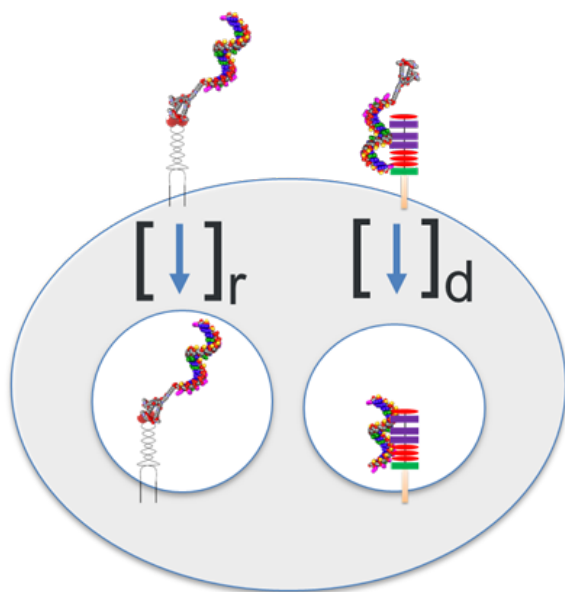


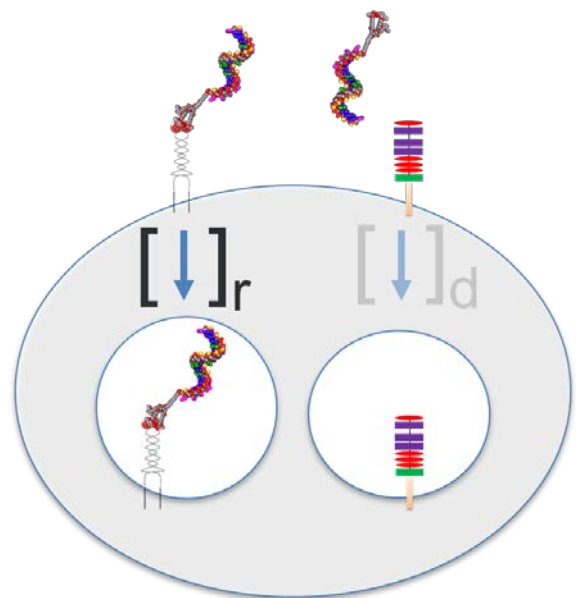
# Supplementary Information

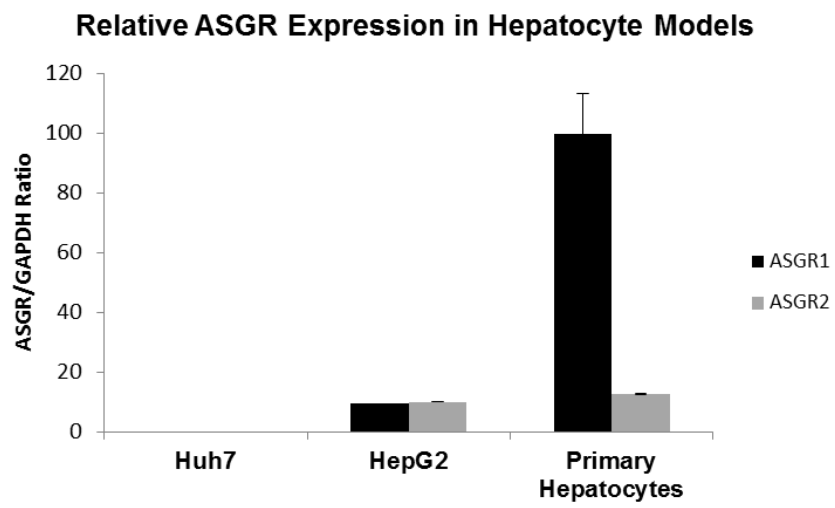
S1

### Phosphorothioate ASO

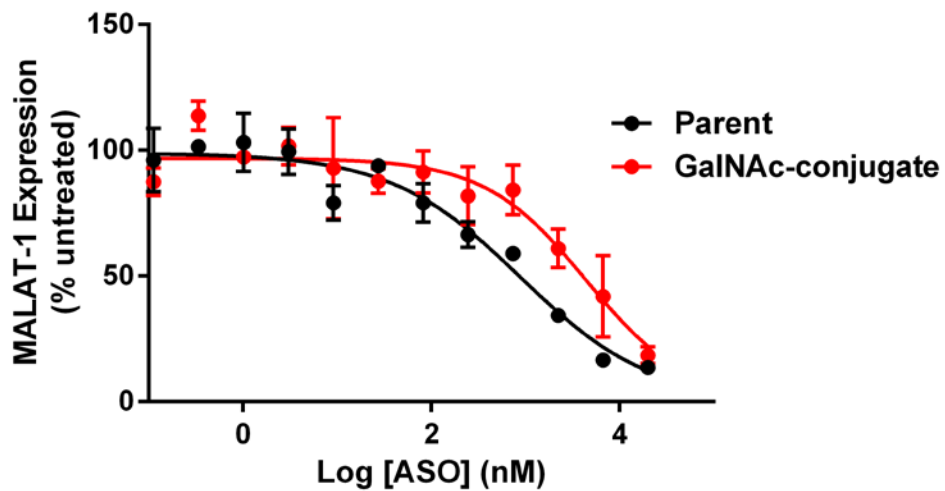


