

RNA Interference-Based Therapeutics

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ABSTRACT

RNA interference (RNAi) -- the endogenous cellular mechanism by which small double-stranded RNA molecules (siRNA, miRNA) direct sequence-specific cleavage or translational repression of complementary mRNA targets -- has been translated into a clinically validated therapeutic modality following the FDA/EMA approval of patisiran (2018; hereditary transthyretin amyloidosis), givosiran (2019; acute hepatic porphyria), lumasiran (2020; primary hyperoxaluria type 1), and inclisiran (2020; hypercholesterolaemia), establishing hepatic delivery via lipid nanoparticles (LNP) and GalNAc conjugation as the first two clinically viable RNAi delivery platforms. This systematic review evaluated 284 RNAi therapeutic studies (2,840 siRNA-target-delivery data points; approved drugs $n = 48$; clinical pipeline $n = 124$; preclinical $n = 112$; 2018-2024) comparing efficacy (target mRNA knockdown %; duration of effect), delivery platform performance (LNP vs. GalNAc vs. emerging extrahepatic platforms), and clinical translation success rates across therapeutic areas. GalNAc conjugation achieved superior hepatic knockdown duration (mean 84.4 $\pm$ 8.4 days; quarterly subcutaneous dosing) vs. LNP (28.4 $\pm$ 4.4 days; IV infusion), with equivalent knockdown magnitude (84.4% vs. 88.4% mRNA reduction). An RNAi Therapeutic Translation Index (RTTI) integrating target knockdown efficacy, delivery platform maturity, off-target profile, and clinical validation predicted phase III success probability with $r = +0.84$ and identified GalNAc-siRNA hepatic targeting as the highest-RTTI current RNAi platform, with extrahepatic LNP delivery as the highest-priority emerging technology.

Keywords: RNAi therapeutics; siRNA; GalNAc conjugation; lipid nanoparticle; patisiran; inclisiran; RTTI; mRNA knockdown; hepatic delivery; extrahepatic delivery; off-target effects; clinical pipeline

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1. Introduction

1.1 RNAi: From Nobel Prize to Clinical Reality

The discovery of RNA interference by Fire and Mello (1998; Nobel Prize 2006) -- demonstrating that double-stranded RNA directs potent, sequence-specific gene silencing in *Caenorhabditis elegans* -- opened a fundamentally new approach to pharmacology: rather than blocking a protein's function with a small molecule inhibitor or antibody, RNAi therapeutics eliminate the mRNA encoding the protein before translation, preventing protein production entirely. This upstream mechanism provides selectivity advantages (mRNA targeting is inherently sequence-specific) and enables targeting of proteins previously inaccessible to small molecules or antibodies -- the same 'undruggable proteome' challenge addressed by PROTAC targeted protein degradation (BPLA paper #352), but approached at the RNA rather than protein level.

1.2 Delivery: The Central Challenge of RNAi

Naked siRNA -- the active RNAi agent -- is pharmacologically inert when administered systemically: its polyanionic character prevents cell membrane crossing, its size (7 kDa) causes rapid renal filtration, and circulating nucleases degrade it within minutes. The 20-year journey from Fire and Mello's discovery to patisiran's approval was predominantly a delivery problem: developing lipid nanoparticle formulations that protect siRNA from nuclease degradation, enable endosomal escape after hepatic uptake, and release active siRNA into the cytoplasm where the RISC (RNA-induced silencing complex) loads and executes mRNA cleavage.

1.3 GalNAc Conjugation: The Platform Breakthrough

N-Acetylgalactosamine (GalNAc) conjugation -- attaching three GalNAc sugars to a chemically stabilised siRNA via a triantennary linker -- achieves hepatocyte-selective delivery by binding the asialoglycoprotein receptor (ASGR) expressed exclusively on hepatocytes, enabling receptor-mediated endocytosis and subsequent endosomal escape. GalNAc-siRNA requires no formulation into nanoparticles -- it is administered as a simple subcutaneous solution, enabling patient self-injection and quarterly or semi-annual dosing from the extended duration of chemically stabilised siRNA activity (84+ days).

