RECENT DEVELOPMENTS IN ANTISENSE OLIGOS (ASO) & SMALL INTERFERING RNAs (siRNA)

Kristine Dorward in Pullan's Pieces #218 September 2025

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The global market for RNAi and antisense oligonucleotide (ASO) drugs is projected to grow at a CAGR of ~ 19% from 2024 to 2033, expanding from ~$5.2B to ~ $30B

Focusing solely on ASO and siRNA market segments implies a forward growth rate of 27% annually, out to 2033

Steady growth trajectory will be driven by substantial expansion into common chronic diseases including oncology, cardiovascular and metabolic disorders, moving beyond rare disease applications at present

Significant advances in delivery technology, including GalNAc conjugation and LNPs has improved tissue specificity and reduced off-target challenges

Integration of artificial intelligence and machine learning in oligonucleotide design has accelerated lead optimization phase and improved predictability of in vivo performance

Novel and enhanced development of long-acting chemistries enables less frequent dosing and enhances patient adherence

Relative Strengths & Contrasting Features of ASO vs. siRNA

ASOs are advantageous and preferred when nuclear targets are pursued, such as with CNS and neuromuscular tissues where nuclear-targeted splice modulation is key

siRNA typically outperforms ASO in liver-centric diseases where robust liver delivery, durability and extended target knockdown drive clinical impact

siRNA treatment preference has emerged for rare genetic, metabolic and cardiovascular lipid-lowering, where durable knockdown and safety influence adoption choice

ASOs provide multi-modal mechanisms through their ability to both recruit RNase H to degrade target mRNA and sterically block splice sites or translation, whereas siRNAs rely solely on RISC-mediated cleavage

Nuclear and cytoplasmic activity: ASOs readily access nuclear pre-mRNA to correct splicing and also act in the cytoplasm, while siRNAs are largely confined to cytosolic RISC complexes

ASOs provide expanded target scope: Beyond mRNA knockdown, ASOs can target non-coding RNAs, intronic sequences, and splice junctions—broadening the range of disease-relevant transcripts addressable

Dosing, Delivery & Safety Profiles Continue to Improve

siRNA-based therapies generally offer less frequent dosing (quarterly or biannually) compared to ASOs, providing therapeutic target suppression for 2–3 months after a single administration, improving adherence and convenience

GalNAc-conjugation for siRNA has demonstrated >10-fold higher hepatocyte uptake than various ASO chemistries, translating into greater, more durable target knockdown in liver tissues

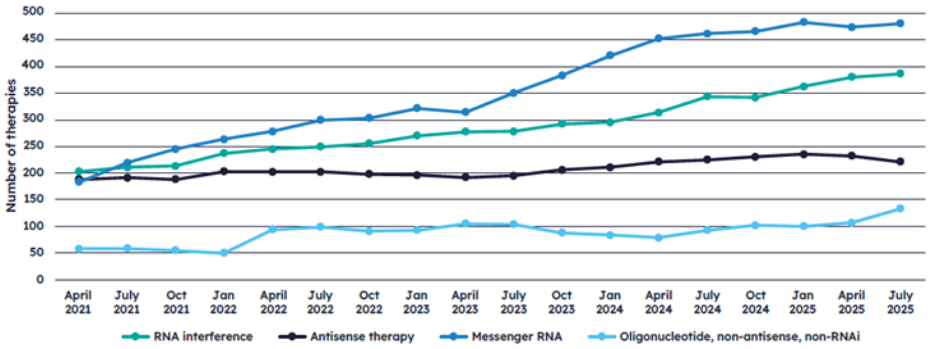
By avoiding RNase H–mediated cleavage and leveraging the RISC machinery, siRNA therapies have shown reduced off-target effects, less thrombocytopenia, and lower injection-site reactions relative to comparable ASO regimens

On the other hand, ASOs may entail simplified delivery: Chemically modified ASOs (e.g., 2'-O-alkyl, phosphorothioate backbones) achieve enhanced stability and tissue uptake without the lipid nanoparticles or carriers typically required for siRNA

RNA Therapy Pipeline Growth Patterns since 2021

Messenger RNA (mRNA) and (RNAi have shown steady growth since Q2, 2021 while Antisense therapies have been consistent and flat

Substantial interest in mRNA technology during and after the pandemic has driven adoption in this specific sub-segment



