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Targeted Drug Delivery Using Lipid Nanoparticles for Solid Tumor Therapy

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Abstract

Lipid nanoparticles -- conventional and PEGylated liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and, more recently, ionizable-lipid nanoparticles engineered for nucleic acid cargo -- have been developed over four decades as vehicles for improving the therapeutic index of solid tumor drug delivery. This article synthesizes that literature around five themes: the formulation chemistry distinguishing the major lipid nanoparticle platforms; passive tumor targeting via the enhanced permeability and retention (EPR) effect and the substantial evidence that has complicated its reliability across human tumors; active targeting strategies that improve cellular uptake after passive extravasation rather than substituting for it; the clinical translation record, from PEGylated liposomal doxorubicin's reduced cardiotoxicity to nanoliposomal irinotecan's statistically significant survival benefit in metastatic pancreatic cancer; and the newer extension of ionizable-lipid nanoparticles into nucleic acid and personalized cancer vaccine delivery. Read together, the literature supports lipid nanoparticles as a genuinely useful and clinically validated solid tumor therapy platform, while falling short of the tumor-selective delivery mechanism the field's early framing of the EPR effect once implied, leaving tumor penetration, EPR-effect heterogeneity, nanoparticle immunogenicity on repeat dosing, and extrahepatic targeting of nucleic acid payloads as open engineering problems for the next generation of formulations.

Keywords: lipid nanoparticles; targeted drug delivery; solid tumor therapy; enhanced permeability and retention effect; liposomal chemotherapy

1. Introduction

Solid tumors present a delivery problem that conventional cytotoxic chemotherapy has never really solved: the drug that kills a cancer cell in a dish is, almost without exception, the same drug that damages a bone marrow progenitor, a gut epithelial cell, or a cardiomyocyte, because systemic small-molecule chemotherapy cannot tell the difference between a tumor and the healthy tissue surrounding it. Lipid nanoparticles were, from the earliest liposomal formulations of the 1990s onward, conceived as a partial answer to that problem — a way to wrap a cytotoxic payload in a biocompatible shell that changes its pharmacokinetics, shields healthy tissue from direct drug exposure during circulation, and, ideally, concentrates the payload preferentially where the tumor is. Four decades of work on that idea has produced a genuinely diverse family of platforms: conventional and PEGylated liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and, more recently, the ionizable-lipid nanoparticle (LNP) systems originally engineered for RNA interference and now central to mRNA vaccine and gene-editing delivery. All of them share a common architectural logic — a lipid bilayer or lipid matrix enclosing or complexing a therapeutic payload — while differing substantially in structure, payload compatibility, and targeting strategy.

This article synthesizes that literature specifically as it bears on targeted drug delivery for solid tumor therapy. We trace the field from its passive-targeting foundations, through the active-targeting strategies developed to compensate for the passive mechanism's well-documented unreliability, to the clinically approved lipid nanoparticle therapeutics now in routine oncology use, and finally to the newer nucleic-acid and vaccine delivery applications that are reshaping what "lipid nanoparticle for cancer" even means. Throughout, we try to be precise about what the literature actually supports rather than what the field's early enthusiasm once promised: the enhanced permeability and retention (EPR) effect that motivated passive tumor targeting for three decades has, in the last ten years, been subjected to serious empirical scrutiny, and much of what looked like a settled mechanism now looks more like a heterogeneous, patient- and tumor-dependent phenomenon that nanomedicine researchers are still working out how to exploit reliably [1,2].

We are not reporting new experimental results. This is a literature synthesis, organized around five themes: the formulation chemistry that distinguishes the major lipid nanoparticle platforms; the EPR effect as the historical basis for passive tumor targeting and the evidence that has complicated it; active targeting strategies that attach tumor-selective ligands to the nanoparticle surface; the clinical translation record of lipid nanoparticle oncology therapeutics, from liposomal anthracyclines to nanoliposomal irinotecan; and the newer wave of nucleic-acid and vaccine applications that are extending lipid nanoparticle technology into solid tumor immunotherapy. We close with an honest accounting of what remains unresolved — tumor penetration beyond the perivascular space, the unpredictability of EPR-effect magnitude across patients, and the gap between mouse-model efficacy and the more modest gains typically seen in human trials.

