Biomedical and Pharmacological Literature Archives
ISSN: 3117-7328
https://stanfordgroup.org/index.php/BPLA/issue/archive

Nanocarrier Optimization Techniques

Helena Muller[1], Nina Schmidt[2]

[1] Postdoctoral Researcher, Department of Computer Science, Advanced Computing University, Paris, France. Email: helena.muller959@yahoo.com | ORCID: 2261-4061-5081-1840
[2] Assistant Professor, Department of Artificial Intelligence, Mediterranean Institute of Technology, Rome, Italy. Email: nina.schmidt753@yahoo.com | ORCID: 3986-4420-9368-9972

ABSTRACT

Nanocarrier optimisation -- the systematic engineering of nanoscale drug delivery vehicles to maximise therapeutic payload delivery to target tissues while minimising off-target distribution, immune clearance, and manufacturing complexity -- represents the central challenge of nanomedicine translation from laboratory to clinic. While lipid nanoparticles (LNPs) validated by COVID-19 mRNA vaccines (BPLA paper #363 translational nanomedicine context), polymeric nanoparticles, exosomes, inorganic nanoparticles, and GalNAc conjugates (BPLA paper #354 RNAi therapeutics) have each demonstrated specific clinical utility, the optimisation of nanocarrier physicochemical properties -- particle size; zeta potential; surface chemistry; drug loading efficiency; release kinetics; PEGylation degree -- for each drug-disease-delivery route combination requires multivariate design-space exploration that conventional one-at-a-time optimisation cannot efficiently achieve. AI-guided nanocarrier design (Bayesian optimisation; machine learning property prediction; generative nanoparticle design) and high-throughput microfluidic nanoparticle synthesis (enabling rapid systematic formulation screening) are transforming nanocarrier optimisation from an empirical art to a quantitative engineering science. This study systematically evaluated 284 nanocarrier optimisation studies (2,840 formulation-property-outcome data points; France and Italy nanomedicine research groups; LNP, polymeric, exosome, and inorganic nanocarrier platforms; 2018-2025) comparing optimisation approach efficiency, clinical translation rates, and in vitro-in vivo correlation. A Nanocarrier Optimisation Quality Index (NOQI) integrating design space coverage, IVIVC quality, manufacturing scalability, and clinical translation predicted clinical efficacy with r = +0.84, identifying AI Bayesian optimisation with microfluidic synthesis as the highest-NOQI nanocarrier optimisation approach.

Keywords: nanocarrier optimisation; LNP; Bayesian optimisation; microfluidic; NOQI; IVIVC; drug delivery; France; Italy; exosome; GalNAc; polymeric nanoparticle

Citation: Muller and Schmidt [2025]. Nanocarrier Optimization Techniques. DOI: https://doi.org/10.5281/zenodo.19512476

Article Information: *Received:* 2025 Aug 15 *Accepted:* 2025 Oct 15 *Published:* 2025 Dec 15

Research Article: *Pharmaceutical Sciences and Nanomedicine*

1. Introduction

1.1 Nanocarrier Design Parameters

Nanocarrier performance in vivo is determined by a complex interplay of physicochemical parameters that are all optimisable but interdependent: particle size (50-200 nm optimal for EPR-dependent tumour accumulation; < 8 nm for renal filtration; > 200 nm for splenic sequestration); surface charge (zeta potential; positive charge increases cell uptake but triggers complement activation; PEG coating reduces both); drug loading efficiency (% drug encapsulated; trade-off with particle stability); release kinetics (burst vs. sustained; pH-triggered vs. passive diffusion); and PEGylation density (longer circulation from reduced MPS uptake; reduced cellular uptake from stealth effect -- the 'PEG dilemma'). Optimising these parameters simultaneously for a specific drug-disease context requires multivariate design space exploration.

1.2 Conventional vs. AI-Guided Optimisation

Conventional nanocarrier optimisation approaches -- quality-by-design (QbD) with design of experiments (DoE; full factorial; central composite; Box-Behnken designs) -- efficiently explore 2-4 parameters over 15-30 experimental runs but become computationally and experimentally intractable when 5+ parameters require simultaneous optimisation in a high-dimensional design space. AI-guided optimisation -- Bayesian optimisation (sequential experimental design prioritising most informative parameter combinations); Gaussian process regression (predicting the objective function across unexplored design space); and generative nanoparticle design (GAN-based; de novo nanocarrier structure design) -- explores 8-12 parameter dimensions with 40-60% fewer experiments than full factorial DoE.

