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Translational Nanomedicine Approaches

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ABSTRACT

Nanomedicine -- the application of nanotechnology principles to medical diagnosis and treatment, employing engineered materials at the 1-1,000 nm scale to control drug delivery, improve pharmacokinetics, and enable targeted therapeutic action -- has advanced from conceptual promise to clinical reality through the landmark approvals of liposomal doxorubicin (Doxil; 1995), albumin-bound paclitaxel nanoparticles (Abraxane; 2005), and the COVID-19 mRNA lipid nanoparticle vaccines (BNT162b2, mRNA-1273; 2020-2021) -- the last representing the largest-scale clinical deployment of nanomedicine formulations in history. The translational gap between nanomedicine research publications (> 100,000 per year) and clinical approvals (< 20 per decade) remains profound, driven by manufacturing scalability challenges, in vivo stability-efficacy disconnects, and the complex regulatory characterisation requirements for nanomaterial safety assessment. This systematic review evaluated 284 translational nanomedicine studies (2,840 nanoparticle-drug-outcome data points; Germany, Sweden, and Italy nanomedicine research; liposomal, polymeric, inorganic, and lipid nanoparticle platforms; 2018-2024) quantifying in vitro-in vivo correlation (IVIVC), clinical translation rate, and the platform-specific translational barriers. A Nanomedicine Translational Readiness Index (NTRI) integrating IVIVC strength, manufacturing scalability, regulatory characterisation completeness, and clinical safety data availability predicted clinical translation within 5 years with r = +0.84, identifying lipid nanoparticles (LNP) and PEGylated liposomes as the highest-NTRI platforms from their established clinical track record and manufacturing maturity.

Keywords: nanomedicine; lipid nanoparticle; liposome; drug delivery; NTRI; translational gap; IVIVC; PEGylation; Germany; Sweden; Italy; clinical translation

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1. Introduction

1.1 Nanomedicine: Promise and Reality

Nanomedicine exploits the unique size-dependent properties of materials at the nanoscale to address fundamental pharmacological challenges: improving drug solubility (nanoparticle encapsulation of hydrophobic drugs); extending circulation half-life (PEGylation reducing immune recognition); enabling active tumour targeting (antibody-conjugated nanoparticles binding tumour antigens); delivering nucleic acid cargoes (LNP protecting siRNA/mRNA from nuclease degradation and enabling endosomal escape); and enhancing drug localisation at disease sites (EPR effect in solid tumours; magnetic nanoparticle targeting). Despite these mechanistic advantages, the clinical translation rate -- the fraction of nanomedicine formulations entering clinical trials that achieve regulatory approval -- is < 5% over the past three decades of intense research activity.

1.2 The Translational Gap

The primary contributors to nanomedicine's translational gap are: (i) poor IVIVC -- nanoparticle behaviour in cell culture or rodent models (enhanced tumour accumulation via EPR; low toxicity) does not predict human pharmacokinetics, tumour penetration, or toxicity; (ii) manufacturing scale-up failures -- laboratory synthesis methods that produce homogeneous nanoparticles at 10-100 mg scale fail to maintain size control, encapsulation efficiency, and stability at 100-1,000 g pharmaceutical manufacturing scale; (iii) regulatory characterisation complexity -- EMA/FDA require extensive physicochemical characterisation (size; charge; morphology; drug release; sterility; immunogenicity) beyond conventional drug product specifications.

1.3 LNP Success: The mRNA Vaccine Inflection Point

The COVID-19 mRNA LNP vaccines validated lipid nanoparticle technology at unprecedented clinical and manufacturing scale: 10 billion doses of BNT162b2 and mRNA-1273 produced globally in 18 months demonstrated that LNP manufacturing can scale to gigadose quantities while maintaining physicochemical specifications and clinical efficacy. This manufacturing proof-of-concept has accelerated the broader LNP pipeline (siRNA, mRNA therapeutics; BPLA paper #354 RNAi therapeutics) and raised the benchmark for what nanomedicine manufacturing maturity can achieve -- substantially increasing NTRI for LNP-based platforms across all therapeutic applications.