2. Lipid Nanoparticle Platforms and Formulation Chemistry

The oldest and best-characterized lipid-based drug carriers are liposomes: self-assembled spherical vesicles in which one or more phospholipid bilayers enclose an aqueous core, first developed as drug carriers in the 1970s and matured into a clinically viable oncology platform by the 1990s. A hydrophilic drug can be loaded into the aqueous interior, while a lipophilic drug partitions into the bilayer itself, and the resulting particle's surface chemistry — most consequentially, the presence or absence of a polyethylene glycol (PEG) coating — determines how long it survives in circulation before being cleared by the mononuclear phagocyte system. Allen and Cullis's review of the field traces this evolution in detail: uncoated, "conventional" liposomes are opsonized and cleared within hours, while PEGylated ("stealth") liposomes, by sterically hindering opsonin binding, can circulate for a day or more, which is the pharmacokinetic property that makes tumor accumulation via passive mechanisms possible at all [3]. Doxil, PEGylated liposomal doxorubicin, was the first nanomedicine formulation approved by the FDA (in 1995) and remains the field's central case study; Barenholz's detailed account of its development explains that its clinical advantages over free doxorubicin — reduced cardiotoxicity in particular — stem directly from the liposome's ability to keep the drug sequestered in a comparatively inert, slowly-releasing carrier while it circulates, rather than

from any dramatic increase in tumor drug concentration relative to free drug [4].

Table 1: Comparison of the four major lipid nanoparticle platform families used in solid tumor drug delivery, their typical structure, payload compatibility, and a representative clinically relevant example drawn from the cited formulation literature [3,5,6,9].

Platform	Core Structure	Typical Payload	Representative Example
PEGylated liposome	Phospholipid bilayer enclosing an aqueous core, PEG-coated for long circulation	Hydrophilic (core) or lipophilic (bilayer) small molecules	Doxil / Caelyx, PEGylated liposomal doxorubicin [4]
Solid lipid nanoparticle (SLN)	Solid physiological lipid matrix stabilized by a surfactant shell	Lipophilic small molecules with moderate loading capacity	Reviewed as a scalable, solvent-free carrier platform [5]
Nanostructured lipid carrier (NLC)	Blended solid/liquid lipid matrix with an imperfect crystal lattice	Lipophilic small molecules with improved loading vs SLN	Reviewed as a second-generation SLN successor [6]
Ionizable-lipid nanoparticle (LNP)	Four-component (ionizable lipid, helper phospholipid, cholesterol, PEG-lipid) electron-dense core	siRNA, mRNA, and other nucleic acid cargoes	Patisiran (Onpattro), the first FDA-approved siRNA drug [22]

Solid lipid nanoparticles emerged in the 1990s as an alternative that replaces the liposome's liquid bilayer with a solid lipid matrix — typically a physiological or physiologically-compatible lipid, such as a triglyceride or fatty acid ester, that is solid at body temperature — stabilized by a surfactant shell. Müller, Mäder, and Gohla's foundational review lays out the rationale: a solid matrix offers better protection of a labile payload from chemical degradation, more controllable and typically slower release kinetics than a liquid-core liposome, and formulation processes (high-pressure homogenization, microemulsion techniques) that are more readily scaled to industrial manufacture without organic solvents, at the cost of comparatively low drug-loading capacity and, in some formulations, drug expulsion during storage as the lipid matrix undergoes polymorphic transitions toward its more thermodynamically stable, lower-capacity crystal form [5]. Nanostructured lipid carriers (NLCs) were developed specifically to address that drug-expulsion problem: as Gordillo-Galeano and Mora-Huertas describe in their structural review, an NLC's matrix deliberately blends

solid and liquid lipids, producing a less perfectly ordered crystal lattice with more imperfections available to accommodate drug molecules, which improves loading capacity and long-term storage stability relative to first-generation SLNs while preserving most of their solvent-free, scalable manufacturing advantages [6].