### Phosphodiester ASO



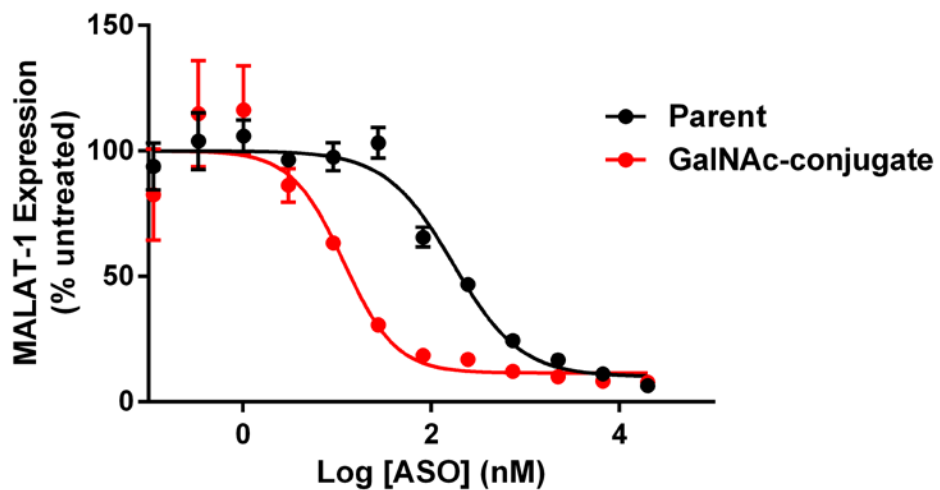


## WT HEK 293



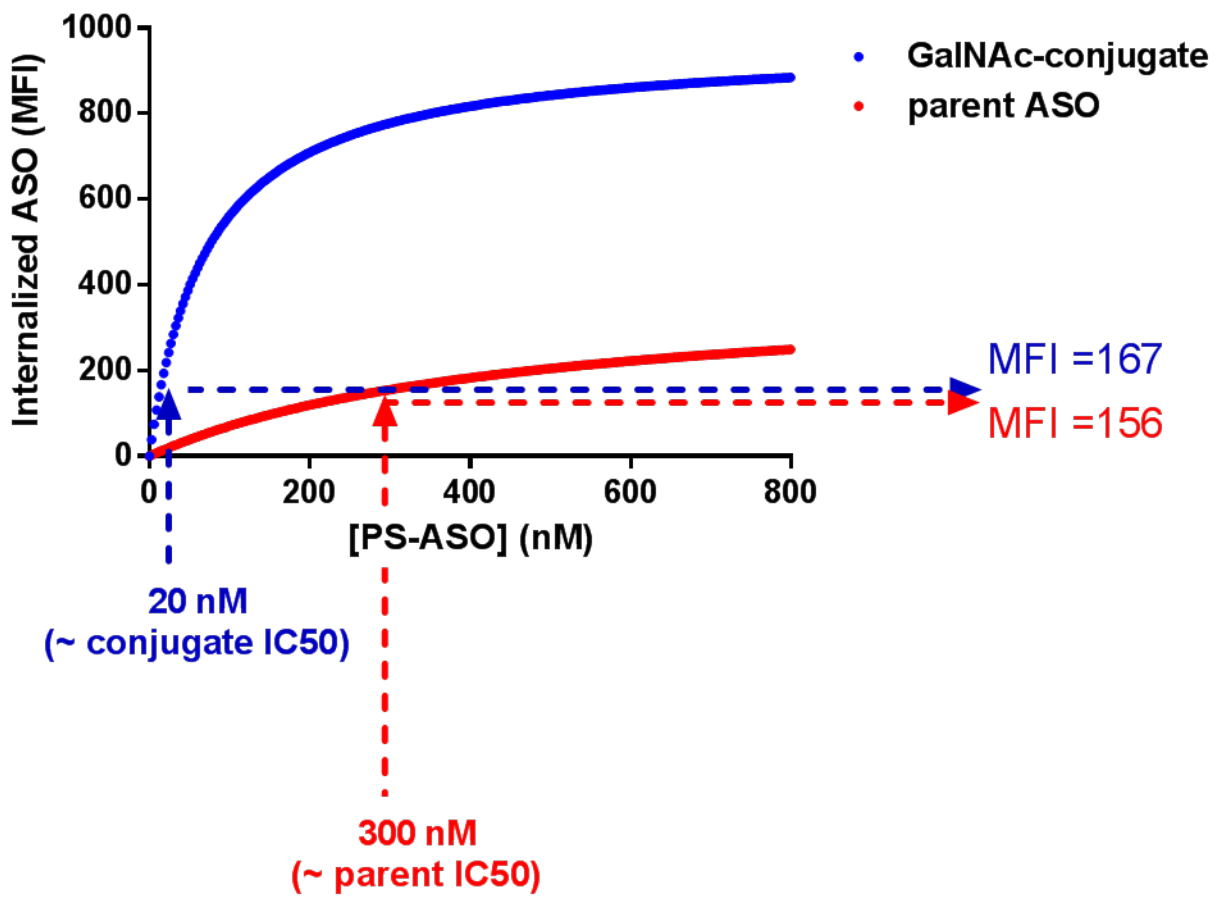
ASO	5-10-5 MOE Parent	5-10-5 MOE GalNAc
IC50 (nM)	845	3865

