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Review Article

Programmable long-acting injectable nanomedicines for chronic inflammation

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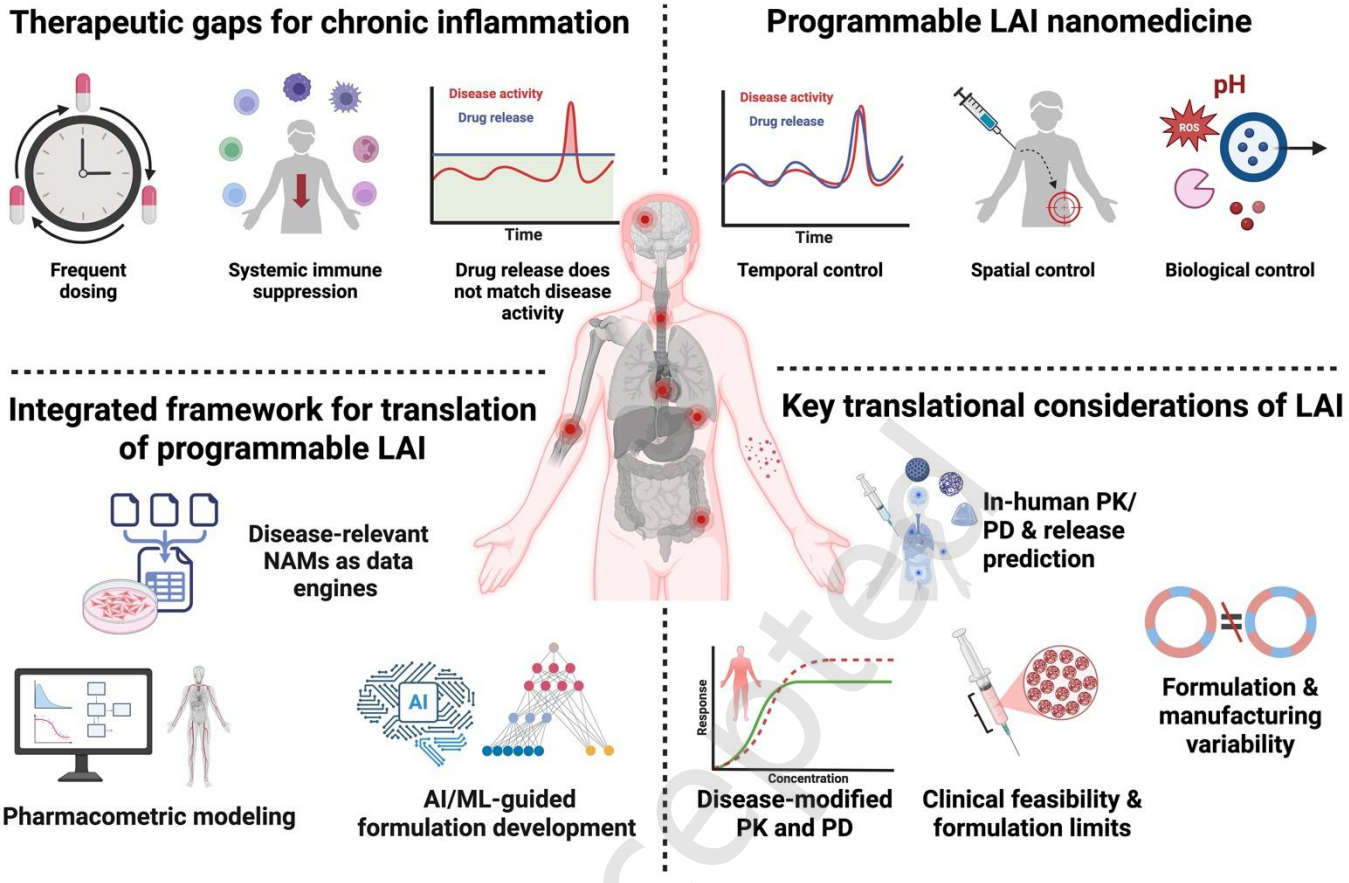
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Chronic inflammation demands programmable long-acting nanomedicines with temporal, spatial, and biological control. Translating this complexity to the clinic requires disease-relevant models, pharmacometric modeling, and AI-guided formulation design.

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Programmable long-acting injectable nanomedicines for chronic inflammation

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ABSTRACT: Many chronic inflammatory diseases (CIDs) are characterized by relapsing-remitting activity that demands long-term, adaptable therapeutic intervention. Yet, most existing therapies, including conventional immunosuppressants and biologics, often require repeated administration over months to years to maintain disease control, creating substantial treatment burden without fully matching fluctuating disease activity. In this Perspective, we discuss how programmable long-acting injectable (LAI) nanomedicines are emerging as therapeutic platforms for chronic inflammation. By integrating temporal control (sustained, sequential, and flare-responsive release), spatial control (depot retention, lymphatic trafficking, and cell-selective uptake), and biological programming (pH-, ROS-, enzyme-, and cytokine-responsive release), these platforms can align drug action with disease biology rather than simply prolong exposure. We organize these three design axes around disease-informed principles and illustrate, through an arthritis case study, how their integration distinguishes next-generation platforms from simple depot formulations. However, increasing programmability also increases translational complexity. We define key translational questions that must be addressed, including depot pharmacokinetics, disease-modified drug disposition, material-driven variability, and clinical feasibility constraints, and propose an integrated framework to address them. Disease-relevant new approach methodologies (NAMs) can serve as experimental data engines, multiscale mechanistic pharmacokinetic and pharmacodynamic modeling can translate these parameters into human exposure and response predictions, and AI/ML tools can accelerate nanoformulation optimization across multiple design parameters. In this framework, these quantitative tools provide the translational infrastructure needed to advance programmable LAI nanomedicines toward clinical implementation.