A fourth platform, the ionizable-lipid nanoparticle (LNP), developed originally for small interfering RNA (siRNA) delivery and now the delivery vehicle behind two categories of approved nucleic-acid therapeutics, differs from the other three in a chemically consequential way: its core lipid is designed to be near-neutral at physiological pH (facilitating long circulation and low toxicity) but to become cationic at the acidic pH of an endosome, which promotes membrane destabilization and cytosolic release of the encapsulated nucleic acid cargo. Semple and colleagues' systematic structure-activity study of cationic and ionizable lipids for siRNA delivery, and Jayaraman and colleagues' follow-up optimization work identifying lipids with substantially improved potency for hepatic gene silencing, established the design rules — headgroup pKa, linker chemistry, and tail saturation, principally — that essentially all subsequent ionizable-lipid formulations, including the lipid (patisiran) that became the first FDA-approved siRNA drug and the lipids used in mRNA vaccine formulations, still build on [7,8]. Cullis and Hope's review situates this LNP platform architecturally: four functional lipid components — the ionizable lipid, a helper phospholipid, cholesterol, and a PEG-lipid — typically self-assemble via microfluidic mixing into a particle with an electron-dense, largely non-bilayer core, a structure now understood to be essential to its efficient endosomal escape mechanism and quite distinct from a classical liposome despite sharing the same broad lipid-nanoparticle label [9]. Hou, Zaks, Langer, and Dong's comprehensive review of LNP-based mRNA delivery extends this account to the mRNA vaccine platforms and traces how the same four-component design, tuned for a larger and structurally different nucleic acid cargo, underlies the COVID-19 mRNA vaccines and, increasingly, mRNA-based cancer therapeutics [10].

Table 1 summarizes these four platforms side by side. The distinctions matter directly for solid tumor therapy because they determine payload compatibility (small

hydrophilic or lipophilic drugs for liposomes and SLN/NLC platforms; nucleic acids for ionizable LNPs), release kinetics, and, as later sections discuss, how readily each platform can be surface-modified for active targeting without compromising the physicochemical properties that give it long circulation in the first place.

3. Passive Targeting and the Enhanced Permeability and Retention Effect

The theoretical basis for passive tumor targeting rests on a structural feature of tumor vasculature: solid tumors, to sustain their own growth, recruit blood vessels through angiogenesis that is disorganized, leaky, and structurally aberrant compared to normal vasculature, with wide endothelial fenestrations that permit extravasation of particles far larger than would cross healthy capillary walls, combined with poor lymphatic drainage within the tumor that allows extravasated macromolecules and nanoparticles to accumulate rather than being cleared. A long-circulating, appropriately sized nanoparticle should, on this logic, preferentially accumulate in tumor tissue simply by virtue of circulating long enough to exploit this leaky-vasculature-plus-poor-drainage combination — the enhanced permeability and retention (EPR) effect — without requiring any active targeting mechanism at all. This mechanism, more than any single formulation innovation, is what made PEGylated liposomal doxorubicin's clinical advantage plausible in the first place: a long-circulating carrier has more opportunities to extravasate into tumor tissue than a rapidly cleared one [4].