Gene, Cell & RNA Therapy Landscape Report

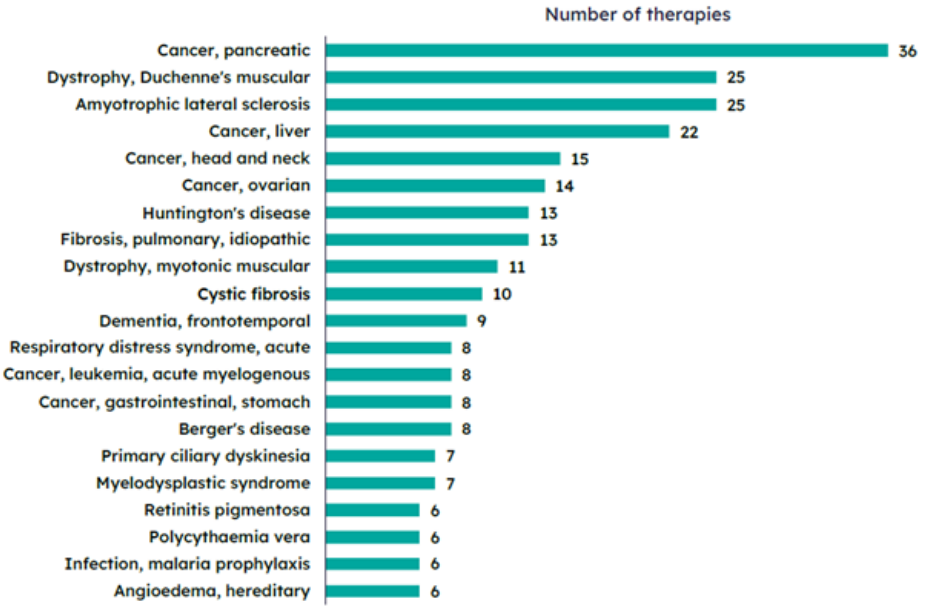
Q2 2025 Quarterly Report; Pharmaprojects; Citeline, July 2025

Most Common Rare Diseases Targeted with RNA Therapies

The RNA rare disease pipeline includes preclinical through to pre-registration therapeutic candidates

The most extensively pursued oncology indications were pancreatic, liver, and head and neck cancer

Duchenne muscular dystrophy, amyotrophic lateral sclerosis and Huntington’s disease were the most frequently targeted non-oncology rare indications



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Tables below list top targets in pancreatic and liver cancer respectively, tackled with either ASO or siRNA approaches

Pancreatic Cancer Gene Targets	
Targets Pursued Exclusively By Respective Modalities	
ASO	**siRNA**
HSP27	HIF1A
CLU (Clusterin)	VEGFA
TGFB2	EGFR
IGF1R	STAT3
EEF2	MCL1
	PLK1
	HDAC1/2
	COX2
	BIRC5 (Survivin)

Liver Cancer Gene Targets	
Targets Pursued Exclusively By Respective Modalities	
ASO	**siRNA**
CTNNB1 (β-catenin)	VEGFA
GPC3 (Glypican-3)	HIF1A
TERT	MET
	PDGFRβ
	EGFR;
	CXCL12
	BIRC5 (Survivin)

Tables below list top targets in ALS or DMD respectively, tackled with either ASO or siRNA approaches

ASO-Only Targets in ALS		
Rank	**Gene / Target**	**Clinical Status / Notes**
1	FUS	ASO (Jacifusen/BIIB067): Phase I completed, splice modulation
2	TARDBP (TDP-43)	Preclinical gapmer ASOs knock down pathological transcript
3	NEK1	Preclinical; genetics-driven target reducing neurotoxicity
4	UBQLN2	Preclinical; targets proteostasis pathways
5	OPTN	Preclinical; ASOs against optineurin mRNA in development
6	ANG	Preclinical; ASOs reduce angiogenin-driven pathology
7	TBK1	Preclinical; ASOs modulate neuroinflammation signaling

siRNA-Only Targets in ALS		
Rank	Gene / Target	Development Status / Notes
1	EIF2AK3 (PERK)	Preclinical siRNAs modulate ER-stress in neuron models
2	CHCHD10	Preclinical; siRNAs targeting mitochondrial dysfunction
3	CCND1 (Cyclin D1)	Preclinical; siRNAs improve motor-neuron survival
4	CYBB (NOX2)	Preclinical; siRNAs reduce oxidative-stress damage
5	RIPK1	Preclinical; siRNAs inhibit necroptosis pathways
6	RELA (NF-κB p65)	Preclinical; siRNAs dampen neuroinflammation
7	STMN2	Preclinical; siRNAs promote axonal repair and outgrowth