## ASGR1 HEK 293



ASO	5-10-5 MOE Parent	5-10-5 MOE GalNAc
IC50 (nM)	243	17

### ASGR1-HEK (Clone 1A4)



**Table S1. Analytical data for ASOs**

<b>ASO No.</b>	<b>Chemistry</b>	<b>Calculated Mass</b>	<b>Observed Mass</b>	<b>%UV Purity</b>
395251	MOE, DNA, PS	7249.3	7248.1	94
890273	MOE, DNA, PS, 3'-GalNAc	8767.9	8766.8	97
730436	MOE, DNA, PS, 5'-Cy3	7772.9	7770.5	77
836716	MOE, DNA, PS, 5'-Cy3, 3'-GalNAc	9291.5	9291.7	94
834490	MOE, PO, 5'-Cy3	8208.5	8208.5	82
841226	MOE, PO, 5'-Cy3, 3'-GalNAc	9727.1	9727.6	97
890266	MOE, DNA, 6PO, 13PS	7152.9	7151.0	87
890267	MOE, DNA, 6PO, 13PS, 3'-GalNAc	8671.5	8672.2	92
890268	MOE, DNA, 6PO, 13PS, 5'-Cy3	7676.5	7675.2	88
890269	MOE, DNA, 6PO, 13PS, 5'-Cy3, 3'-GalNAc	9195.1	9194.5	95
758054	cEt BNA, DNA, PS	5430.6	5429.4	91
404071	MOE, DNA, PS	7234.3	7233.1	99
757741	cEt BNA, DNA, PS	5420.6	5419.2	93

## Supplementary Figure Legends

**S1** Illustration of the relative contributions of phosphorothioate-, phosphodiester- and receptor-mediated uptake of parent ASOs and their respective conjugates.

Phosphorothioate-ligand conjugates internalize via “default” PS pathway (brackets noted as “d”) and a receptor-mediated pathway (brackets noted as “r”), whereas phosphodiester-ligand conjugates are internalized almost exclusively by the receptor pathway.

**S2** Relative mRNA levels of ASGR1 and ASGR2 in Huh7, HepG2 and, primary murine hepatocytes. RNA purified from the indicated cells was subjected qRT-PCR for the ASGR1, ASGR2, and GAPDH. Expression was normalized to GAPDH mRNA and expressed as percent primary murine hepatocyte expression.

**S3** ASGR1 expressing HEK 293 show increased sensitivity to unconjugated phosphorothioate ASOs. Parental and ASGR1-expressing HEK 293 cells were treated with the indicated ASO for potency determination as described in “Material and Methods”

**S4** Interpolated values for cy3-ASO (730436, 836716 from Table S1) uptake at all concentrations of applied cy3-ASO were calculated in order to compare cy3-ASO uptake of the parent and GalNAc-conjugated ASOs at the IC<sub>50</sub>'s of their respective unlabeled gapmers (395251, 890273 from Table S1), as indicated in the figure.

**Table S1** Analytical data for ASOs used in this manuscript