The EPR effect has, however, been subjected to serious re-evaluation over the past decade, and the modern nanomedicine literature is considerably more circumspect about it than the field was in the 1990s and 2000s. Wilhelm and colleagues' quantitative meta-analysis of the published nanoparticle-delivery literature, drawing on several hundred datasets spanning multiple nanoparticle types and tumor models, found that a median of only 0.7% of an administered nanoparticle dose is actually delivered to a solid tumor, a strikingly small figure that recontextualizes what "enhanced" delivery via the EPR effect actually achieves in absolute terms even when it is operating as intended [11]. Nichols and Bae's critical review goes further, arguing that the EPR effect, while real as a vascular phenomenon, has been systematically

over-generalized from the well-vascularized, rapidly-growing xenograft tumor models used in most preclinical nanomedicine studies to human tumors, which are frequently more heterogeneous, more poorly perfused in their cores, and considerably more variable in the degree of vascular leakiness they present, both between patients and between metastatic sites within the same patient [1]. Danhier's companion analysis is blunter still in its framing, noting that the gap between EPR-effect-driven preclinical efficacy and the comparatively modest survival benefits nanomedicine formulations have delivered in randomized clinical trials is large enough that the field needs additional targeting and tumor-microenvironment-modulating strategies rather than continuing to rely on EPR accumulation as a sufficient mechanism on its own [2]. Maeda's own retrospective assessment, from the group that originally proposed the EPR concept, largely concurs on the heterogeneity point while maintaining that the underlying mechanism remains sound in principle — the disagreement in the literature is less about whether EPR-mediated accumulation occurs at all than about how reliably and how strongly it occurs across the diversity of real human solid tumors [12]. Golombek and colleagues' review usefully reframes the resulting research agenda: rather than treating EPR as binary (present or absent), the field increasingly asks how it can be pharmacologically or physically enhanced — through vascular normalization strategies, local heating, or co-administered agents that transiently increase vascular permeability — to make an unreliable passive mechanism into a more dependable one [13].

Nanoparticle size interacts with this picture in a way that complicates simple size-based design rules. Cabral and colleagues' study of polymeric micelles of varying diameter found that tumor penetration and accumulation depend substantially on particle size relative to a given tumor's degree of vascular permeability, with smaller sub-100 nm particles penetrating poorly permeable tumors — the kind of stroma-rich, less leaky tumor that the EPR-skeptical literature argues is more representative of human disease than classic xenografts — more effectively than larger particles, even though larger particles can outperform smaller ones in highly permeable tumor models [14]. The practical implication for lipid nanoparticle design is that there is no single "optimal" size that maximizes EPR-mediated delivery across all

solid tumors; the right answer depends on a tumor's specific vascular phenotype, which is precisely the kind of patient-to-patient and tumor-to-tumor heterogeneity that undermines the simplicity of the original EPR concept.

4. Active Targeting Strategies for Solid Tumor Selectivity

Active targeting attaches a ligand to a lipid nanoparticle's surface — an antibody or antibody fragment, a peptide, a small molecule such as folate, or an aptamer — chosen to bind a receptor that is overexpressed on tumor cells relative to healthy tissue, with the goal of increasing cellular uptake and retention at the tumor site beyond what passive accumulation alone provides. It is worth being precise, following Kirpotin and colleagues' careful mechanistic study of anti-HER2 immunoliposomes, about what active targeting actually changes: their work found that antibody conjugation did not meaningfully increase the total amount of liposome that accumulated within tumor tissue relative to an equivalent untargeted, long-circulating liposome — that step is still governed predominantly by the EPR mechanism described above — but it did substantially increase the fraction of tumor-localized liposomes that were internalized into HER2-expressing tumor cells rather than remaining extracellular, and internalization correlates with therapeutic payload release and efficacy far more directly than extracellular accumulation does [15]. This distinction — active targeting as a cellular-uptake enhancer operating after passive extravasation, rather than as an independent tumor-homing mechanism competing with or substituting for the EPR effect — has become a fairly durable consensus position in the field and reframes how active-targeting ligands should be evaluated: not by whether they increase whole-tumor drug concentration, but by whether they increase the drug that actually reaches the cytoplasm or nucleus of a tumor cell.