KEYWORDS: long-acting injectables; chronic inflammatory diseases; PBPK; machine learning

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1 Introduction

Chronic inflammatory diseases (CIDs), including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS), and related immune-mediated disorders, impose a substantial global health burden through long-term morbidity, disability, and disease-specific mortality [1]. These conditions are driven by persistent immune dysregulation and thus typically require long-term treatment to provide symptom relief and to prevent irreversible tissue damage [2]. Moreover, CIDs are often characterized by relapsing-remitting courses driven by multiple, shifting immune pathways that establish inflammatory tissue memory and predispose to future flares [3, 4]. Using RA as an example, single-cell analyses of RA patients have shown that flare onset is accompanied by expansion of circulating memory $CD4^+$, $CD8^+$ T cells, and memory B cells [4]. Longitudinal transcriptomic analyses in humans have shown that RA flares are preceded by B-cell activation, followed by the expansion of circulating pre-inflammatory mesenchymal cells approximately one week before symptom onset, which then traffic from the blood into the synovium during flares [5]. Such flaring events are also common in MS [6], IBD [7, 8], and lupus [9]. This trafficking of cells across compartments over time reveals that CIDs shift across both space and time, demanding programmable therapies capable of spatial targeting, temporal responsiveness, and inflammation sensing, while offering durable disease control.

Current pharmacotherapies, while transformative, were generally not designed to provide this degree of spatiotemporal control. Frequent dosing and short half-lives of small molecules like nonsteroidal anti-inflammatory drugs (NSAIDs) impose a significant burden on patients, demanding longer-acting therapies. Moreover, current first-line therapies lack active targeting for affected tissues or cells, leading to systemic toxicity and off-target immunosuppression. Broad-spectrum immunosuppressants, such as corticosteroids and biologics, may globally suppress immune function, increasing susceptibility to infection, reactivation of latent infection, and drug-induced autoimmune complications [2, 10, 11].

Drug delivery technologies, including polymeric, liposomal, and hydrogel-based carriers, have begun to address some of these limitations. For example, Zilretta is an FDA-approved

extended-release formulation of triamcinolone acetonide encapsulated in biodegradable poly(lactic-co-glycolic acid) (PLGA) microspheres for intra-articular treatment of knee osteoarthritis. Following a single injection, triamcinolone remains quantifiable in synovial fluid for up to 12 weeks while peak plasma exposure is substantially reduced compared with immediate-release triamcinolone [12]. Such formulations demonstrate the clinical feasibility of long-acting local delivery. However, their release profiles primarily address pharmacokinetic limitations while retaining fixed-rate release kinetics regardless of inflammatory state. To bridge this gap, preclinical research has advanced next-generation long-acting nanomedicines equipped with spatiotemporally tunable release profiles and stimuli-responsive triggers, designed to align drug delivery with the dynamic biology of CIDs.

In this Perspective, we define "programmable long-acting injectable (LAI) nanomedicines", to describe systems that coordinate temporal control (sustained, sequential, or flare-responsive release), spatial control (local retention, tissue access, and cellular targeting), and biological programming (microenvironment-responsive and logic-gated behavior) within a single injectable platform. The injectable route is particularly well-suited to realizing these goals, enabling direct depot formation at or near sites of inflammation, bypassing hepatic first-pass metabolism, and facilitating lymphatic access [13, 14], advantages that also explain its predominance among clinically approved nanomedicines [15].

However, the same programmability that makes these LAI nanoplatforms therapeutically compelling also introduces substantial translational complexity. The pharmacokinetic behavior of programmable LAI nanoplatforms, where release kinetics depend on pathological stimuli and therapeutic duration is a function of both formulation design and disease-state physiology, makes empirical extrapolation from animal data to human dosing unreliable. The formulation-dependent variability in particle properties and release behavior adds another layer of uncertainty. Bridging this gap requires more disease-relevant *in vitro* tools and mechanistic pharmaco-metric frameworks capable of connecting formulation properties to human tissue exposure, therapeutic duration, and pharmacodynamic response, and of predicting how dosing regimen can determine clinical outcomes. These modeling tools are the basic quantitative infrastructure that makes translation possible. Artificial Intelligence (AI) and machine learning (ML) can further complement this framework by navigating the high-dimensional formulation design space and uncovering nonlinear structure-property-function relationships that neither experimentation nor mechanistic modeling alone can efficiently resolve.

The design and translation of programmable LAI nanomedicines are inseparable challenges that must be addressed in parallel. Temporal control, spatial targeting, and biological programming should be guided by the pathophysiology of chronic inflammatory diseases, while predictive translational tools need to be integrated early in LAI nanomedicine development to connect formulation behavior with clinical outcomes. This Perspective outlines how a disease-informed design framework, coupled with predictive modeling and AI-guided optimization, can accelerate the clinical translation of programmable LAI nanomedicines for CIDs.

2 What Makes a Long-Acting Injectable Nanomedicine Programmable

While first-generation LAI offer a promising path for durable therapy that can reduce frequent dosing and systemic exposure, the spatiotemporal complexity of CIDs creates opportunities to move beyond simple depot persistence. Programmable LAIs can further control when therapeutics are released, where they distribute, which tissues or cells they engage, and how their activity responds to inflammatory cues. The following sections organize these three design axes, temporal control, spatial control, and biological programming (**Figure 1**), around disease-informed principles, proposing representative LAI design strategies, and highlighting their associated translational challenges from a disease-informed perspective.

2.1 Temporal control: sustained, sequential, and flare-responsive release

The most intuitive form of programmability is temporal control. For chronic inflammatory diseases, therapeutic exposure often needs to persist for weeks to months, while avoiding the peaks and adherence burden associated with repeated administration. Temporal programming can take several forms, including sustained release that maintains steady drug exposure, sequential release that stages multiple payloads against a multi-node pathology, and flare-responsive release that modulates output according to changes in disease-associated signals. Representative release profiles are illustrated in the temporal-control axis of **Figure 1**.