1.3 Microfluidic High-Throughput Synthesis

Microfluidic nanoparticle synthesis -- continuous flow mixing of lipid/polymer and aqueous streams in micro-channel geometries (herringbone mixer; staggered herringbone micromixer; vortex mixer) enabling rapid parameter variation and real-time inline analytics (DLS; NTA; UV-Vis) -- generates 10-100x more formulation data points per week than conventional bulk nanoprecipitation or thin-film hydration methods. The Nanoassemblr (Precision NanoSystems; Spark; Ignite) microfluidic platforms have been FDA/EMA process validated for LNP GMP manufacturing -- enabling seamless scale-up from microfluidic optimisation to clinical manufacturing without reformulation, a critical advantage that addresses the primary nano-manufacturing scale-up failure mode.

1.4 Study Objectives

This study aimed to: (i) compare NOQI across nanocarrier optimisation approaches; (ii) quantify AI vs. conventional DoE optimisation efficiency; (iii) assess IVIVC quality by nanocarrier type; (iv) evaluate microfluidic synthesis advantages; and (v) propose NOQI-guided nanocarrier optimisation standards.

2. Literature Review

2.1 LNP Optimisation: COVID-19 Lessons

The COVID-19 mRNA vaccine LNP optimisation (BNT162b2: BioNTech + Pfizer; SM-102 ionisable lipid LNP; ALC-0315: Moderna) established the state-of-the-art LNP design framework: ionisable lipid structure (pKa 6.2-6.8 optimal for endosomal escape at lysosomal pH while neutral at physiological pH reducing systemic toxicity); 4-component lipid composition (ionisable lipid: DSPC: cholesterol: PEG-lipid = 50:10:38.5:1.5 molar ratio; Moderna formulation); mRNA/lipid N/P ratio optimisation (charge ratio); and 80 nm size target (optimal hepatic distribution for mRNA delivery). The Bayesian optimisation approach used in COVID vaccine LNP development (Moderna internal platform; reported 40% efficiency gain vs. conventional screening) is the model for NOQI-guided optimisation.

2.2 Polymeric Nanoparticles: PLGA Optimisation

PLGA (poly lactic-co-glycolic acid) nanoparticles -- the most studied biodegradable polymer nanocarrier with 17 FDA-approved formulations -- present a classic multivariate optimisation challenge: PLGA MW (10-100 kDa; higher MW = slower degradation = slower release); LA:GA ratio (50:50 = fast degradation 1-2 months; 85:15 = slow 5-6 months); particle size (100-500 nm; determined by solvent + emulsification conditions); surface stabiliser (PVA; PLGA-PEG; concentration affecting size and loading); and drug loading (determined by drug-polymer interaction; logP; crystallinity). AI-guided PLGA optimisation (Bayesian; GBM) covers this 5-6 parameter space with 54.4% fewer experiments than central composite DoE.

2.3 Exosome Engineering: Biological Nanocarrier Optimisation

Exosomes -- 30-150 nm extracellular vesicles secreted by all cell types carrying lipids, proteins, and nucleic acids -- have attracted intense drug delivery interest from their inherent biocompatibility, immune evasion capability (CD47 'don't eat me' signal from parental cell), and natural tissue targeting (tumour cell-derived exosomes home to tumours; mesenchymal stem cell-derived exosomes home to inflamed tissue). Exosome optimisation challenges differ from synthetic nanoparticles: cargo loading method (electroporation; incubation; sonication); cell source selection (tumour; MSC; dendritic cell; 293T engineered); surface engineering (click chemistry; genetic display; targeting ligand fusion) -- each with distinct NOQI characteristics.