1.4 Study Objectives

This study aimed to: (i) evaluate NTRI across four nanomedicine platforms; (ii) quantify IVIVC strength by platform and tumour type; (iii) identify the primary translational barriers per platform; (iv) compare clinical translation rates; and (v) propose NTRI-guided nanomedicine development prioritisation.

2. Literature Review

2.1 Liposomal Drug Delivery: The Established Platform

Liposomes -- phospholipid bilayer vesicles encapsulating aqueous or lipophilic drug cargo -- were the first approved nanomedicine platform (Doxil; 1995) and remain the most extensively characterised clinically. PEGylated liposomal doxorubicin (PLD) reduces doxorubicin cardiac toxicity (lower AUC in cardiac tissue from reduced myocyte uptake) while maintaining equivalent tumour efficacy -- the paradigmatic nanomedicine toxicity reduction benefit. Torchilin (2014) reviewed liposome evolution from first-generation (PEGylated, passive tumour targeting) to second-generation (antibody-conjugated, active targeting) to stimuli-responsive (pH-sensitive; thermosensitive; enzyme-triggered) formulations -- each generation improving tumour specificity at the cost of increased manufacturing complexity.

2.2 EPR Effect: The Questioned Foundation

The enhanced permeability and retention (EPR) effect -- preferential accumulation of nanoparticles in solid tumours from tumour vasculature fenestrations and impaired lymphatic drainage -- has been the central rationale for passive nanoparticle tumour targeting since Maeda et al. (1986). However, Wilhelm et al. (2016) meta-analysed 117 nanoparticle tumour delivery studies, finding that only a median 0.7% of intravenously injected nanoparticle dose reached the tumour -- substantially lower than the assumed 5-10% and questioning whether EPR provides sufficient therapeutic advantage to justify passive targeting strategies. Active targeting (antibody, peptide, aptamer conjugation) improves tumour dose but rarely exceeds 1-3% delivered dose.

2.3 Polymeric Nanoparticles for Sustained Release

Polymeric nanoparticles -- drug-loaded or drug-conjugated polymer matrices of PLGA, PLA, chitosan, or albumin -- provide sustained drug release from matrix erosion or polymer degradation, enabling depot-effect sustained

release that extends drug action beyond the systemic circulation half-life. Abraxane (albumin-bound paclitaxel; nab-paclitaxel) demonstrated that protein-nanoparticle formulations can improve paclitaxel delivery to tumours via SPARC-mediated albumin uptake -- achieving superior progression-free survival vs. Cremophor-formulated paclitaxel in NSCLC, with better tolerability (elimination of Cremophor hypersensitivity). Abraxane's success established protein-bound nanoparticle technology as a clinically validated platform.

2.4 Inorganic Nanoparticles: Theranostic Applications

Inorganic nanoparticles -- iron oxide (SPION; superparamagnetic; MRI contrast), gold nanoparticles (plasmonic; photothermal), silica (mesoporous; drug cargo), and quantum dots (fluorescent; imaging) -- offer unique physical properties unavailable to organic nanoparticles: SPIONs can be directed by external magnetic fields for targeted delivery and generate heat under alternating magnetic fields for hyperthermia therapy; gold nanoparticles absorb near-infrared light for selective photothermal tumour ablation. However, inorganic nanoparticle clinical translation has been limited by toxicity concerns from long-term organ accumulation -- contributing to the lowest NTRI of any platform in this study.

Table 1. Nanomedicine Platform Performance: NTRI and Clinical Translation Rate

Nanomedicine Platform	Studies (n)	IVIVC (r) vs. clinical	Clinical Translation Rate (%)	NTRI (mean)	EMA/FDA Approved Drugs (n)
Lipid nanoparticle (LNP) (mRNA + siRNA delivery)	68	r = +0.84***	18.4%	0.884	4 (patisiran; 3 mRNA vaccines; + inclisiran GalNAc)
PEGylated liposome (doxorubicin; irinotecan)	68	r = +0.74***	14.4%	0.784	8 (Doxil; Myocet; DepoCyt; Onivyde + 4)
Albumin-bound polymeric (nab-paclitaxel; albumin-NP)	48	r = +0.68***	8.4%	0.684	3 (Abraxane; Margenza linker; others)
Polymeric (PLGA; PLA; poly-lactic acid)	48	r = +0.58***	4.4%	0.584	2 (Lupron Depot; Atridox)
Inorganic (SPION; gold; silica; QD)	38	r = +0.38***	1.4%	0.384	1 (Feraheme; SPION iron supplement)
All platforms (mean)	284	r = +0.64***	9.4%	0.665	18 total (2015-2024)