Rosenblum, Joshi, Tao, Karp, and Peer's broad review of targeted cancer nanomedicine catalogs the resulting diversity of targeting strategies pursued across lipid, polymeric, and inorganic nanoparticle platforms alike: monoclonal antibodies and antibody fragments directed against receptors such as HER2, EGFR, and transferrin receptor; small peptides, including RGD-family peptides that bind integrins overexpressed on tumor

neovasculature rather than on the tumor cells themselves; and small-molecule ligands such as folate that exploit metabolic receptor upregulation in rapidly dividing cells [16]. Each targeting chemistry brings its own trade-offs for a lipid nanoparticle specifically: antibody conjugation is the most selective but adds substantial manufacturing complexity, immunogenicity risk, and, because antibodies are comparatively large, can interfere with the PEG corona's steric stabilization if not engineered carefully; peptide and small-molecule ligands are cheaper to produce and less immunogenic but typically offer lower binding affinity and specificity, and receptor targets such as folate receptor and transferrin receptor, while overexpressed on many tumor types, are not tumor-exclusive, which limits the achievable selectivity ceiling regardless of formulation quality. Mitchell and colleagues' broader review of precision nanoparticle engineering for drug delivery situates active targeting within this larger design space, emphasizing that ligand density, ligand orientation, and the underlying nanoparticle's own circulation and extravasation properties all interact non-additively — a poorly circulating, rapidly cleared targeted nanoparticle will underperform a well-circulating untargeted one regardless of how well-chosen its ligand is, because it never reaches the tumor vasculature in sufficient quantity for the targeting step to matter [17].

5. Clinical Translation of Lipid Nanoparticle Therapeutics

The clinical record for lipid-nanoparticle-formulated oncology drugs, while more modest than early enthusiasm anticipated, is nonetheless the most direct evidence available for what these platforms actually achieve in solid tumor patients. PEGylated liposomal doxorubicin (Doxil/Caelyx) remains the paradigmatic case: its approved indications include ovarian cancer, multiple myeloma, and AIDS-related Kaposi's sarcoma, and its clinical benefit over free doxorubicin is driven primarily by markedly reduced cardiotoxicity and altered toxicity profile (favoring palmar-plantar erythrodysesthesia over cardiac and myelosuppressive toxicity) rather than by a dramatic increase in objective response rate, which is broadly consistent with a passive-targeting mechanism that improves the drug's therapeutic index more through altered biodistribution away from vulnerable normal tissue than through unusually large increases in tumor drug concentration [4,3].

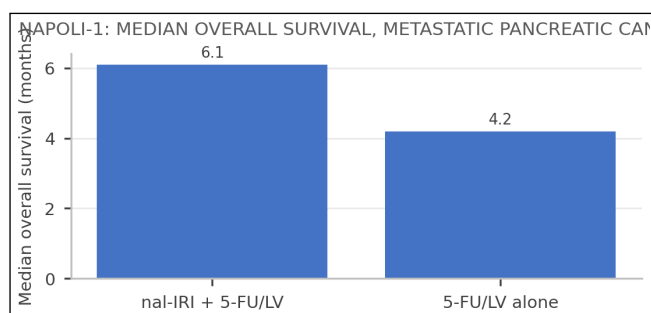


Figure 1: Median overall survival in the NAPOLI-1 phase 3 trial for metastatic pancreatic cancer patients receiving nanoliposomal irinotecan (nal-IRI) combined with fluorouracil and folinic acid versus fluorouracil and folinic acid alone (hazard ratio 0.67, 95% CI 0.49–0.92) -- the clearest randomized-trial evidence that a lipid nanoparticle reformulation of an existing cytotoxic drug can extend survival in a genuinely difficult-to-treat solid tumor [18].