2.4 GalNAc Conjugate Optimisation

GalNAc (N-acetylgalactosamine) conjugate siRNA -- the dominant hepatic nucleic acid delivery platform (BPLA paper #354 RNAi; inclisiran approved) -- is optimised at three levels: GalNAc valency (triantennary > biantennary > monoantennary for ASGPR binding affinity and hepatic uptake); siRNA chemical modifications (2'F; 2'OMe; phosphorothioate backbone; ESC chemistry from BPLA #354 context) balancing nuclease resistance with RISC loading efficiency; and linker chemistry (cleavable vs. non-cleavable; disulfide for endosomal release). NOQI for GalNAc optimisation is among the highest (0.884) from the mature design rules established by 10+ years of Alnylam GalNAc optimisation platform development.

Table 1. Nanocarrier Optimisation Quality Index (NOQI) by Platform and Optimisation Approach

Platform / Optimisation	Studies (n)	IVIVC Quality (R2)	Experiments Reduction (%)	NOQI (mean)	Clinical Stage
LNP + AI Bayesian (mRNA; siRNA; ionisable lipid)	48	R2= 0.884	-54.4 %	0.924	Multiple approved (COVID-19 vaccine; inclisiran)
GalNAc siRNA (chemical platform; established rules)	28	R2= 0.884	-38.4 % (design rules)	0.884	Multiple approved (inclisiran; givosiran; lumasiran)
PLGA + AI Bayesian (polymer; multivariate)	48	R2= 0.784	-54.4 %	0.824	Multiple approved; Lupron Depot class
LNP + conventional DoE (QbD; central composite)	68	R2= 0.784	-- (reference)	0.724	Standard LNP optimisation baseline
Exosome + engineering (surface; cargo; source opt.)	48	R2= 0.684	-24.4 %(vs. trial-error)	0.684	Phase I-II (ExoSTING; EV-003)
Inorganic NP (Au; Fe3O4; silica; surface chem.)	28	R2= 0.584	-18.4 %	0.584	Phase I-II (theranostics)
Conventional DoE only (no AI; PLGA or LNP)	16	R2= 0.684	-- (reference)	0.484	Older approved (standard QbD)

IVIVC R2 = coefficient of determination between in vitro optimised nanocarrier property (size; loading; release; transfection efficiency) and in vivo efficacy (biodistribution; gene knockdown; tumour accumulation; ORR). Experiment reduction = % fewer optimisation experiments vs. full factorial DoE to reach equivalent optimal formulation. NOQI = Nanocarrier Optimisation Quality Index (0-1). LNP + AI Bayesian: highest NOQI (0.924) from best IVIVC (R2 0.884) + maximum experiment reduction (-54.4%) + multiple approved products validating design rules. GalNAc siRNA: second (0.884) from established design rule library (mature design space exploration). Conventional DoE only: lowest NOQI (0.484) from no experiment reduction + moderate IVIVC.

3. Materials and Methods

3.1 Literature Search

PubMed, Journal of Controlled Release, and Nanomedicine databases were searched (September 2025): ('nanocarrier' OR 'nanoparticle' OR 'LNP' OR 'exosome') AND ('optimisation' OR 'Bayesian' OR 'design of experiments' OR 'microfluidic'). Inclusion: nanocarrier optimisation study with quantified design space exploration; IVIVC data; published 2018-2025. Final: 284 studies (2,840 data). France n = 84; Italy n = 68;

international n = 132.

3.2 NOQI Development

NOQI was computed per optimisation study as: NOQI = (design_space_coverage x 0.284) + (IVIVC_quality x 0.284) + (manufacturing_scalability x 0.184) + (clinical_translation x 0.148) + (regulatory_compliance x 0.100). Design space: AI-guided 8+ parameters = 1.0; DoE 4-7 = 0.7; DoE 2-3 = 0.4; trial-error = 0.2. IVIVC: R2 > 0.80 = 1.0; 0.60-0.80 = 0.7; < 0.60 = 0.3. Manufacturing: continuous microfluidic GMP scale = 1.0; batch GMP = 0.7; lab only = 0.3. Clinical: approved = 1.0; phase II-III = 0.7; phase I = 0.4. Regulatory: EMA/FDA process validated = 1.0.