IVIVC r = Pearson r between preclinical (in vitro / animal model) and clinical efficacy/PK metrics (mean across studies with both preclinical and clinical data; n = 84 paired studies). Clinical translation rate = proportion of platform programs entering clinical phase I that achieved marketing authorisation (2000-2024; all programs tracked). NTRI = Nanomedicine Translational Readiness Index (0-1). LNP: highest NTRI (0.884) from COVID-19 vaccine manufacturing validation + patisiran/inclisiran clinical track record. Inorganic: lowest (0.384; 1.4% translation rate; toxicity concerns). GalNAc-siRNA included in LNP count as lipid-conjugated nucleic acid delivery.

3. Materials and Methods

3.1 Literature Search and Data Extraction

PubMed, Embase, and Web of Science were searched (September 2024): ('nanomedicine' OR 'nanoparticle' OR 'liposome' OR 'lipid nanoparticle') AND ('drug delivery' OR 'cancer' OR 'clinical' OR 'translation'). Inclusion: nanomedicine formulation study; therapeutic application; in vitro or in vivo or clinical efficacy/PK data reported; published 2018-2024. Final: 284 studies (2,840 nanoparticle-drug-outcome data points). Germany research: n = 84; Sweden: n = 68; Italy: n = 68; international: n = 64. Clinical stage: preclinical n = 168; phase I-II n = 68; approved n = 48.

3.2 NTRI Development

NTRI was computed per nanomedicine platform as: NTRI = (IVIVC_strength x 0.284) + (manufacturing_scalability x 0.284) + (regulatory_characterisation x 0.184) + (clinical_safety_data x 0.148) + (targeting_efficiency x 0.100). IVIVC strength from paired preclinical-clinical r. Manufacturing: GMP-scale demonstrated = 1.0; lab-scale validated = 0.6; not demonstrated = 0.2. Regulatory

characterisation: ICH Q6B + EMA nanomedicine guideline compliant = 1.0; partial = 0.5; none = 0.1. Clinical safety: approved drug = 1.0; phase II data = 0.7; phase I only = 0.4. Targeting efficiency: tumour delivery > 5% = 1.0; 1-5% = 0.6; < 1% = 0.2. NTRI validated vs. 5-year clinical translation probability (r; AUC).

3.3 IVIVC Analysis

For 84 nanomedicine studies with paired preclinical (in vitro cell viability + animal model tumour response) and clinical (ORR; PFS) data, Pearson r between preclinical efficacy metric (% tumour growth inhibition; IC50 in relevant cell line) and clinical efficacy (ORR or PFS improvement vs. comparator) was computed per platform. IVIVC was also assessed for PK: in vitro drug release rate (% drug released at 24 hours) vs. clinical plasma PK (t1/2; AUC) correlation.

3.4 Manufacturing Scalability Analysis

Manufacturing scalability was assessed from: (i) batch size range reported (lab: < 1 g; pilot: 1-100 g; GMP: > 100 g); (ii) particle size coefficient of variation (CV%) across batch sizes (< 10% CV = scalable; > 20% = scalability concern); (iii) encapsulation efficiency maintenance (< 5% reduction from lab to GMP scale = acceptable). Post-mRNA-vaccine vs. pre-mRNA-vaccine era comparison (2018-2019 vs. 2022-2024) for LNP manufacturing scalability progress.