Sustained-release depots, such as polymeric microspheres [16], hydrogels [17], and porous inorganic carriers[18], can extend drug exposure by controlling diffusion, matrix erosion, or carrier degradation. The clinical example of PLGA microsphere-based triamcinolone acetonide for osteoarthritis illustrates how local depot design can convert a conventional corticosteroid into a long-acting intra-articular therapy [16]. Similar principles have been explored in preclinical inflammatory models such as a rheumatoid arthritis (RA) model using radially mesoporous silica nanoparticles (RMSNs) loaded with dexamethasone to prolong local residence and reduce systemic exposure [18].

However, duration alone is not always sufficient. Chronic inflammation is dynamic and frequently involves sequential activation of multiple immune and tissue-remodeling pathways. Staged delivery of multiple payloads therefore offers a second layer of temporal programming. Synchronized co-delivery can suppress complementary inflammatory pathways at the same time, such as combining a small molecule anti-inflammatory agent with siRNA against a cytokine target [19]. Sequential release, by contrast, can be useful when early inflammation control should be followed by tissue repair or immune resolution, layered or core-shell constructs are particularly suited to this goal, in which an outer compartment degrades first to release an early-phase payload and exposes an inner compartment whose subsequent degradation releases a later-phase payload [17].

While sustained-release depots maintain steady-state exposure, they do not match the intermittent flare pattern of most inflammatory diseases, and steady dosing during quiescent periods produces unnecessary immunosuppression. Flare-responsive systems modulate output in proportion to disease activity, drawing on either enzyme-labile linkers or engineered cellular sensors [20, 21]. Enzyme-responsive, ROS-responsive,

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pH-responsive, and cytokine-responsive systems can increase drug output when inflammatory cues rise that changes the microenvironment. For example, enzyme-cleavable carriers respond to matrix metalloproteinases (MMPs) and other esterases upregulated in inflamed tissue, such that higher enzyme concentrations during a flare drive accelerated particle disassembly and increased drug release, matching the release profile to flare severity [21]. A conceptually distinct flare-responsive platform uses engineered cells as autonomous sensor–effector units: induced pluripotent stem cells modified by CRISPR-Cas9 insertion of the IL-1 receptor antagonist (*Il1rn*) or soluble TNF receptor transgene produce biologic inhibitors in proportion to ambient IL-1 or TNF-α levels, generating cartilage that produces durable, demand-driven biologic output from a single implantation procedure[20]. This form of "on-demand" release is especially attractive for long-acting depots because it could reduce unnecessary immunosuppression during quiescent periods while preserving rapid therapeutic availability during flare. This flare-responsive behavior follows a temporal pattern, in which drug release increases and decreases with disease activity, but represents only one dimension of programmability in LAI nanomedicine. Additional forms of biological programming are discussed in Section 2.3, along with the underlying microenvironment-sensing mechanisms, including pH, ROS, enzymes, and cytokines.

2.2 Spatial control: local retention, tissue access, and cellular targeting

For an LAI to retain its dosing advantage, therapeutic exposure must be maintained within the relevant tissue or immune compartment. Spatial control encompasses depot retention at the injection site, penetration into the inflamed compartment, biological recognition of target cell populations, and access to draining lymphatics where many of the relevant immune populations reside. In these settings, carrier size, surface charge, matrix affinity, and degradation rate determine whether a formulation remains in the synovial space, penetrates cartilage, is cleared through lymphatics, or is taken up by resident immune cells [22]. Tissue-binding ligands, electrostatic interactions with inflamed matrix components, and magnetically assisted retention have also been used to increase local retention [23–25].

For diseases in which immune activation is distributed across tissues or lymphoid compartments, spatial programming may require a different design logic. Subcutaneously or interstitially administered nanomedicines can access draining lymphatics and lymph nodes depending on particle sizes, surface charge/chemistry, interstitial transport, and cellular uptake. Depending on these properties, nanomedicines may remain near the injection site, accumulate in draining lymph nodes, or move through afferent lymphatics, efferent lymphatics, and ultimately venous circulation, thereby extending the pharmacologic effect beyond the local depot [26]. Furthermore, immune cells activated or reprogrammed in local tissues and draining lymph nodes can traffic through lymphatic and blood circulation to distant inflammatory sites [27]. This may be advantageous when the goal is not simply to suppress inflammation at one anatomical site, but to modulate antigen-presenting cells, such as macrophages and dendritic cells, or lymphocyte populations that sustain systemic immune activation.

At the cellular level, targeting ligands and biomimetic interfaces provide other strategies for spatial control. Receptors such as folate receptor β (FR-β) [25], CD44 [24], and CD206 [23] have been exploited to direct nanocarriers toward activated macrophages, fibroblast-like synoviocytes, or other disease-relevant cell populations. Biomimetic carriers, including cell-membrane-coated nanoparticles and extracellular vesicle-inspired systems, extend this idea by using native membrane proteins to provide homing, immune evasion, or cytokine-scavenging functions. One such explicit example is the use of macrophage-membrane-coated nanoparticles (MΦ-CNPs) to target the central effector cell of chronic inflammation. The construct achieves inflammatory-site homing via inherited macrophage surface markers and repolarizes macrophages from M1 to M2 phenotype around the rheumatoid joint following intra-articular injection [21]. The cell targeting design might also need to be disease-specific. For example, a macrophage-targeted depot may be logical for rheumatoid arthritis or inflammatory bowel disease [21, 28] whereas a cartilage-retentive or synovium-retentive system may be more appropriate for osteoarthritis [17, 29].