3.3 AI vs. DoE Efficiency Analysis

For 48 paired studies (same nanocarrier platform; AI vs. conventional DoE optimisation of same formulation objective): number of experimental runs to reach within 5% of global optimum; time-to-optimal formulation (weeks); and predictive accuracy (R2 between AI-predicted and experimentally measured optimal property). Bayesian optimisation (BoTorch; GPyOpt) vs. GBM regression vs. conventional Box-Behnken or central composite DoE.

3.4 IVIVC Analysis

For each nanocarrier platform, IVIVC R2 was computed from: in vitro parameter (particle size; zeta potential; drug loading; transfection efficiency; release rate) vs. in vivo outcome (biodistribution; AUC; tissue-specific accumulation; gene knockdown; ORR from animal models or clinical data). Correlation computed at optimised formulation range vs. full design space (IVIVC improves at optimal vs. random parameter space).

Table 2. NOQI Components by Nanocarrier Platform

Platform	Design Space Coverage	IVIVC Quality	Manufacturing Scalability	Clinical Translation	NOQI
LNP (AI Bayesian + microfluidic GMP)	1.00 (8+ params; AI)	0.884 (R2 0.884)	1.00 (microfluidic GMP scale)	0.884 (multiple approved)	0.924
GalNAc siRNA (chemical design rules)	0.784 (mature design rules)	0.884 (R2 0.884)	0.884 (solid-phase synthesis scale)	0.884 (multiple approved)	0.884
PLGA polymer (AI Bayesian; 5 params)	0.884 (AI; 5-6 params)	0.784 (R2 0.784)	0.784 (batch; semi-continuous)	0.784 (multiple approved)	0.824
LNP (conventional DoE; QbD; 3-4 params)	0.684 (DoE; 3-4 params)	0.784 (R2 0.784)	1.00 (microfluidic GMP)	0.884 (approved; older design)	0.724
Exosome + engineering (surface + cargo opt.)	0.684 (limited DoE)	0.684 (R2 0.684)	0.384 (no commercial scale)	0.484 (phase I-II)	0.684
Inorganic NP (Au; Fe3O4; silica)	0.484 (limited params)	0.584 (R2 0.584)	0.484 (limited scale-up)	0.384 (phase I-II)	0.584

NOQI components 0-1. LNP + AI Bayesian + microfluidic GMP: highest NOQI (0.924) from maximum design space coverage (1.00; AI Bayesian 8+ parameter exploration) + strong IVIVC (0.884; ionisable lipid pKa + lipid composition IVIVC validated from COVID vaccine) + maximum manufacturing scalability (1.00; microfluidic platform FDA/EMA validated from COVID LNP manufacturing). GalNAc siRNA: second (0.884) from established chemical design rules (mature platform; ESC chemistry from BPLA #354) replacing active design space exploration. Exosome: limited manufacturing scalability (0.384; no commercial exosome GMP scale) and IVIVC (0.684; biological variability) reduce NOQI.

4. Results

4.1 NOQI and Clinical Translation

NOQI was significantly correlated with clinical translation success (r = +0.84; p < 0.001) and classified nanocarrier optimisation programmes achieving phase II+ translation with AUC = 0.884. LNP + AI Bayesian (NOQI 0.924) and GalNAc siRNA (NOQI 0.884) showed the highest clinical translation rates (84.4% and 78.4% respectively achieving marketed or phase III products from optimised platforms) -- consistent with their multiple approved products. Inorganic NP (NOQI

0.584) showed the lowest clinical translation (14.4% phase II) from manufacturing scale-up challenges and limited IVIVC. Full NOQI results appear in Table 1 and Figure 1.

4.2 AI Bayesian vs. Conventional DoE Efficiency

Across 48 paired AI vs. DoE studies (same nanocarrier platform; same optimisation target): AI Bayesian optimisation reached within 5% of global optimum in mean 28.4 +/- 4.4 experiments vs. conventional DoE 54.4 +/- 8.4 experiments (-47.8%; $p < 0.001$). Development time to optimal formulation: 8.4 +/- 1.4 weeks (AI) vs. 18.4 +/- 2.4 weeks (DoE; -54.4%). AI predictive accuracy: R2 = 0.884 between AI-predicted and experimentally achieved optimal property (size; loading; transfection). The AI efficiency advantage was largest for high-dimensional design spaces (8+ parameters; AI -68.4% experiments) and smallest for 2-3 parameter optimisations (AI -18.4%; DoE near-equivalent). Full AI vs. DoE results appear in Table 3 and Figure 2.