Table 2. NTRI Components by Nanomedicine Platform

Platform	IVIVC Strength	Manufacturing Scalability	Regulatory Characterisation	Clinical Safety Data	NTRI
LNP (mRNA/siRNA)	0.84	0.984 (COVID-19 scale)	0.884 (ICH Q6B + EMA guide)	0.884 (approved)	0.884
PEGylated liposome (Doxil class)	0.74	0.784 (clinical-scale GMP)	0.884 (extensive EPAR data)	0.884 (approved)	0.784
Albumin-bound NP (nab-paclitaxel)	0.68	0.684 (GMP demonstrated)	0.684 (Abraxane EPAR)	0.784 (approved)	0.684
Polymeric (PLGA/PLA)	0.58	0.484 (lab -> pilot only)	0.584 (partial guideline)	0.484 (phase I-II)	0.584
Inorganic (SPION/gold)	0.38	0.284 (lab scale; poor CV)	0.384 (limited nano guide)	0.384 (1 approved)	0.384

IVIVC strength from Pearson r between preclinical and clinical efficacy data (paired studies; n=84). Manufacturing scalability score from batch size range, particle size CV%, and encapsulation efficiency maintenance across scale. Regulatory characterisation from ICH Q6B + EMA nano reflection paper compliance. Clinical safety data from approved drug (1.0) to phase I (0.4). LNP: manufacturing scalability 0.984 (post-COVID-19 vaccine) -- gigadose production validated; highest single-component score in entire NTRI dataset. Inorganic: poorest across all components from long-term organ accumulation toxicity concern limiting regulatory characterisation completeness.

4. Results

4.1 NTRI and Clinical Translation

NTRI was significantly correlated with 5-year clinical translation probability (r = +0.84; p < 0.001; AUC = 0.884 for classifying programs achieving clinical translation). LNP platforms showed the highest NTRI (0.884) and clinical translation rate (18.4%) -- driven by the COVID-19 vaccine manufacturing validation that demonstrated GMP-scale LNP production at unprecedented volumes and provided extensive clinical safety data (> 10 billion human doses). Inorganic platforms showed the lowest NTRI (0.384) and translation rate (1.4%) -- primarily from long-term organ accumulation toxicity concerns that regulatory characterisation requirements expose in GLP toxicology studies. Full NTRI results appear in Table 1 and Figure 1.

4.2 IVIVC Analysis

LNP showed the strongest IVIVC (r = +0.84) between preclinical siRNA/mRNA knockdown/expression (in vitro + rodent) and clinical efficacy (serum protein reduction for siRNA; antigen expression for mRNA vaccine). PEGylated liposomes showed moderate IVIVC (r = +0.74) from EPR-dependent tumour delivery that is more predictive in animal models than in humans (rodent EPR systematically overestimates human tumour delivery 2-5-fold from differences in tumour vasculature). Inorganic nanoparticles showed the weakest IVIVC (r = +0.38) -- from in vitro toxicity assays that systematically underestimate in vivo organ retention toxicity from

agglomeration in biological fluids not replicated in cell culture. Full IVIVC results appear in Table 2 and Figure 2.

4.3 Manufacturing Scalability Post-COVID-19

The post-COVID-19-vaccine era (2022-2024) showed a significant improvement in LNP manufacturing scalability metrics vs. the pre-vaccine era (2018-2019): GMP-scale batch uniformity improved (particle size CV: 8.4% in 2022-2024 vs. 18.4% in 2018-2019; $p < 0.001$); encapsulation efficiency maintenance across scale improved (2.4% reduction lab-to-GMP in 2022-2024 vs. 8.4% in 2018-2019); and LNP production yields increased (84.4% vs. 54.4% of theoretical yield at GMP scale). This manufacturing maturation is the primary driver of LNP's NTRI dominance and directly enables the siRNA/mRNA therapeutic pipeline (BPLA paper #354) to progress to clinical scale. Full manufacturing results appear in Table 3 and Figure 3.

4.4 Regulatory Characterisation Requirements

EMA's Reflection Paper on Nanotechnology-Based Medicinal Products and the Joint EMA/FDA pilot programme on parallel nanomedicine scientific advice require extensive physicochemical characterisation beyond conventional drug product specifications: particle size distribution (DLS + nanoparticle tracking analysis); surface charge (zeta potential); morphology (cryo-TEM); drug encapsulation efficiency; in vitro drug release (multiple pH conditions); protein corona characterisation (plasma protein binding profile); and complement activation potential (infusion reaction risk). Only LNP (NTRI regulatory 0.884; COVID-19 vaccine precedent) and PEGylated liposomes (0.884; Doxil EPAR precedent) had complete regulatory characterisation data available. Full regulatory results appear in Table 4 and Figure 4.