2.3 Biological programming: microenvironment-responsive and logic-gated behavior

Biological programming links therapeutic activity to signals within the inflamed microenvironment. Inflamed tissues differ from healthy tissues in pH [30, 31], oxidative stress [30, 32], protease activity [21, 30], cytokine levels [2], vascular permeability [33], immune cell composition [2] , and extracellular matrix remodeling [2]. These differences may provide local inputs that can be used to gate release, enhance uptake or activate therapeutic function.

The sensing mechanisms used for biological programming also provide the molecular basis for the inflammation-responsive temporal behavior described in Section 2.1. pH-responsive LAI nanomedicines exploit the gradient between physiological pH and the mildly acidic environments of inflamed tissue and the endolysosome of activated phagocytes. For example, acid-labile linkers (hydrazone, acetal, and ketal) between the active pharmaceutical ingredient and carrier can be cleaved on exposure to non-physiological pH, releasing payload selectively within activated immune cells [25]. Inflamed tissue also carries elevated reactive oxygen species (hydrogen peroxide, hydroxyl radical) and reactive nitrogen species (nitric oxide), providing a second endogenous trigger axis. ROS- and RNS-responsive LAI platforms use elevated oxidative or nitrosative stress as triggers for carrier disassembly [34, 35]. For example, Wilson and colleagues used poly(1,4-phenyleneacetone dimethylene thioketal) (PPADT) nanoparticles for site-selective payload release in inflamed tissue [32]. Inflammation-associated enzymes (primarily MMPs and various esterases) ,as well as cytokines such as IL-1, TNF-α, and IL-6 provide quantitative biological inputs that can be wired into release kinetics. Enzyme-responsive systems, particularly those sensitive to matrix metalloproteinases or esterases, can link release kinetics to tissue remodeling and inflammatory activity [21]. Cytokine-responsive systems, including engineered cellular depots, represent a more biologically direct form of sensing, in which therapeutic output is coupled to inflammatory signaling itself [20].

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Multiple biological inputs can also be integrated within a single system. A carrier may require both target-cell binding and acidic pH, or both receptor engagement and elevated ROS, before releasing its payload [25, 34]. Such AND-gate behavior is especially relevant for long-acting systems, because the formulation may reside in the body for extended periods and needs to remain inactive in non-target tissues. Conversely, negative-feedback designs, such as ROS-scavenging systems that consume the same cue that activates them, may naturally reduce therapeutic output as the inflammatory burden resolves [36].

Programmability therefore reflects the coordinated control of therapeutic duration, localization, and biological responsiveness instead of the presence of any single advanced feature. Compelling LAI nanomedicines for chronic inflammation will likely combine durable depot behavior with tissue- or cell-selective localization and disease-responsive release. This multidimensional design logic creates substantial opportunities, but also increases translational complexity.

2.4. Disease-informed design rules for chronic inflammation

The performance of a programmable LAI nanomedicine relies on its coherence and adaptability to the biology of the target inflammatory disease. These criteria are of increased significance pertaining to long-acting nanomedicine since their defining factor and intended purpose is to deliver therapeutics continuously/responsively over a long duration lasting weeks to months. A poorly matched design may therefore prolong not only therapeutic activity but also off-target exposure, local or systemic toxicity, or material-associated adverse effects.

Disease-informed design should begin with a small set of clinically relevant questions. How long should therapeutic exposure persist? Where should the drug remain or distribute? Which cells or tissue compartments should be engaged? Should release remain constant or respond to changes in inflammatory activity? What happens to the carrier after its therapeutic function is complete? Finally, can these behaviors be predicted and scaled from preclinical models to humans? **Table 1** reframes representative strategies around these questions. The problem-oriented framework shifts attention away from maximizing platform complexity and toward selecting the minimum set of programmable features needed to address defined biological and translational goals.

2.5 Arthritis as a disease-informed design case.

Arthritis provides a representative case for illustrating how disease-specific pathophysiology can inform the design of programmable LAI nanomedicines. In rheumatoid arthritis and osteoarthritis, the joint provides an anatomically accessible but biologically complex compartment, with synovial inflammation, macrophage and fibroblast-like synoviocyte activation, cartilage matrix barriers, protease activity, oxidative stress, and fluctuating disease activity [22]. *In this setting, an intra-articular depot can reduce systemic exposure if the formulation remains in the joint, penetrates or anchors within relevant tissue structures, and releases drug at a rate compatible with both inflammation suppression and tissue repair.*

Sustained local release is the most clinically established of these design principles, exemplified by the approved intra-articular triamcinolone acetonide PLGA-microsphere depot (Zilretta) for knee osteoarthritis [16]. *Building on this, sustained local release has now been validated clinically across several delivery modalities in knee osteoarthritis. An extended-release fluticasone propionate formulation using a diffusion-controlled depot design (EP-104IAR) provided clinically meaningful pain relief for up to 14 weeks in a Phase 2 trial* [37]*; a liposomal dexamethasone formulation (TLC599) sustained pain relief through 24 weeks after a single injection in Phase IIa [38]; and a non-viral, plasmid-based intra-articular gene therapy encoding an anti-inflammatory cytokine (XT-150) reached Phase 2, illustrating a durable-biologic-delivery strategy conceptually adjacent to the engineered cellular depots discussed above [39] These programs establish the clinical feasibility of weeks- to months-long intra-articular exposure while sparing systemic corticosteroid effects, but they also expose the limitation of duration alone: all rely on fixed release kinetics that do not distinguish a flare from remission, or adapt to changes in the inflammatory microenvironment.*