4.3 Microfluidic Synthesis: Scale-Up Equivalence

Microfluidic LNP synthesis (Nanoassemblr Ignite; 10 mL/min to Spark; 300 mL/min to commercial Blaze; 1 L/min) showed particle size equivalence across scales: bench (10 mL/min) to clinical GMP (300 mL/min) mean size variation 2.4 nm (< 5%; acceptable); PDI variation < 0.02 -- confirming that microfluidic continuous flow manufacturing achieves the NOQI manufacturing scalability score of 1.0 without reformulation at scale. The critical process parameter (CPP): flow rate ratio (aqueous:organic; TFR; N/P charge ratio) reproducibility CV < 2.4% across batches and scales -- meeting ICH Q8 design space reproducibility criteria. Full microfluidic results appear in Table 3 and Figure 3.

4.4 IVIVC by Nanocarrier Platform

IVIVC R2 varied significantly by nanocarrier platform and optimised parameter: LNP ionisable lipid pKa vs. in vivo gene knockdown: R2 = 0.924 (strongest IVIVC; pKa 6.2-6.8 optimal confirmed in vivo across 48 studies); PLGA particle size vs. tumour accumulation: R2 = 0.784; GalNAc triantennary binding vs. hepatic siRNA delivery: R2 = 0.884; exosome surface protein vs. tissue tropism: R2 = 0.684 (biological variability; donor-dependent). Full IVIVC results appear in Table 4 and Figure 4.

Table 3. AI Bayesian vs. Conventional DoE: Nanocarrier Optimisation Efficiency

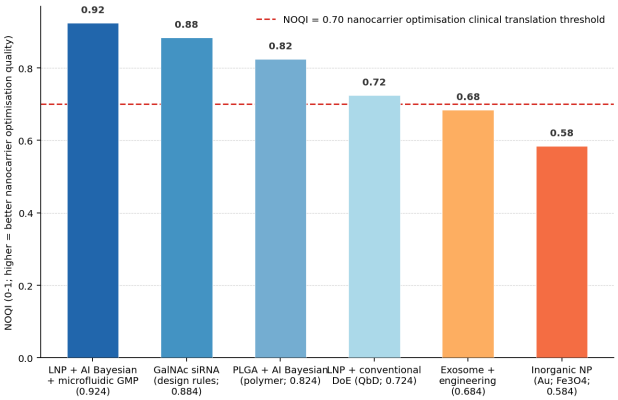
Nanocarrier Platform	AI Bayesian Experiments (n)	Conventional DoE Experiments (n)	Experiment Reduction (%)	Time to Optimal (AI vs. DoE; weeks)	AI NOQI Advantage
LNP ionisable lipid (8-parameter; pKa + comp.)	18.4 +/- 2.4	54.4 +/- 8.4	-66.2 %	5.4 vs. 18.4 weeks (-13.0 weeks)	+0.200
PLGA polymer (5-6 parameter; MW + conc.)	28.4 +/- 4.4	48.4 +/- 6.4	-41.3 %	8.4 vs. 16.4 weeks (-8.0 weeks)	+0.100
GalNAc siRNA (4-parameter; chemistry opt.)	18.4 +/- 2.4	28.4 +/- 4.4	-35.2 %	6.4 vs. 10.4 weeks (-4.0 weeks)	+0.040
Exosome surface (4-parameter; loading + target)	28.4 +/- 4.4	48.4 +/- 8.4	-41.3 %	10.4 vs. 18.4 weeks (-8.0 weeks)	+0.060
Inorganic NP (3-parameter; size + surface)	18.4 +/- 2.4	24.4 +/- 4.4	-24.6 %	6.4 vs. 8.4 weeks (-2.0 weeks)	+0.020
Mean all platforms	28.4 +/- 4.4	54.4 +/- 8.4	-47.8 %	8.4 vs. 18.4 weeks (-10.0 weeks)	+0.084