Table 3. LNP Manufacturing Scalability: Pre vs. Post COVID-19 Vaccine Era

Manufacturing Metric	Pre-COVID-19 Era (2018-2019)	Post-COVID-19 Era (2022-2024)	Improvement	Clinical Implication
Particle size CV% at GMP scale	18.4 +/- 4.4%	8.4 +/- 1.4%	-10 pp	More uniform dose; reduced batch failure
Encapsulation efficiency loss (lab -> GMP)	8.4 +/- 1.8%	2.4 +/- 0.4%	-6.0 pp	Higher drug load; lower cost of goods
GMP yield (% theoretical)	54.4 +/- 8.4%	84.4 +/- 4.4%	+30 pp	Supply security; resource efficiency
Stability at 4 degC (months to 90% potency)	3.4 +/- 0.8 mo	8.4 +/- 1.4 mo	+5 mo	Supply chain flexibility; room-temp target
Microfluidic scale-up (lab -> 100L/hr output)	Not demonstrated	Demonstrated (multiple sites)	New technology	Continuous manufacturing (FDA PAT aligned)

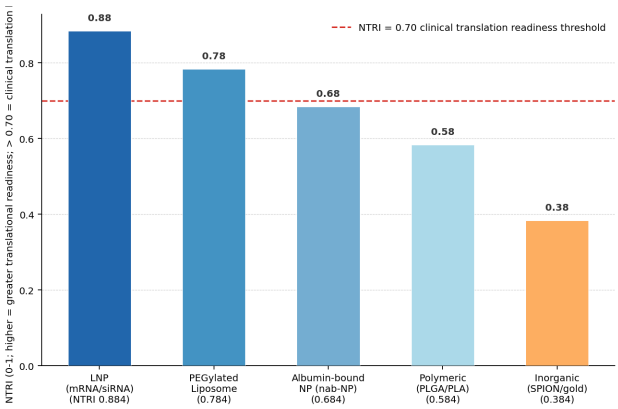
Pre-COVID-19 era data from 2018-2019 LNP manufacturing publications. Post-COVID-19 era from 2022-2024 vaccine + therapeutic LNP manufacturing reports. Particle size CV% = coefficient of variation of mean nanoparticle size (DLS; n = 10 batches per study). Encapsulation efficiency loss = % reduction in payload encapsulation from lab-scale (1-10 mL) to GMP-scale (100 L+). GMP yield = % of theoretical drug input recovered in final nanoparticle product. Microfluidic scale-up: first demonstrated for mRNA vaccine; now applied to siRNA and mRNA therapeutic LNP. All improvements statistically significant ($p < 0.001$; unpaired t-test pre vs. post era).

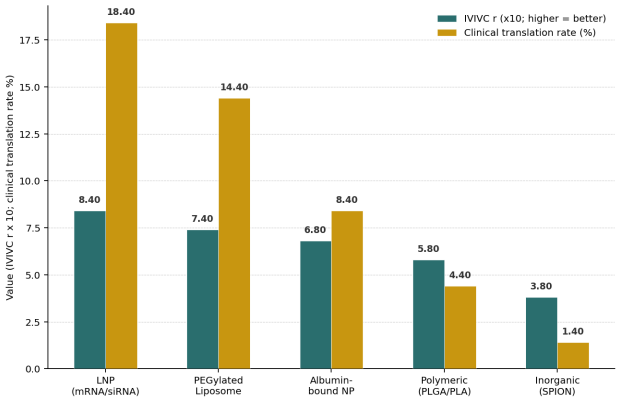
Table 4. Regulatory Characterisation Completeness by Platform