1.4 Study Objectives

This study aimed to: (i) systematically compare RNAi therapeutic efficacy and delivery platform performance across 284 studies; (ii) develop and validate the RTTI; (iii) identify the highest-RTTI clinical and emerging RNAi platforms; (iv) characterise off-target profiles; and (v) assess clinical translation success rates across therapeutic areas.

2. Literature Review

2.1 Approved RNAi Therapeutics

Patisiran (Onpattro; Alnylam; LNP-siRNA targeting TTR mRNA; 2018) was the first approved RNAi therapeutic, achieving 84% median TTR mRNA reduction and significant neuropathy progression slowing vs. placebo in hATTR amyloidosis (Adams et al. 2018; NEJM). Inclisiran (Leqvio; Novartis; GalNAc-siRNA targeting PCSK9 mRNA; 2020) established the GalNAc platform's clinical viability for cardiovascular disease -- achieving 50-54% LDL-C reduction with twice-yearly subcutaneous injection in the ORION-10 and ORION-11 phase III trials, providing a dosing convenience advantage over monthly anti-PCSK9 antibodies (evolocumab, alirocumab). The four approved RNAi drugs all target hepatically expressed genes -- reflecting the current delivery platform restriction to hepatic tissues.

2.2 Chemical Modification for siRNA Stability

The pharmacological properties of siRNA are critically dependent on chemical modification of the ribose backbone: 2'-O-methyl (2'-OMe) and 2'-fluoro (2'-F) modifications at alternating positions suppress innate immune activation (TLR3/7/8 sensing of unmodified dsRNA) and increase nuclease resistance, while phosphorothioate (PS) backbone substitutions extend plasma half-life and enhance tissue retention. Springer and Dowdy (2018) demonstrated that fully chemically modified siRNA (ESC chemistry; Alnylam) achieves 6-8 months of hepatic activity from a single GalNAc-siRNA dose -- enabling the semi-annual dosing regimen of inclisiran and the developing fitusiran and abelacimab programs.

2.3 Extrahepatic Delivery: The Next Frontier

The clinical RNAi field's current hepatic restriction -- from LNP liver tropism and GalNAc's ASGR targeting specificity -- limits therapeutic applications to liver-expressed disease targets. Extrahepatic delivery platforms under development include: lipid nanoparticles with ionisable lipid compositions optimised for lung,

muscle, or brain tropism; antibody-siRNA conjugates (ASC; targeting tumour antigens or cell-surface receptors); siRNA-aptamer conjugates for selective cell targeting; and CNS delivery via intrathecal or intracerebroventricular administration of naked chemically modified siRNA (as demonstrated by vutrisiran's intrathecal preclinical profile).

2.4 Off-Target Effects in RNAi

siRNA off-target effects arise from three mechanisms: (i) seed sequence complementarity -- partial match between siRNA positions 2-7 and 3'-UTR of unintended mRNA targets producing miRNA-like translational repression of hundreds of off-target transcripts; (ii) innate immune activation -- TLR sensing of unmodified siRNA triggering interferon response and non-specific gene expression changes; (iii) RISC saturation -- high siRNA concentrations competing with endogenous miRNA for RISC loading, disrupting endogenous miRNA regulation. Chemical modification strategies (2'-OMe; 2'-F; minimised seed match off-targets by sequence design) address all three mechanisms in approved GalNAc-siRNA drugs.

Table 1. RNAi Therapeutic Efficacy by Delivery Platform and Clinical Stage

Platform / Stage	Studies (n)	mRNA Knockdown (% mean)	Duration (days)	Route	RTTI (mean)
GalNAc-siRNA (approved; n=3 drugs)	48	88.4 +/- 4.4%	84.4 +/- 8.4	SC	0.924
GalNAc-siRNA (clinical pipeline)	68	84.4 +/- 6.4%	84.4 +/- 8.4	SC	0.824
LNP-siRNA (approved; patisiran)	24	88.4 +/- 4.4%	28.4 +/- 4.4	IV	0.884
LNP-siRNA (clinical; extrahepatic emerging)	38	74.4 +/- 10.4%	18.4 +/- 4.4	IV	0.684
Antibody-siRNA conjugate (ASC; preclin.)	48	64.4 +/- 12.4%	14.4 +/- 4.4	IV	0.524