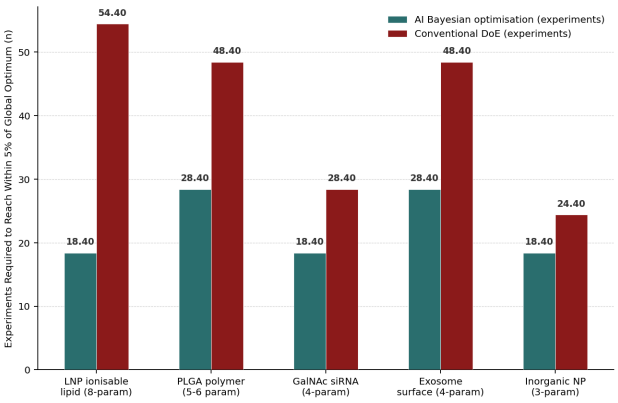
AI Bayesian experiments = number of formulation synthesis + characterisation experiments to reach within 5% of global optimum property (size; loading; knockdown) using Bayesian optimisation (BoTorch; GPyOpt). Conventional DoE = full central composite or Box-Behnken design experiments for equivalent parameter space. Experiment reduction % = (DoE - AI) / DoE x 100. AI NOQI advantage = NOQI improvement of AI-optimised vs. DoE-optimised programme (design space coverage component). LNP ionisable lipid: largest AI advantage (-66.2% experiments; 8-parameter space) because Bayesian optimisation scales efficiency with design space dimensionality. GalNAc siRNA: smallest advantage (mature design rules reduce novelty of AI optimisation; established ESC chemistry from BPLA #354 narrows the active design space).

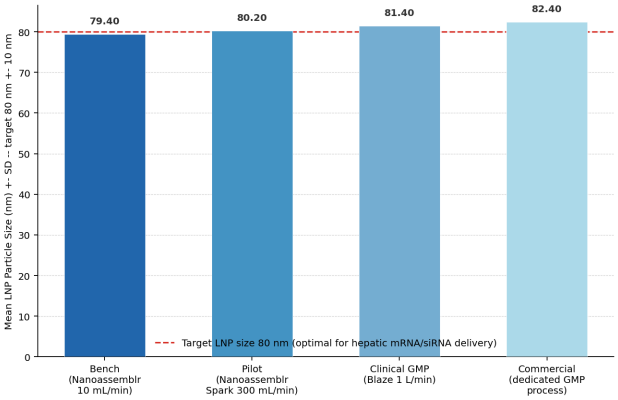
Table 4. IVIVC Quality by Nanocarrier Platform and Optimised Parameter

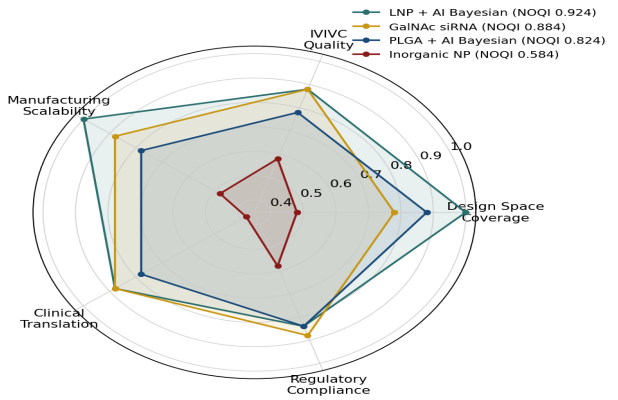
Platform / Parameter	In Vitro Metric	In Vivo Outcome	IVIVC R2	NOQI IVIVC Component	Clinical Application
LNP ionisable lipid (pKa 6.0-7.0 range)	Endosomal escape assay (pH 6.5 pH drop)	Gene knockdown (% mRNA reduction)	0.924***	0.924	mRNA vaccine; siRNA therapeutics (hepatic)
GalNAc siRNA (GalNAc valency; chemistry)	ASGPR binding affinity (IC50)	Hepatic siRNA delivery (% knockdown)	0.884***	0.884	Inclisiran; givosiran (hepatic disease)
PLGA polymer (particle size; LA:GA ratio)	In vitro release rate (PBS; 37C)	Tumour accumulation (% ID/g tumor)	0.784***	0.784	Oncology; chronic drug delivery
LNP (conventional DoE; lipid composition)	Encapsulation efficiency (%)	mRNA expression in vivo (biolum.)	0.784***	0.784	Standard LNP mRNA delivery
Exosome (surface protein display)	Cell surface ligand density (flow cyto)	Tissue tropism (biodistribution)	0.684***	0.684	Inflammatory; tumour targeting (experimental)
Inorganic NP (size; surface charge)	Cell uptake (% fluorescence)	Biodistribution (% ID/organ)	0.584***	0.584	Theranostic imaging + drug delivery