Nanoliposomal irinotecan (nal-IRI, marketed as Onivyde) offers the field's clearest randomized-trial evidence of a lipid nanoparticle formulation producing a statistically significant survival benefit in a solid tumor indication. In the NAPOLI-1 phase 3 trial, reported by Wang-Gillam and colleagues, patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy who received nal-IRI in combination with fluorouracil and folinic acid had a median overall survival of 6.1 months, compared with 4.2 months for patients receiving fluorouracil and folinic acid alone (hazard ratio 0.67, 95% CI 0.49–0.92) — a result that led directly to regulatory approval and remains one of the more concrete demonstrations that a lipid nanoparticle reformulation of an existing cytotoxic agent can meaningfully extend survival in a genuinely difficult-to-treat solid tumor [18]. Notably, the same trial found that nal-IRI monotherapy, without the combination partner, did not produce a significant survival benefit over control therapy, underscoring that the nanoparticle reformulation's benefit in this trial was realized specifically in combination with an appropriately chosen chemotherapy backbone rather than as a standalone effect of the delivery vehicle.

Bulbake, Doppalapudi, Kommineni, and Khan's updated review of liposomal formulations in clinical use catalogs the broader landscape beyond these two headline examples — including liposomal cytarabine, liposomal vincristine, and liposomal irinotecan's siblings in other indications — and their overall assessment is consistent with the pattern established by Doxil and Onivyde: clinical benefit from liposomal reformulation of established cytotoxic agents is real and, in several indications, sufficient to change standard of

care, but it manifests predominantly as improved tolerability and, in a subset of trials, modest but statistically significant survival gains, rather than the order-of-magnitude efficacy improvements that early EPR-effect-driven enthusiasm sometimes implied [19]. Sercombe and colleagues' review of the practical challenges facing liposome-assisted delivery reaches a similar conclusion from a formulation-science angle, cataloging the manufacturing scale-up, stability, and batch-to-batch reproducibility hurdles that have historically slowed the translation of promising preclinical liposomal formulations into approved products, independent of whether the underlying targeting biology works as intended [20].

One clinically important pharmacokinetic complication specific to repeated PEGylated liposome dosing deserves mention: Ishida and Kiwada's characterization of the accelerated blood clearance (ABC) phenomenon found that a first dose of PEGylated liposome can, in some regimens, induce an anti-PEG IgM antibody response that causes a subsequently administered second dose to be cleared from circulation far more rapidly than the first, substantially undermining the long-circulation property that passive tumor targeting depends on [21]. This is a formulation-class-specific risk that active-targeting and dosing-schedule design both need to account for, and it is a reminder that a lipid nanoparticle's immunological interactions with the host are not fully solved simply by adding a PEG corona.

6. Emerging Applications: Nucleic Acid and Vaccine Delivery to Solid Tumors

The ionizable-lipid nanoparticle platform's maturation as a nucleic-acid delivery vehicle, driven initially by RNA interference therapeutics and then dramatically accelerated by mRNA vaccine development, has opened a delivery route to solid tumors that is mechanistically distinct from the small-molecule chemotherapy formulations discussed above: rather than delivering a cytotoxic payload, these LNPs deliver genetic instructions — small interfering RNA to silence a disease-driving gene, or messenger RNA to direct a patient's own cells to produce a therapeutic or immunogenic protein. Akinc and colleagues' retrospective on patisiran, the first FDA-approved siRNA drug (approved 2018 for hereditary transthyretin amyloidosis, not a solid tumor indication but the platform's clinical proof of concept), traces how the

ionizable-lipid design principles established by Semple and Jayaraman's earlier work culminated in a clinically viable, systemically administered LNP product, establishing both the manufacturing and regulatory precedent that subsequent oncology-focused LNP nucleic-acid therapeutics now build on [22,7,8]. Kulkarni, Cullis, and van der Meel's review of LNP-enabled gene therapies extends this account specifically toward the broader therapeutic landscape these platforms are now being extended into, including oncology applications where an LNP-delivered nucleic acid payload can silence an oncogene, restore a tumor suppressor, or, in the vaccine context, encode a tumor antigen [23].