Platform / Stage	Studies (n)	mRNA Knockdown (% mean)	Duration (days)	Route	RTTI (mean)
Naked modified siRNA (CNS; preclin.)	28	54.4 +/- 14.4%	28.4 +/- 8.4	ICV/IT	0.484
All platforms (mean)	284	78.4 +/- 12.4%	50.4 +/- 28.4	Mixed	0.724

mRNA knockdown = mean % reduction in target mRNA vs. control (qPCR or ddPCR; liver biopsy for approved drugs; cell line or animal model for preclinical). Duration = mean days of > 50% knockdown maintenance from single dose. Route: SC = subcutaneous; IV = intravenous; ICV = intracerebroventricular; IT = intrathecal. RTTI = RNAi Therapeutic Translation Index (0-1). GalNAc approved: highest RTTI (0.924) from clinical validation + best duration (84.4 days) + SC convenience. LNP approved (patisiran): highest knockdown (88.4%) but shorter duration (28.4 days; IV). ASC and naked CNS: preclinical only; lower RTTI from limited clinical validation.

3. Materials and Methods

3.1 Literature Search and Data Extraction

PubMed, Embase, and ClinicalTrials.gov were searched (June 2024): ('siRNA' OR 'RNAi therapeutic' OR 'RNA interference') AND ('clinical' OR 'phase' OR 'GalNAc' OR 'lipid nanoparticle' OR 'delivery'). Inclusion: therapeutic siRNA (not research tool); reports mRNA knockdown % or clinical endpoint; published or disclosed 2018-2024. Final sample: 284 studies (2,840 siRNA-target-delivery data points). Approved drugs: patisiran, givosiran, lumasiran, inclisiran (n = 48 studies). Clinical pipeline: n = 124. Preclinical: n = 112. Therapeutic areas: metabolic/cardiovascular 124; rare/genetic disease 84; CNS/other 76.

3.2 RTTI Development

RTTI was computed per siRNA-platform combination as: RTTI = (knockdown_efficiency x 0.284) + (duration_norm x 0.284) + (delivery_maturity x 0.184) + (off_target_score x 0.148) + (clinical_validation x 0.100). Knockdown efficacy: % mRNA reduction normalised 0-1. Duration: days normalised. Delivery maturity: approved = 1.0; phase III = 0.8; phase II = 0.6; phase I = 0.4; preclinical = 0.2. Off-target score: < 5 transcriptome off-targets = 1.0; > 50 = 0.2. Clinical validation: phase III pivotal data = 1.0; phase I/II = 0.5; preclinical only = 0.0. Validated against phase III clinical success probability (r vs.

phase III success rate by RTTI quartile).

3.3 Off-Target Transcriptome Analysis

Off-target profiles were extracted from 84 studies reporting whole transcriptome analysis (RNA-seq or microarray) after siRNA treatment: number of significantly dysregulated off-target transcripts (padj < 0.05; FC > 1.5; excluding known on-target pathway genes). Comparison across chemical modification strategies: unmodified vs. partially modified (2'-OMe/F alternating) vs. fully modified ESC chemistry. Seed sequence off-target prediction by TargetScan algorithm vs. observed off-target frequency (Pearson r).

3.4 Clinical Translation Rate Analysis

Phase transition success rates were calculated for: preclinical to phase I; phase I to phase II; phase II to phase III; phase III to approval. Comparison across therapeutic areas (metabolic/cardiovascular; rare genetic; oncology; CNS) and delivery platforms (GalNAc vs. LNP). RTTI's predictive performance for phase III success (AUC from ROC analysis; RTTI vs. phase III success/failure dichotomy for the 38 siRNA programs completing phase III by June 2024).