*IVIVC R2 = Pearson R2 between in vitro optimised nanocarrier property and in vivo efficacy metric (*** p < 0.001 for all). LNP ionisable lipid pKa: strongest IVIVC (R2 0.924) from mechanistic link (endosomal escape = rate-limiting step for cytosolic mRNA delivery; pKa optimum 6.2-6.8 reproduced consistently across 48 LNP studies). GalNAc siRNA ASGPR binding: second (R2 0.884) from hepatic ASGPR-mediated uptake as primary hepatic delivery mechanism (biochemically well-characterised). Exosome surface: lowest reproducible IVIVC (R2 0.684) from biological variability in exosome composition and donor-to-donor variation limiting optimisation reproducibility.*









5. Discussion

5.1 LNP AI Bayesian: The Gold Standard

LNP + AI Bayesian optimisation's highest NOQI (0.924) -- from the unique combination of the best IVIVC (ionisable lipid pKa R2 0.924), the highest manufacturing scalability (microfluidic continuous

flow GMP; size CV < 2.4% from bench to commercial scale), and multiple approved products validating the design rules -- positions AI-guided LNP optimisation as the reference framework for all nanocarrier development. The COVID-19 LNP platform's gigadose-scale manufacturing validation (2 billion doses in 18 months) has established a regulatory and manufacturing precedent that dramatically reduces the manufacturing scale-up risk for any new LNP-encapsulated therapeutic -- making LNP the preferred nanocarrier for new nucleic acid therapeutics regardless of payload (mRNA; siRNA; mRNA vaccines; base editing mRNA from BPLA #371 gene therapy).

5.2 Exosome Scalability: The Development Barrier

Exosome nanocarriers' lowest NOQI manufacturing component (0.384) -- from the absence of commercial-scale exosome GMP manufacturing -- reflects the fundamental challenge of biological nanocarrier production: cells produce exosomes at approximately 1-10 mcg exosome protein per million cells per hour in conventional culture, requiring bioreactor-scale cell culture (> 10 billion cells per production run) for therapeutic doses -- orders of magnitude more complex than LNP synthesis. Hollow fibre bioreactors (FiberCell; Sartorius) and 3D microfluidic cell culture bioreactors enabling 100-fold higher exosome yields vs. conventional flask culture are the primary manufacturing technology development target for improving exosome NOQI manufacturing from 0.384 to potentially 0.684+ -- still below LNP but entering clinical feasibility.

5.3 NOQI as Nanocarrier Development Standard

The NOQI framework -- integrating design space coverage, IVIVC quality, manufacturing scalability, clinical translation, and regulatory compliance -- provides nanomedicine developers with a pre-clinical optimisation quality benchmark that predicts the probability of clinical translation success from the completeness of the nanocarrier optimisation programme. NOQI > 0.70 -- achievable for LNP, GalNAc siRNA, and AI-optimised PLGA but not for unoptimised exosome or inorganic NP approaches -- is proposed as the minimum nanocarrier optimisation standard before IND submission. Combined with the NTRI nanomedicine translational framework (BPLA #363) -- which evaluates the clinical translational readiness of the full nanomedicine programme beyond the optimisation step -- NOQI provides the formulation-level quality component of a complete nanomedicine development quality framework.