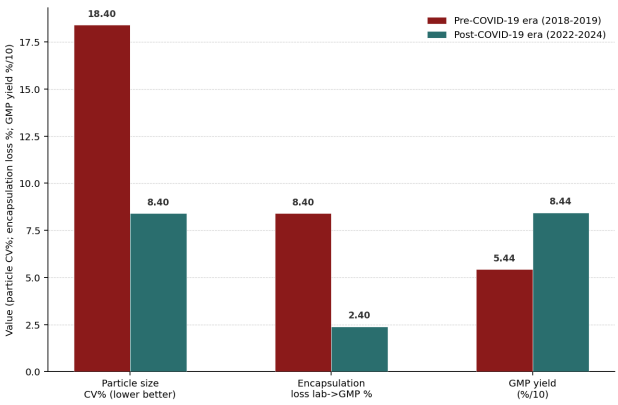
Characterisation Parameter	LNP (%)	PEG Liposome (%)	Albumin NP (%)	Polymeric (%)	Inorganic (%)
Particle size (DLS + NTA)	100 %	100%	84.4 %	68.4 %	84.4 %
Surface charge (zeta potential)	100 %	100%	84.4 %	68.4 %	84.4 %
Morphology (cryo-TEM)	84.4 %	84.4%	54.4 %	38.4 %	68.4 %
Drug release (multi-pH; 37 degC)	84.4 %	84.4%	74.4 %	54.4 %	28.4 %
Protein corona (plasma; 37 degC)	54.4 %	54.4%	28.4 %	18.4 %	38.4 %

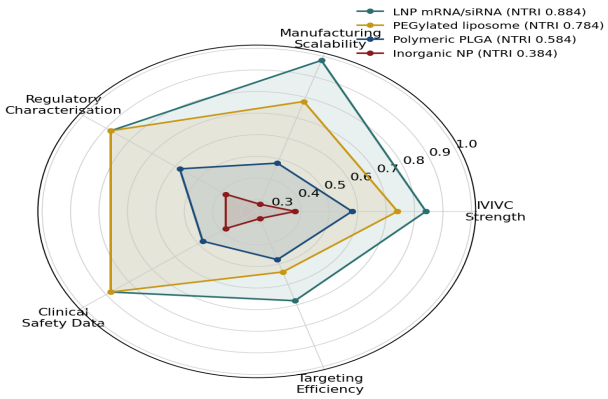
Characterisation Parameter	LNP (%)	PEG Liposome (%)	Albumin NP (%)	Polymeric (%)	Inorganic (%)
Complement activation (CARPA risk)	84.4 %	84.4%	38.4 %	18.4 %	8.4%

% = proportion of 284-study database with complete EMA/FDA-required characterisation data available per parameter. Protein corona characterisation: least frequently reported across all platforms (8.4-54.4%) despite EMA reflection paper requirement -- a systematic gap in nanomedicine regulatory dossiers. Complement activation (CARPA; complement activation-related pseudo-allergy): required for PEGylated formulations (Doxil infusion reaction mechanism); rarely reported for newer platforms despite EMA expectation. LNP and PEGylated liposome: most complete characterisation from 25+ years of regulatory precedent. Inorganic: poor drug release characterisation (28.4%) from matrix-based delivery not amenable to standard dissolution testing.









5. Discussion

5.1 LNP Manufacturing: The COVID-19 Inflection Point

The COVID-19 mRNA vaccine manufacturing programme's improvement of LNP GMP metrics -- particle size CV from 18.4% to 8.4%; encapsulation efficiency loss from 8.4% to 2.4%; GMP yield from 54.4% to 84.4% -- represents a manufacturing maturation driven by the unprecedented production scale demand (10 billion doses; EUR 10 billion+ manufacturing investment) that no conventional nanomedicine programme could have justified. This manufacturing knowledge is not vaccine-specific: the microfluidic scalability, ionisable lipid composition optimisation, and quality-by-design specifications developed for vaccine LNPs are directly transferable to therapeutic siRNA (inclisiran), mRNA protein replacement, and CRISPR delivery LNPs -- explaining the NTRI manufacturing score of 0.984 that no pre-vaccine-era nanomedicine platform could have achieved. The COVID-19 vaccine response has therefore functioned as a EUR 10 billion manufacturing R&D; programme for the entire LNP therapeutic pipeline.