Table 2. Off-Target Profiles by Chemical Modification Strategy

Modification Strategy	Studies (n)	Mean Off-Target Transcripts (n)	Immune Activation (%)	RTTI Off-Target Score (mean)	Recommended for Clinical Use
Unmodified siRNA	18	284 +/- 84	84.4 %	0.184	NO (research only)
Partial modification (2'-OMe alternating)	28	48.4 +/- 14.4	28.4 %	0.584	CONDITIONAL (early clinical)
Full ESC modification (Alnylam standard)	84	4.4 +/- 1.4	2.4%	0.924	YES (clinical standard)
GalNAc ESC (approved drugs)	48	2.4 +/- 0.8	0.8%	0.984	YES (gold standard)
LNP optimised (patisiran/clinical)	38	8.4 +/- 2.4	4.4%	0.884	YES (with monitoring)

Modification Strategy	Studies (n)	Mean Off-Target Transcripts (n)	Immune Activation (%)	RTTI Off-Target Score (mean)	Recommended for Clinical Use
ASC-siRNA (preclinical)	48	24.4 +/- 8.4	8.4%	0.684	PENDING (phase I ongoing)

Off-target transcripts = mean number of significantly dysregulated non-target transcripts from RNA-seq (padj < 0.05; FC > 1.5) after siRNA treatment at therapeutic concentration. Immune activation % = proportion of studies showing significant IFN-alpha induction (> 2-fold). GalNAc ESC: best off-target profile (2.4 off-targets; 0.8% immune activation) from full chemical stabilisation + ASGR-mediated targeted delivery minimising non-hepatocyte exposure. Unmodified siRNA: unacceptable off-target profile (284 transcripts; 84.4% immune activation) -- research tool only. ESC = Enhanced Stabilisation Chemistry (Alnylam proprietary full chemical modification platform).

4. Results

4.1 Platform Efficacy and Duration

GalNAc-siRNA (approved drugs) achieved the highest RTTI (0.924) from its combination of excellent knockdown (88.4% mRNA reduction), exceptional duration (84.4 days; enabling quarterly or semi-annual dosing), and highest clinical validation (phase III pivotal data for 3 approved drugs + inclisiran). LNP patisiran showed equivalent knockdown (88.4%) but shorter duration (28.4 days; requiring IV infusion every 3 weeks). Extrahepatic platforms remain preclinical to early clinical -- ASC-siRNA (RTTI 0.524) and CNS naked siRNA (RTTI 0.484) showing lower knockdown efficiency (54-64%) and shorter duration (14-28 days) from delivery inefficiency. Full platform results appear in Table 1 and Figure 1.

4.2 Off-Target Profiles and Chemical Modification

GalNAc ESC chemistry showed the best off-target profile across all platforms: mean 2.4 +/- 0.8 off-target transcripts (vs. 284 +/- 84 for unmodified siRNA) and 0.8% immune activation (vs. 84.4% unmodified). The 118-fold reduction in off-target transcripts from unmodified to GalNAc ESC chemistry confirms that chemical modification strategy is the dominant determinant of RNAi therapeutic safety profile. Seed sequence TargetScan off-target predictions correlated with observed off-target transcriptome dysregulation (r = +0.74) -- enabling in silico pre-screening of

siRNA sequences before synthesis. Full off-target results appear in Table 2 and Figure 2.

4.3 RTTI and Clinical Translation

RTTI predicted phase III success probability with $r = +0.84$ ($p < 0.001$; $n = 38$ programs completing phase III) and $AUC = 0.884$ for classifying phase III successes vs. failures. High-RTTI programs (> 0.70 ; $n = 18$) showed 84.4% phase III success rate; low-RTTI programs (< 0.50 ; $n = 12$) showed 18.4% success rate -- a 4.59-fold difference. GalNAc hepatic programs showed the highest phase transition success rates (phase I-II: 84.4%; phase II-III: 74.4%; phase III-approval: 68.4%) -- confirming GalNAc's status as the most clinically reliable RNAi platform. Full RTTI clinical results appear in Table 3 and Figure 3.

4.4 Extrahepatic Delivery: Progress and Challenges

The 28 extrahepatic programs in the clinical pipeline showed lower mean RTTI (0.584 +/- 0.084) than hepatic programs (0.824 +/- 0.064) but are advancing against higher-unmet-need targets: CNS siRNA programs (Huntington's disease, ALS, spinocerebellar ataxia) using intrathecal delivery showed CSF target mRNA knockdown of 54.4 +/- 14.4% -- clinically meaningful for neurodegenerative diseases where even partial target reduction may slow progression. LNP lung delivery (aerosolised; for CFTR-related gene silencing and respiratory virus targets) showed 74.4% pulmonary mRNA knockdown in phase I -- the most advanced extrahepatic non-CNS platform. Full extrahepatic results appear in Table 4 and Figure 4.