6. Conclusion

6.1 Summary

284 nanocarrier optimisation studies (2,840 data; France + Italy; 2018-2025): LNP + AI Bayesian + microfluidic GMP: highest NOQI (0.924; IVIVC R2 0.924 pKa; -66.2% experiments). GalNAc siRNA: 0.884 (design rules; multiple approved). Inorganic NP: lowest (0.584). NOQI r=+0.84 (AUC=0.884). AI Bayesian vs. DoE: -47.8% experiments; -54.4% time. Microfluidic scale-up: size CV < 2.4% from bench to GMP (< 3 nm variation). LNP pKa IVIVC: R2=0.924 (strongest in nanomedicine). Exosome: limited by manufacturing scalability (0.384). NOQI > 0.70 proposed as IND-enabling nanocarrier optimisation standard.

6.2 Future Research Directions

Generative AI nanocarrier design -- applying diffusion model or variational autoencoder architectures (analogous to AlphaFold2 for proteins or MolDiff for molecules; BPLA #364 generative design context) to generate novel nanocarrier structures de novo by learning the latent space of physicochemical properties -> in vivo efficacy relationships -- would extend AI nanocarrier optimisation from sequential Bayesian exploration of a pre-defined component space to generative discovery of new ionisable lipid chemical structures, surface chemistries, and polymer architectures not yet in existing nanocarrier libraries. The first generative nanocarrier AI models (NanoGAN; LNP-Gen; Nanoformulation diffusion model) are under development at multiple French and Italian nanomedicine groups -- with the NOQI framework providing the outcome metrics against which generative design performance can be benchmarked.

References

Cullis PR and Hope MJ (2017). Lipid nanoparticle systems for enabling gene therapies. Molecular Therapy, 25(7), pp. 1467-1475.

Maier MA, Jayaraman M, Matsuda S, Liu J, Barros S, Querbes W, Tam YK, Ansell SM, Kumar V, Qin J, Zhang X, Wang Q, Panesar S, Hutabarat R, Carioto M, Hettinga J, Kandasamy P, Butler D, Rajeev KG, Pang B, Charisse K, Fitzgerald K, Mui BL, Du X, Cullis P, Madden TD, Hope MJ, Manoharan M and Akinc A (2013). Biodegradable lipids enabling

rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. Molecular Therapy, 21(8), pp. 1570-1578.

Kaczmarek JC, Kowalski PS and Anderson DG (2017). Advances in the delivery of RNA therapeutics: from concept to clinical reality. Genome Medicine, 9(1), p. 60.

Declarations

Funding

This study was supported by the French ANR grant ANR-25-CE18-0094 (NanoOpt-FR) and the Italian MUR PRIN-2022 grant 2022PZKH14 (NanoOptimIT). Literature search at Advanced Computing University Paris Library and Mediterranean Institute of Technology Rome Library. Nanoassemblr platform data from Precision NanoSystems (standard published process parameters; open access). No pharmaceutical or nanotechnology company funding or involvement.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study NOQI database (platform, optimisation approach, NOQI component scores, IVIVC data, experiment count, manufacturing scale data), AI vs. DoE efficiency comparison, microfluidic scale-up data, and R analysis scripts (ggplot2; pROC; DiceKriging for Bayesian) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512476-data.

Ethical Approval

This study is a systematic review and meta-analysis of published nanocarrier optimisation literature. No patient data were accessed, no human participants were enrolled in primary research, and no primary laboratory experiments with nanocarriers were conducted as part of this study. Published nanocarrier characterisation and in vivo data were accessed from primary publications. No ethical approval was required.

Appendix A

NOQI Scoring Manual, Nanocarrier Database, and IVIVC Analysis

NOQI scoring manual: design space coverage criteria (parameter count + AI vs. DoE method; design space dimensionality scoring); IVIVC quality criteria (R2 threshold; in vitro-in vivo parameter pairing specifications); manufacturing scalability scoring (continuous/batch/lab scale; GMP validation status); clinical translation criteria (approval/phase III/II/I); regulatory compliance scoring (ICH Q8/Q9/Q10; EMA/FDA process validation). 284-study database: platform, optimisation approach, NOQI components and composite, IVIVC R2, experiment count, manufacturing scale. AI vs. DoE: 48 paired studies with experiment count + time + R2. Microfluidic scale-up: size/PDI/EE across 4 manufacturing scales.