ASO-Only Targets in Duchenne Muscular Dystrophy		
Rank	Target	Exon(s) Skipped / Notes
1	Dystrophin pre-mRNA Exon 51	Eteplirsen (FDA approved); Drisapersen (discontinued); SRP-5051 (preclinical)
2	Dystrophin pre-mRNA Exon 53	Golodirsen (FDA approved); Viltolarsen (FDA approved)
3	Dystrophin pre-mRNA Exon 45	Casimersen (FDA approved)
4	Dystrophin pre-mRNA Exon 44	Suvodirsen (preclinical; Wave/Ionis program)
5	Dystrophin pre-mRNA Exon 2	WVE-210201 (Wave Life Sciences/Ionis; preclinical)
6	Dystrophin pre-mRNA Exon 8	WVE-210203 (Wave Life Sciences; preclinical)
7	Dystrophin pre-mRNA Exon 60	Preclinical ASO programs in academic and biotech labs

siRNA-Only Targets in Duchenne Muscular Dystrophy		
Rank	Target	Development Status / Rationale
1	Myostatin (MSTN)	siRNA preclinical; knockdown to enhance muscle mass and strength
2	Connective Tissue Growth Factor (CTGF)	siRNA preclinical; reduces fibrotic remodeling in dystrophic muscle
3	Transforming Growth Factor-β1 (TGF-β1)	siRNA preclinical; attenuates inflammation and fibrosis
4	NF-κB p65 (RELA)	siRNA preclinical; downregulates chronic inflammatory signaling
5	Histone Deacetylase 4 (HDAC4)	siRNA preclinical; promotes muscle regeneration and function
6	Osteopontin (SPP1)	siRNA preclinical; limits extracellular matrix deposition and muscle fibrosis
7	NADPH oxidase 4 (NOX4)	siRNA preclinical; mitigates oxidative stress-induced damage in muscle fibers

Licensing & Co-Development Alliances Executed in '25 YTD

Companies Involved	Modality	Target(s)	Upfront / Total Value	Notes
Alloy Tx & Sanofi	ASO	Not Disclosed	$27.5M UF & NT / > $428M Total	Discovery & Preclinical work leveraging AntiClastic Antisense Platform for CNS target
Ionis & Ono	ASO	TMPRSS6; Hepcidin	$280M Upfront / $940M Total	Sapablursen in Phase 2 for Polycythemia Vera; Mid-Teen Royalties
Stoke & Biogen	ASO	SCN1A	$165M Upfront / $550M Total	Zorevunersen, Phase 3-Ready for Rare Genetic Epilepsy; ex-North America Rights Only
Ionis & SOBI	ASO	APOC3 mRNA	Not disclosed	FDA-approved therapy in December 2024; Regional license rights Ex-US, Canada & China
Olix & Eli Lilly	siRNA	MTARC1	Up to $630M Total	GWAS-discovered; MASH & fibrosis; GalNAc-conjugated asymmetric siRNA; Phase 1
Sirius Tx & CRISPR Tx	siRNA	Multiple Targets	$25M Cash; $70M Equity Upfront	Thrombotic Diseases; 50/50 Cost and Profit Share Agreement On Lead Asset SRSD107
Arrowhead & Novartis	siRNA	Alpha-Synuclein	$200M Upfront / $2.2B Total	Validated TRIM technology; Pre-clinical asset for synucleinopathies
Sovargen & Angelini	ASO	mTOR	Upfront not disclosed / $550M Total	Option-to-License; Preclinical asset with potential in Neuro & Psych conditions

- The Stoke-Biogen and Ionis-SOBI are geographic-specific, regional deals, not including US rights
- The Sovargen-Angelini agreement is an option & license deal for SVG-1050
- There is a general divergence in modality-disease application with siRNA gaining momentum in cardiometabolic and hepatic

programs, while ASOs retain strategic advantages in CNS and splicing applications

- However recent deal exceptions include the Arrowhead-Novartis siRNA alliance which focuses on Alpha-Synuclein and synucleinopathies

There is a broad range in both upfront and total deal values, yet the long-term, potential ‘bio-bucks’ deal values for transactions in 2025 reflects a space with increasing momentum and investment interest from strategic partners and big pharma