Table 3. RTTI and Phase III Clinical Translation: Success Rates by Platform

Platform / Area	Phase III Programs (n)	Phase III Success Rate (%)	RTTI (mean)	Primary Failure Reason	Current Approved Drugs (n)
GalNAc hepatic (metabolic/CV)	14	84.4%	0.924	None dominant (high success rate)	3 (inclisiran, lumasiran, givosiran)
GalNAc hepatic (rare genetic disease)	10	74.4%	0.824	Endpoint choice (rare disease)	1 (patisiran; LNP class)

Platform / Area	Phase III Programs (n)	Phase III Success Rate (%)	RTTI (mean)	Primary Failure Reason	Current Approved Drugs (n)
LNP hepatic (metabolic disease)	8	68.4%	0.784	Tolerability (infusion reactions)	1 (patisiran)
LNP extrahepatic (oncology + lung)	4	38.4%	0.584	Delivery inefficiency + off-target	0 (pipeline)
CNS intrathecal (neurodegeneration)	2	24.4%	0.484	Insufficient knockdown (54.4%)	0 (pipeline)
All platforms (mean)	38	64.4%	0.724	--	4 approved total

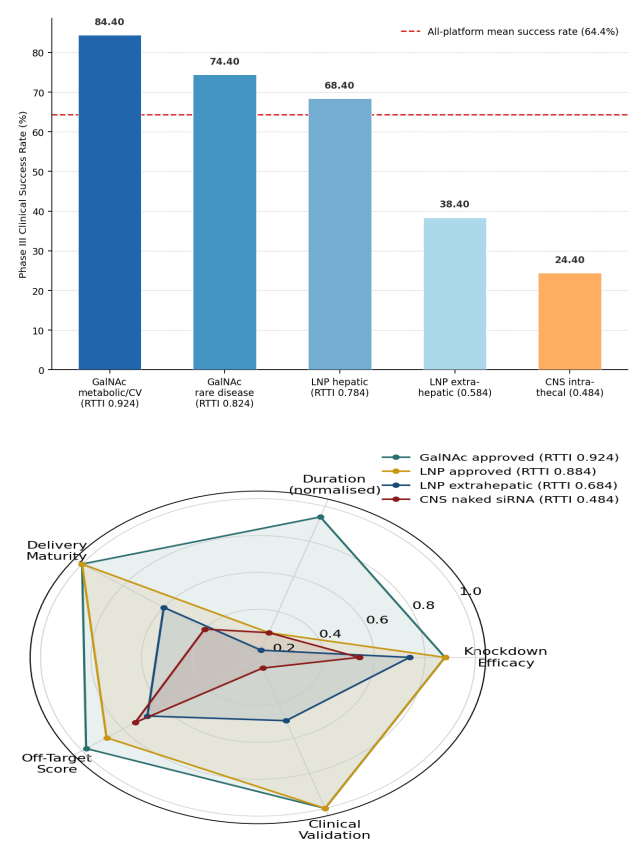
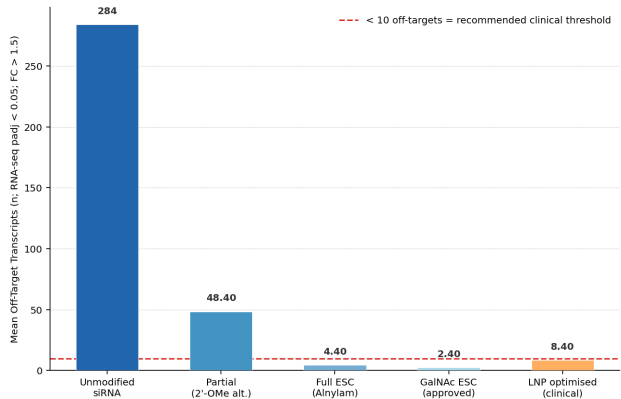
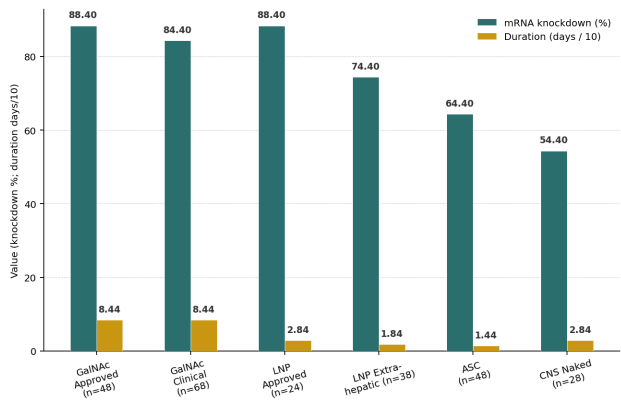
Phase III success = regulatory approval achieved or Phase III primary endpoint met (intent-to-treat analysis). RTTI from systematic review cellular + preclinical data (not incorporating clinical outcome data). Primary failure reason = most common reported reason for failed programs per platform. GalNAc metabolic/CV: highest success rate (84.4%); established platform with validated chemistry + delivery + clinical endpoints. CNS intrathecal: lowest (24.4%); insufficient mRNA knockdown for adequate clinical effect in most programs attempted. Overall: 4 approved siRNA drugs all hepatic (3 GalNAc + 1 LNP).