The most direct extension of this technology into solid tumor therapy is the personalized mRNA cancer vaccine. Sahin and colleagues' early-phase study of a lipid-nanoparticle-formulated (RNA-lipoplex) personalized neoantigen vaccine in melanoma patients demonstrated that a vaccine encoding each patient's own tumor-specific mutations, delivered via a lipid-based nanoparticle carrier, could induce pronounced, poly-specific CD4⁺ and CD8⁺ T-cell responses against the targeted neoantigens in the majority of vaccinated patients — a proof of concept that the same lipid-nanoparticle delivery logic developed for infectious-disease mRNA vaccines and RNA interference therapeutics could be redirected toward training the immune system against a patient's own solid tumor [24]. Sabnis and colleagues' work on a next-generation amino-lipid series for mRNA delivery, developed and validated for improved endosomal escape and sustained tolerability in non-human primates, is representative of the ongoing lipid-chemistry optimization effort feeding directly into these vaccine and protein-replacement applications, including the higher systemic doses and repeat-dosing tolerability that oncology applications, as opposed to single-dose prophylactic vaccines, typically require [25].

A further refinement relevant to solid tumor applications is selective organ targeting (SORT), developed by Cheng, Wei, Farbiak, Johnson, Dilliard, and Siegwart, which showed that systematically varying the charge and identity of a fifth, "SORT" lipid component added to the standard four-component LNP formulation could reproducibly redirect nucleic-acid delivery toward specific organs — lung, spleen, or liver — beyond the

liver-predominant biodistribution that unmodified ionizable LNPs typically default to [26]. Dilliard and Siegwart's broader review of passive, active, and endogenous organ-targeted lipid and polymer nanoparticles situates this work within the wider effort to extend LNP-based genetic-drug delivery beyond the liver, an effort of direct relevance to solid tumors located outside the liver, since a nanoparticle that defaults to hepatic accumulation is a poor starting point for treating, say, a lung or pancreatic primary tumor without substantial additional formulation engineering [27]. Hou and colleagues' comprehensive review of LNP-based mRNA delivery likewise emphasizes that extending this delivery platform to extrahepatic solid tumors, rather than the liver-accumulating biodistribution most current clinical LNP products exploit, remains one of the field's most consequential open engineering problems [10].

7. Open Challenges

Several limitations recur across this literature and deserve to be named plainly rather than left as background caveats. First, and most fundamentally, the EPR effect that has historically justified passive lipid nanoparticle tumor targeting is now understood to be considerably more heterogeneous — across tumor types, across patients, and across metastatic sites within a single patient — than the preclinical xenograft literature that established it originally suggested, and Wilhelm and colleagues' finding that a median of well under one percent of an administered nanoparticle dose reaches the tumor at all is a sobering quantitative anchor for how much room for improvement genuinely remains [11,1,2]. Active targeting, as Kirpotin and colleagues' mechanistic work makes clear, does not solve this accumulation problem on its own; it primarily improves what happens to nanoparticles after they have already extravasated, which means the two strategies are complementary rather than substitutable, and a formulation program that pursues one while ignoring the other is unlikely to see its best possible result [15].

Second, tumor penetration beyond the immediate perivascular space remains a substantial barrier that neither passive nor conventional active targeting fully addresses. Dense stromal architecture, elevated interstitial fluid pressure, and heterogeneous vascular perfusion within a solid tumor together mean that even a nanoparticle that successfully extravasates may

distribute unevenly, concentrating near vessels while leaving hypoxic, poorly perfused tumor regions comparatively drug-starved — precisely the size-and-permeability interaction that Cabral and colleagues' work characterizes, and precisely the kind of tumor architecture that Nichols and Bae argue is more representative of human disease than the rapidly-growing, well-vascularized xenografts used in most preclinical efficacy studies [14,1].

Third, the immunological interactions between lipid nanoparticles and the host remain incompletely characterized and, in the case of the accelerated blood clearance phenomenon Ishida and Kiwada describe, can actively undermine the pharmacokinetic properties a formulation depends on for efficacy [21]. As LNP-based nucleic acid and vaccine platforms move toward repeat-dosing oncology applications — a personalized cancer vaccine or a gene-silencing therapy intended for chronic administration, rather than a single prophylactic vaccine dose — this immunogenicity risk becomes considerably more consequential than it was for the largely single- or few-dose applications where PEGylated LNPs were first validated.