Next-generation arthritis platforms can build on this foundation by adding programmable features only where disease biology provides a clear rationale. For where, cartilage-retentive carriers use cationic charge-based binding or explicit matrix ligands, such as ultrasmall iron oxide nanoparticles displaying the collagen II–binding peptide [29], while synovial retention is achieved largely through size, as in microenvironment-responsive hydrogel microspheres [17]. Cell-selective approaches can exploit receptors enriched on activated macrophages or fibroblast-like synoviocytes, including folate receptor β [25], CD44 [24], and CD206 [23]. Biomimetic macrophage- [21], neutrophil- [40], and platelet-membrane [41] coatings extend this by inheriting whole adhesion repertoires and often acting as cytokine decoys. For when, the inflamed synovium is enriched in MMPs, low pH, and ROS, each able to gate release to the diseased state, MMP-cleavable linkers [17], pH-responsive carriers [25], and ROS-responsive chemistries that also scavenge ROS to repolarize macrophages [32, 34]. Taken to the limit, this points toward closed-loop systems whose output tracks inflammatory input [20].

Table 1. A disease-informed framework for programmable long-acting nanomedicines in chronic inflammation.

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Design question	Disease-informed rationale	Programmable design features	Representative strategies	Translational challenge
How long should the drug persist?	Disease duration requires frequent dosing drives for small molecules (shorter half-lives) and can lead to rebound flares	Depot architecture with tunable diffusion/degradation, high drug loading, predictable sustained release over weeks to months.	PLGA-microsphere depot [16], dexamethasone-loaded radially mesoporous silica nanoparticles [18]	Reproducible scaled-up and control of burst-release; matching *in vitro* release to *in vivo* PK, long-term local tissue tolerance.
Where should the drug go and stay?	Local diseases such as arthritis may benefit from tissue retention, whereas systemic disease may require longer half-life, lymphatic access or immune-cell trafficking.	Size tuning for matrix penetration, charge for electrostatic retention, matrix-binding ligands, lymphatic transport.	Collagen- or matrix-binding particles [29], intra-articular depots [17], lymphatic accessible subcutaneous formulations [26].	Retention vs. penetration trade-off, quantifying true intra-compartment residence, reliance on external hardware limits routine use, reproducible biodistribution across patients.
Which cells should receive it?	The relevant effector cells differ across diseases and disease stage	Receptor-selective ligands (FR-β, CD44, CD206), cell-membrane biomimetic coatings, decoy surfaces for cytokine capture.	FR-β [25], CD44 [24], CD206 [23] , integrin, antibody/aptamer, macrophage- [21], neutrophil- [40], platelet- [41], or EV-based targeting [28].	Receptor expression heterogeneity between patients and disease stages, batch consistency of membrane coatings, immunogenicity
When should the drug release?	Inflammation is often intermittent, so fixed zero-order release may not match flare-remission kinetics.	Inflammation-triggered release, sequential release, synchronized co-delivery; proportional (not binary) output.	pH- [25] , ROS/RNS- [34, 35], MMP- [17], cytokine-responsive [20] systems.	Validating dose-proportionality to flare severity *in vivo*, avoiding lag between flare onset and release, added formulation complexity
What happens to the carrier after delivery?	A carrier dwelling for weeks should remain biocompatible; long residence and repeated dosing raise safety questions.	Biodegradation, clearance route, depot reversibility, foreign-body response.	Biodegradable hydrogels/microspheres/nanoparticles [17], biologically inert biomaterials and resorbable inorganic carriers [18].	Fibrosis, chronic inflammation, carrier accumulation, repeat-dose feasibility, long-term safety.
Can the platform be translated predictively?	Rodent release, biodistribution, and efficacy often do not scale directly to human doses.	Model-informed release, PBPK/MBPK, PKPD, AI-guided optimization, disease-relevant *in vitro/ex vivo* models	Organ-on-chip, lymphatic models, formulation-informed PBPK [42, 43], and ML-guided formulation design [44, 45].	Limited human data, platform-specific parameters, scaling from animal to human, and limited validation datasets.

3 Predictive Translation of Programmable Long-Acting Injectable Nanomedicine for Chronic Inflammation

The three design axes and representative examples discussed above provide a framework for engineering programmable LAI nanomedicines tailored to the biology of chronic inflammatory diseases. However, despite compelling preclinical efficacy, most nanomedicine candidates fail to rea-

-ch clinical settings [15]. This translational gap is widened by the complexity of programmable LAI platforms and by whether stimuli-responsive release and spatiotemporally controlled kinetics can be predicted across species and disease states.

Bridging this gap requires an integrated predictive framework in which disease-relevant experimental models generate mechanistic parameters that standard assays often