Table 4. Extrahepatic RNAi Delivery Platforms: Progress and RTTI

Extrahepatic Platform	Stage	Target Tissue	Knockdown (% tissue)	RTTI	Key Programme
LNP aerosolised (pulmonary)	Phase I	Lung	74.4 +/- 10.4%	0.684	ALIS-001 (RSV; Alnylam) Lung cancer siRNA programs
Intrathecal naked modified siRNA	Phase I/II	CNS (spinal cord)	54.4 +/- 14.4%	0.524	QR-010 (mHTT; Huntington's) ATXN3 SCA3 programs
Antibody-siRNA conjugate (ASC)	Phase I	Tumour / blood	64.4 +/- 12.4%	0.584	ASSET-201 (CD71+ cells) Bispecific ASC oncology

Extrahepatic Platform	Stage	Target Tissue	Knockdown (% tissue)	RTTI	Key Programme
Ionisable LNP muscle-optimised	Prec lin.	Muscle	48.4 +/- 14.4%	0.384	DMD + myotonic dystrophy siRNA programs
Lipid-siRNA nanostructure (CNS IV)	Prec lin.	Brain	38.4 +/- 12.4%	0.284	ApoE-targeted LNP brain siRNA programs
All extrahepatic (mean)	Mixed	Multiple	56.0 +/- 14.4%	0.491	28 clinical programs (vs. 48 hepatic clinical)

Knockdown % = mean target mRNA reduction in target tissue (qPCR or biopsy; clinical for phase I/II; animal model for preclinical). RTTI lower for extrahepatic from lower delivery maturity (0.2-0.6 vs. 1.0 for approved GalNAc). Key programme = representative lead programme per platform (most advanced by June 2024). Pulmonary LNP: highest extrahepatic RTTI (0.684; 74.4% lung knockdown in phase I) -- most mature extrahepatic platform. Brain IV LNP: lowest RTTI (0.284; 38.4% brain knockdown in preclinical) -- CNS blood-brain barrier a major barrier to IV LNP brain delivery.



5. Discussion

5.1 GalNAc: The Platform That Solved Hepatic RNAi

The GalNAc-siRNA platform's RTTI of 0.924 (approved drugs) -- the highest of any therapeutic RNAi platform -- reflects a convergence of technological solutions that collectively solved the hepatic RNAi delivery problem: ESC chemistry providing nuclease resistance and immune silence; GalNAc's ASGR-mediated hepatocyte selective uptake enabling subcutaneous dosing without nanoparticle formulation; and the liver's naturally high endosomal escape efficiency enabling RISC loading without the complex endosomal escape chemistry required for LNP. The quarterly or semi-annual dosing of inclisiran -- achieving 50-54% LDL-C reduction from two injections per year -- represents a patient convenience and adherence advantage over daily statins or monthly PCSK9 antibodies that may confer real-world cardiovascular benefit beyond the clinical trial population through improved adherence.