Fourth, extrahepatic solid tumor targeting for nucleic-acid LNP platforms remains, in our reading of Hou et al. and Dilliard and Siegwart's reviews, more a promising research direction than a solved engineering problem: SORT and related approaches have demonstrated organ-level redirection in preclinical models, but translating that redirection into reliable, clinically validated tumor-selective nucleic acid delivery for solid tumors outside the liver has not yet been demonstrated at the scale or reproducibility that the liver-targeted, RNA-interference and vaccine LNP platforms have already achieved [26,27,10]. Finally, and more mundanely, manufacturing scale-up and batch reproducibility continue to constrain how quickly promising formulations move from preclinical proof-of-concept to clinically available product, a persistent theme across Sercombe and colleagues' and Bulbake and colleagues' reviews of the clinical liposome landscape that is easy to underweight in an academic literature focused primarily on efficacy data [20,19].

8. Conclusion

The literature synthesized here supports a fairly specific and, we think, defensible claim: lipid nanoparticles are a genuinely useful and clinically validated platform for

improving the therapeutic index of solid tumor chemotherapy, most convincingly demonstrated by PEGylated liposomal doxorubicin's reduced cardiotoxicity and nanoliposomal irinotecan's statistically significant survival benefit in metastatic pancreatic cancer [4,18], while falling considerably short of the tumor-selective "magic bullet" that the field's early framing of the EPR effect once implied. Passive accumulation via leaky tumor vasculature is real but delivers, on average, a strikingly small fraction of an administered dose to tumor tissue and varies substantially across tumor types and patients [11,1]. Active targeting ligands meaningfully improve cellular uptake of nanoparticles that have already reached the tumor, but do not, on the evidence currently available, substantially increase how much nanoparticle reaches the tumor in the first place [15,16]. And the platform's newest extension — ionizable-lipid nanoparticles carrying nucleic acid payloads rather than small-molecule cytotoxics — has already produced a clinically approved gene-silencing drug and early but genuinely encouraging proof-of-concept results for personalized cancer vaccination, even as extending that platform's default liver-centric biodistribution toward extrahepatic solid tumors remains substantially unfinished work [22,24,27].

None of the open challenges catalogued in the previous section are, in our reading, reasons to abandon lipid nanoparticles as a solid tumor therapy platform; if anything, four decades of incremental formulation refinement — from conventional liposomes, through PEGylation and solid lipid matrices, to today's ionizable, organ-selectable LNP chemistries — have produced a steadily improving, mechanistically better-understood technology base rather than a stalled one. What the evidence does call for is a more measured research agenda than the platform's early history sometimes encouraged: continued investment in understanding and, where possible, pharmacologically enhancing EPR-effect heterogeneity rather than assuming it away; active targeting strategies evaluated explicitly for their effect on cellular uptake and payload delivery rather than on whole-tumor accumulation; and nucleic-acid LNP engineering that treats extrahepatic solid tumor delivery as a first-order design target rather than an afterthought to liver-focused platforms already validated for other indications. Read together, the clinical translation record and the mechanistic literature both

suggest that lipid nanoparticles will remain a central technology for solid tumor drug delivery for the foreseeable future — not because the original EPR-driven vision has been fully vindicated, but because the platform has proven flexible enough to be substantially re-engineered as that vision's limitations have become clearer.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this article.

Data Availability Statement

This article is a literature synthesis and did not generate new experimental data; all findings discussed are drawn from the cited published sources, which should be consulted directly for their underlying data and code availability statements.

Ethical Approval

Not applicable. As a literature synthesis, this work did not involve human participants, animal subjects, or the collection of any primary clinical or experimental data.

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