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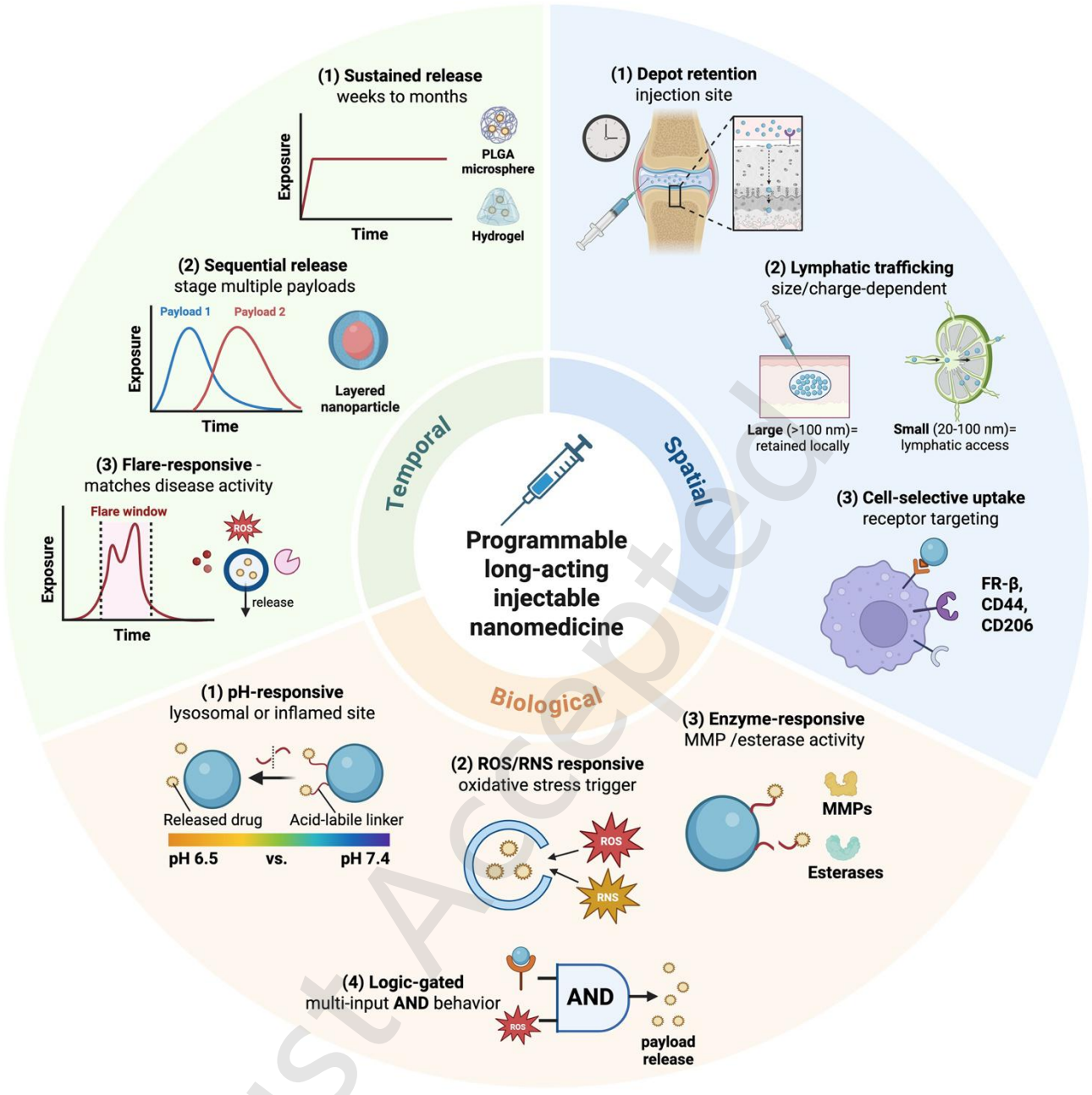


Figure 1. Disease-informed design axes for programmable long-acting injectable (LAI) nanomedicine. Three orthogonal design axes define LAI nanomedicine programmability: temporal control over release duration and kinetics, spatial control over depot retention, lymphatic trafficking, and cell-selective uptake, and biological programming that couples drug release to inflammatory microenvironment cues. These axes collectively define a disease-informed design framework for programmable LAI nanomedicines in chronic inflammation. Abbreviations: PLGA, poly(lactic-co-glycolic acid); FR-β, folate receptor beta; ROS, reactive oxygen species; RNS, reactive nitrogen species; MMP, matrix metalloproteinase. Created with BioRender.com.

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miss, pharmacometric models translate those parameters into human exposure and response predictions, and AI and ML tools accelerate formulation optimization across design spaces too large for empirical screening alone (**Figure 2**). The following sections address what needs to be predicted for successful translation, and how each component of this framework contributes to advancing programmable LAI nanomedicines toward the clinic, as summarized in **Table 2**.

3.1 Key translational considerations for programmable LAI nanomedicine development

Translating preclinical *in vitro* and animal data on programmable LAI nanomedicines into reliable human predictions requires identifying which parameters can be scaled across species and which must be adjusted for species-specific differences. LAI systems require prediction across multiple time scales, from injection-site depot formation and drug release to lymphatic transport, systemic disposition, and long-term pharmacodynamic response [43]. These processes can be substantially altered due to interspecies differences in anatomy, physiology, and immunology [46, 47].

Drug disposition and depot kinetics are the most fundamental parameters requiring translation. Key questions include where the LAI nanomedicine distributes after parenteral administration, how long it persists at the injection site, when and where drug release occurs, how much reaches the target tissue, and how it is

ultimately cleared. Because these processes depend on both formulation properties and species-specific physiology, human-relevant prediction requires integrated modeling across local and systemic scales. Physiologically representative *in vitro* systems can define organ-specific transport behaviors and rate constants; mechanism-based pharmacokinetic (MBPK) models can characterize local depot behavior within selected compartments [42]; and physiologically based pharmacokinetics (PBPK) frameworks with humanized parameters can extend these predictions to whole-body disposition and interspecies scaling.

A second set of translational questions concerns disease-modified PK and PD: how does chronic inflammation alter nanomedicine transport, immune cell uptake, local release kinetics, tissue exposure, and target engagement? Because inflamed tissues differ substantially from healthy tissues [30, 48], parameters derived from healthy animals may not accurately predict drug PK and PD in inflamed human tissues. Beyond exposure, translation must also predict whether sustained delivery produces sufficient and durable immunomodulation while avoiding safety-related responses such as immunogenicity and organ-specific toxicity. Disease-relevant *in vitro* systems, humanized or inflammation-relevant animal models, and PK/PD models can help connect preclinical efficacy data to disease-adjusted dosing parameters, including dosing interval and duration of therapeutic response.