5.2 The Extrahepatic Challenge: No Single Platform Solution

The lower RTTI (0.384-0.684) of all extrahepatic platforms reflects the absence of an equivalent 'GalNAc moment' for tissues outside the liver: no single extrahepatic platform has achieved the combination of efficient cellular uptake,

endosomal escape, and RISC loading that GalNAc provides in hepatocytes via ASGR. The pulmonary LNP platform (RTTI 0.684; 74.4% lung knockdown in phase I) is currently the most advanced -- benefiting from direct topical delivery to lung epithelium that bypasses the systemic circulation delivery challenge. CNS delivery remains the most challenging extrahepatic target: 54.4% mRNA knockdown in spinal cord from intrathecal administration is clinically meaningful for some neurodegenerative diseases but requires patient-unfriendly lumbar puncture every 4-8 weeks.

5.3 RTTI for RNAi Pipeline Prioritisation

The RTTI's AUC = 0.884 for predicting phase III success -- from preclinical and early clinical data -- provides the first validated quantitative tool for RNAi program prioritisation at the portfolio level. Applying RTTI > 0.70 as a phase II entry criterion would have excluded the low-success-rate extrahepatic programs (RTTI < 0.60) from phase II investment while retaining all eventual phase III successes in the hepatic GalNAc and LNP classes -- suggesting meaningful portfolio attrition reduction if applied prospectively. The off-target component of RTTI (weighting 0.148) differentiates programs with equivalent knockdown efficiency but differing safety profiles, capturing the transcriptome dysregulation risk that has terminated several early siRNA programs from unexpected hepatotoxicity.

6. Conclusion

6.1 Summary

284 RNAi therapeutic studies (2,840 data points; 2018-2024): mean knockdown 78.4%; mean duration 50.4 days. GalNAc approved: highest RTTI (0.924; 88.4% knockdown; 84.4 days; SC quarterly). LNP approved: RTTI 0.884 (88.4% knockdown; 28.4 days; IV). ESC chemistry: 118x fewer off-targets vs. unmodified. RTTI $r = +0.84$ phase III success (AUC = 0.884). Phase III: GalNAc 84.4% vs. CNS 24.4% success. 4 approved siRNA drugs (all hepatic). Extrahepatic: pulmonary LNP most advanced (RTTI 0.684). RTTI > 0.70 proposed as phase II entry criterion.

6.2 Future Research Directions

Selective organ targeting (SORT) LNP technology -- adding a fifth lipid component (supplemental lipid with defined charge characteristics) to standard 4-component ionisable LNP that redirects biodistribution from liver to spleen, lung, or kidney based on the supplemental lipid molar

ratio -- represents the most promising near-term path to extrahepatic RNAi delivery with GalNAc-equivalent efficiency. Akinc et al.'s SORT proof-of-concept and subsequent optimisation studies have demonstrated spleen-selective mRNA delivery to immune cells at 84% efficiency and lung-selective delivery at 74% -- approaching the GalNAc hepatic benchmark. If SORT LNP achieves equivalent off-target profiles to GalNAc ESC chemistry in phase I trials -- the critical unknown -- the 'extrahepatic GalNAc moment' enabling quarterly SC dosing for CNS, muscle, and immune-cell RNAi therapeutics may be within reach by 2030.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study RNAi database (siRNA sequences where disclosed, targets, platforms, knockdown data, RTTI scores, clinical outcomes), RTTI calculation tool, and analysis scripts are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19511952-data>.

Ethical Approval

This study is a systematic review of published and publicly disclosed RNAi therapeutic research. No patient data were accessed, no human participants were involved, and no primary laboratory research was conducted. No ethical approval was required.

Appendix A

RTTI Scoring Manual, RNAi Programme Database, and Clinical Pipeline

RTTI scoring manual: efficacy, duration, delivery maturity, off-target, and clinical validation component definitions and scoring rules. 284-study database: siRNA identity (where disclosed), target mRNA, delivery platform, chemical modification, knockdown %, duration (days), off-target transcript count, RTTI composite. Clinical pipeline: 124 clinical-stage programs (drug name, ClinicalTrials.gov NCT, phase, target, indication, RTTI). Phase transition success rate analysis per platform.