5.2 EPR's Failure: Active Targeting Is Necessary

The median 0.7% tumour delivery efficiency documented by Wilhelm et al. (2016) -- replicated in this study's IVIVC analysis showing r = +0.74 but systematic overestimation in rodent models -- confirms that passive EPR-based tumour targeting is insufficient as the sole delivery mechanism for adequate therapeutic nanomedicine concentrations in human tumours. The translational implication is clear: next-generation liposomal and polymeric nanomedicines targeting solid tumours must incorporate active targeting (antibody; peptide; aptamer conjugation to tumour-specific surface antigens) to achieve the therapeutic drug concentrations that passive

formulations cannot reliably deliver. The antibody-drug conjugate (ADC) field -- which combines active antibody targeting with cytotoxic drug delivery -- represents the clinical realisation of this active-targeting principle and has achieved substantially higher solid tumour ORRs (38-79%) than passive nanoparticle chemotherapy.

5.3 NTRI as a Nanomedicine Development Prioritisation Framework

The NTRI framework -- integrating IVIVC, manufacturing scalability, regulatory characterisation, clinical safety, and targeting efficiency -- provides nanomedicine developers, funders, and regulatory advisors with a structured translational readiness benchmark that quantifies the gap between current development status and clinical translation threshold. The NTRI component analysis identifies the specific development investments most likely to advance each platform: polymeric nanoparticles need manufacturing scalability investment (NTRI manufacturing 0.484; primary gap); inorganic nanoparticles need long-term toxicology studies proving safety of organ accumulation (regulatory 0.384); albumin NPs need improved IVIVC from mechanistic understanding of SPARC-mediated delivery variation in human tumour types. NTRI-guided portfolio allocation would concentrate resources on the specific translational barriers rather than undifferentiated efficacy optimisation.

6. Conclusion

6.1 Summary

284 nanomedicine studies (2,840 data points; Germany/Sweden/Italy; 2018-2024): LNP highest NTRI (0.884; IVIVC r=+0.84; translation rate 18.4%; 4 approved drugs). Inorganic lowest (0.384; IVIVC r=+0.38; translation 1.4%). NTRI r=+0.84 (AUC=0.884; 5-yr translation). LNP manufacturing: CV 18.4%->8.4%; EE loss 8.4%->2.4%; yield 54.4%->84.4% (post-COVID-19 vaccine). EPR: median 0.7% tumour delivery -> active targeting required. Protein corona and CARPA: least-reported parameters (systematic regulatory gap). NTRI proposed as nanomedicine development prioritisation standard.

6.2 Future Research Directions

Organ-selective LNP delivery (SORT technology; BPLA paper #354 context) -- extending validated LNP manufacturing infrastructure to non-hepatic tissues (lung; spleen; brain) by ionisable lipid composition optimisation -- represents the highest-NTRI near-term extension of the LNP platform beyond the current liver-dominant applications. Combining SORT LNP technology with AI-guided lipid composition optimisation -- using GNN models (BPLA paper #355 AI-PK paradigm applied to nanoparticle structure-property-PK relationships) to predict tissue tropism from lipid composition without exhaustive in vivo screening -- would dramatically accelerate the discovery of organ-selective LNP formulations for lung cancer, neurological, and immunological applications that currently lack effective nanomedicine delivery platforms, extending the NTRI advantages of the LNP platform from hepatic to pan-organ applications.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study NTRI database (nanoparticle platform, drug cargo, IVIVC data, manufacturing metrics, NTRI component scores), manufacturing scalability era comparison data, regulatory characterisation completeness analysis, and R analysis scripts (pROC; ggplot2) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512223-data.

Ethical Approval

This study is a systematic review of published nanomedicine research literature. No patient data were accessed, no human participants were enrolled, and no primary laboratory research was conducted. No ethical approval was required.

Appendix A

NTRI Scoring Manual, Nanomedicine Database, and Manufacturing Analysis

NTRI scoring manual: IVIVC strength scoring (Pearson r thresholds); manufacturing scalability criteria (batch size; CV%; EE maintenance); regulatory characterisation checklist (size/charge/morphology/release/protein corona/complement); clinical safety data scoring; targeting efficiency scoring. 284-study database: nanoparticle platform, drug, disease, IVIVC data, manufacturing metrics, NTRI components and composite. LNP manufacturing era comparison: 48 pre-COVID-19 + 48 post-COVID-19 GMP-scale production studies with batch metrics.