A third translational consideration is formulation and manufacturing variability. For LAI nanomedicine, material selection and batch-to-batch consistency may alter critical quality properties such as drug loading, release kinetics, and subsequent cellular uptake, tissue distribution, and pharmacodynamic response. This challenge becomes particularly important for stimuli-responsive or multicomponent systems, in which variability may shift the threshold or magnitude of biological responsiveness [49]. Even mature platforms such as PLGA-based nanocarriers face regulatory obstacles due to PLGA's intrinsic heterogeneity as a random copolymer whose properties are sensitive to manufacturing conditions [50]. Biomimetic carriers, such as extracellular vesicle-based systems, exhibit substantial intra- and inter-batch variability in membrane composition and size distribution [51, 52], which can compromise targeting specificity and yield subpopulations with divergent release profiles [51]. Therefore, reproducible manufacturing, identification of critical material and process attributes, and orthogonal physicochemical and biological characterization should be integrated early in development. Human-relevant *in vitro* and *ex vivo* models may further help determine whether formulation variability translates into meaningful differences in biological performance, while data-driven approaches can support optimization of complex material and process parameter spaces.

A final translational consideration is clinical feasibility. Preclinical animal studies may use injection volumes and drug concentrations that are experimentally acceptable but unrealistic when scaled to humans. For example, recommended subcutaneous dose volumes for common laboratory animals typically fall within the range of 1–5 mL/kg [53, 54], but this number cannot be simply translated to human dose, where conventional human subcutaneous injections are generally limited to approximately 1.5 mL [55]. Therefore, dose, drug loading, viscosity, injection volume, and dosing interval should be considered early in formulation development and co-optimized using formulation screening, injectability testing, release assays, and PK/PD modeling before clinical translation.

3.2 Disease-relevant new approach methodologies (NAMs)

Addressing the translational questions outlined above requires data that standard monoculture assays, release studies, and healthy-animal PK experiments cannot reliably provide. Those conventional approaches often fail to capture the multicellular architecture, fluid dynamics, immune cell interactions, and disease-state microenvironment that govern LAI nanomedicine behavior in chronically inflamed tissues, producing parameters that are poorly predictive of human *in vivo* performance. For example, the Caco-2 monolayer remains a standard drug permeability benchmark, yet it is a single cancer-derived cell type that lacks the multicellular architecture, immune components, and transporter expression profile of inflamed intestinal tissue [56, 57]. Advanced *in vitro* and *ex vivo* models, or new approach methodologies (NAMs), incorporating multiple human-relevant cell types, tissue architecture, and inflammatory cues offer a complementary middle ground between standard assays and animal studies.

Among the disease-relevant NAMs, human *ex vivo* tissue models, including patient-derived tissue explants, lymph node slices, and other tissue sections from disease-relevant tissues, offer a level of biological resemblance that engineered platforms and stimulated inflammations cannot replicate. Unlike organoids or microfluidic devices, which are reconstructed from selected cell types or lines, *ex vivo* tissue maximally retains the native cellular architecture, extracellular matrix, and immune cell compositions while being less complex than *in vivo* models [58]. This similarity to native inflamed tissue enables reliable evaluation of nanomedicine performance, including protein corona formation [59], tissue binding [60], local retention [61], and nanoparticle-induced immune responses [62] under true disease settings. However, their short-term viability remains a key limitation for evaluating long-acting platforms. Recent hydrogel-embedding methods extended human lymph node slice viability to seven days [63], offering new possibilities for LAI nanomedicine studies.

While *ex vivo* tissue offers high biological authenticity, its short viability, limited availability, and donor variability limit its use for long-duration, high-throughput, reproducible studies in LAI nanomedicine development [58]. Primary and engineered immune organoids [64, 65], along with artificial lymph node systems [66], address this gap by offering reproducible, scalable platforms that recreate 3D stromal structure, antigen presentation, and multicellular immune interactions while remaining viable for weeks [64, 67, 68]. The multicellular self-organization also preserves native gene expression, antigen-specific responses, and cytokine secretion profiles in response to antigen or nanoparticle exposure [64, 68, 69], making these platforms reliable tools for predicting how sustained drug delivery shapes immunological outcomes over weeks *in vivo.* This is especially relevant for LAI nanomedicines, whose immunological effects could change over time as the drug releases.

Most organoid and *ex vivo* systems, however, remain static and lack the flow and shear stress needed to capture how nanomedicines release and distribute over time. Microfluidic-

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based models, including lymph node-on-chip and inflammation-on-chip systems, introduce continuous fluid flow into cultures of human endothelial or lymphatic endothelial cells, stromal cells, immune cells, and extracellular matrix. These models particularly recapitulate key dynamic features of inflamed immune tissues [70]. By introducing inflammatory cues such as chemokines, cytokines, altered pH, or elevated reactive oxygen species levels [58, 71], these platforms can generate real-time, disease-relevant data on nanoparticle transport, depot degradation, endothelial transfer, and cell-type-specific uptake under dynamic conditions that more closely resemble the perfused inflamed target sites. Importantly, inflammation-on-chip systems can also provide flow-dependent immune-cell readouts, including leukocyte migration and cell-cell interactions that static systems cannot model [71].

Compared to animal models, these platforms offer greater biological tunability, reduced confounding variability, and direct human relevance while remaining more manageable than *in vivo* studies for systematic parameter measurement. Their primary limitation is that most remain under development and lack formal validation against clinical or *in vivo* benchmarks. Rather than replacing animal studies, these systems act more as fit-for-purpose data engines that generate human-relevant transport, uptake, release, and immune-response parameters. These measurements can then inform MBPK, PBPK, PK/PD, and quantitative systems pharmacology (QSP) models, bridging the gap between overly simplified *in vitro* assays and the full biological complexity of the human inflammatory environment.

