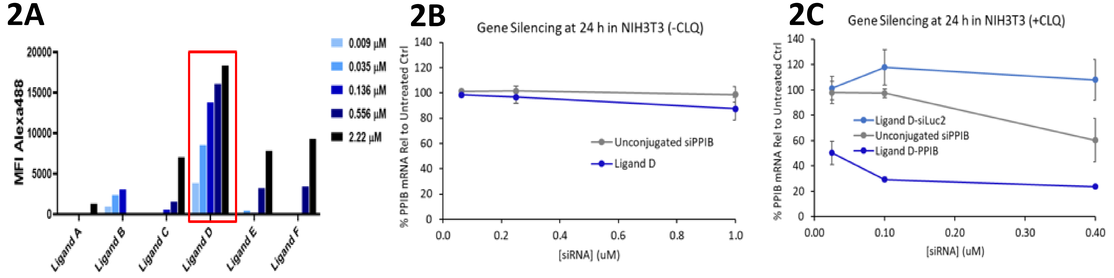
Mannose targeted Conjugates for Macrophages

- Mannose receptor (CD206) is present on surface of macrophages and immature dendritic cells
- Mannose, but not GalNAc ligands, were taken up by macrophages (1A)
- Mannose targeted ligand conjugates knockdown macrophage gene target CD45 in the presence of an endosomal release agent. GalNAc targeted controls exhibited no knockdown.



Hepatic Stellate Cell Conjugates Also Require Endosomal Release

- Hepatic stellate cells (HSC) are strongly implicated in fibrosis.
- Lead Ligand D showed good HSC binding and internalization in FACS-based assay with LX-2, Human HSC line (2A)
- Ligand D-targeted RNAi conjugates demonstrated KD, but only in presence of endosomal release agent (2B/C)



CONCLUSIONS

- Endosomal escape is a limiting step for ligand conjugates
- A subcutaneously administered endosomolytic polymer dramatically boosted activity of a GalNAc conjugate in NHP
- Activity of RNAi conjugates based on other ligand-receptor pairs eliminated in absence of endosomal escape.
- We are directing our endosomolytic polymer to these ligands to support delivery beyond hepatocytes

CONTACT INFORMATION

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