3.3 Mechanistic models for human prediction

The mechanistic data generated from disease-relevant experimental systems can next be incorporated into predictive pharmacometric frameworks, including MBPK, PBPK, PK/PD, and QSP models. These models allow formulation and dosing variables, such as dose amount, dosing interval, injection volume, and release rate, to be systematically perturbed to predict their effects on tissue exposure, therapeutic duration, and safety profiles [72]. For LAI nanomedicines in chronic inflammation, this predictive capacity is especially important because treatment success depends on how long a given dose can sustain immunomodulatory activity before inflammatory signaling rebounds or tissue damage progresses. Thus, these models help determine whether prolonged persistence actually translates into sufficient target-tissue exposure across the intended dosing interval.

Unlike free drugs, whose disposition is largely governed by intrinsic molecular properties, nanoformulated drugs often exist in multiple pharmacokinetic states, including formulation-associated and released drug, with disposition shaped by formulation-specific characteristics such as particle size, surface chemistry, protein corona formation, and MPS recognition [73–75]. To address this complex question, MBPK and PBPK modeling operate as complementary tools at different scales. MBPK models are particularly useful for resolving formulation- or depot-specific mechanisms within selected compartments, such as local depot absorption, nanoparticle-associated versus released drug kinetics, lymphatic transport, and lymph node retention, when full physiological parameterization is not yet feasible [42, 43]. PBPK models can then build on these mechanistic data by embedding them into anatomically defined structures, enabling whole-body exposure prediction, tissue-specific accumulation analysis, and interspecies scaling [76, 77]. This layered relationship of MBPK and PBPK modeling is illustrated by two related studies of a lymphatic-targeted, long-acting injectable antiretroviral drug-combination nanoparticle formulation [42, 43]. Kraft et al. first used MBPK modeling to characterize the formulation-specific mechanisms underlying multiphasic plasma exposure following subcutaneous dosing, including lymphatic uptake, delayed lymphatic transit, lymph node retention, and slow drug release [42]. Subsequently, Perazzolo et al. extended these mechanisms into a PBPK framework with anatomically defined lymphatic and systemic compartments, supporting more physiologically grounded predictions of tissue distribution and interspecies translation [43]. While developed for HIV, this example is highly relevant to chronic inflammatory diseases because lymphoid tissues, immune cell trafficking, and sustained target tissue exposure are also central to achieving durable immunomodulation and preventing inflammation rebound.

When the translational question shifts from exposure to therapeutic effect, PK/PD and QSP models become essential. PK/PD models link drug exposure to measurable responses, such as receptor occupancy, cytokine suppression, immune cell phenotype shifts, or clinical disease scores, helping to predict therapeutic duration and dosing regimens [78]. QSP frameworks extend this approach further by integrating mechanistic models of drug action with disease biology across multiple scales, including molecular signaling pathways, cellular interactions, immune compartments, and tissue-level pathology. These models can therefore simulate how sustained drug delivery influences disease-level outcomes such as flare control and remission maintenance [79]. For nanomedicine, QSP-based multiscale modeling has similarly been applied to capture the spatiotemporally dependent kinetic processes governing NP target site exposure, such as protein corona formation and MPS-mediated clearance [80]. Incorporating these processes can help distinguish target-tissue exposure from systemic exposure and provide a more mechanistic link between nanomedicine disposition and therapeutic effects.

Overall, the central value of mechanistic modeling is its ability to translate formulation behavior into clinically relevant predictions. For LAI nanomedicines in chronic inflammation, the next step is to integrate these tools into frameworks that can guide optimal dosing regimens for sustained inflammation control. Although integrated PBPK/QSP models remain limited for inflammation-focused nanomedicines, they represent a logical path toward model-informed translation of programmable LAI therapies.

3.4 AI/ML as the optimization and integration layer

Translating LAI nanoplatforms into the clinic requires efficient identification and optimization of candidates that satisfy both PK, PD, and product-development requirements. This is challenging because physicochemical properties, release kinetics, tissue distribution, immune-cell interactions, and therapeutic response are highly interdependent and often nonlinearly coupled, creating a design space too large to navigate through experimentation alone. AI and ML tools can serve as the optimization and integration layer that makes this process more manageable by prioritizing candidate formulations

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before synthesis, identifying nonlinear relationships among formulation variables and biological outcomes, and accelerating iterative refinement using data from high-throughput characterization, disease-relevant *in vitro* systems, animal studies, and PBPK/QSP models.

One key role of ML is candidate prioritization before experimental synthesis. Models trained on formulation, physicochemical, and biological datasets can rank candidate formulations *in silico* before synthesis based on desired properties such as stability, drug loading, release kinetics, and biological performance [81, 82]. This strategy has already been applied to predict drug-excipient combinations for carrier-free co-assembled nanosystems [83, 84], identify lipid nanoparticle formulations with improved delivery efficiency [85], and design ionizable lipids with favorable apparent pKa, organ targeting, and mRNA delivery [86, 87]. For LAI nanomedicines in chronic inflammation, similar models could prioritize formulations predicted to combine high drug loading, depot stability, formulations *in silico* before synthesis based on desired properties such as stability, drug loading, release kinetics, and sustained release, and inflamed-tissue targeting. Importantly, clinically relevant constraints, such as maximum injection volume, minimum drug loading, viscosity, and dosing interval, could be incorporated as optimization boundaries so that computational screening selects candidates with both biological activity and translational feasibility.

The second role is identifying nonlinear structure-activity relationships between formulation variables and performance. Since formulation parameters are deeply interdependent, changes in drug loading could alter particle size, which affects stability, release kinetics, and cellular uptake simultaneously, producing outcomes that are not easily predictable from individual parameters alone [81, 88]. AI/ML models can integrate formulation descriptors, physicochemical characterization, real-time release profiles, and biological readouts to determine which variables most strongly control performance. For example, ML models have been used to predict and tune release profiles from long-acting polymeric delivery systems using polymer, drug, form-

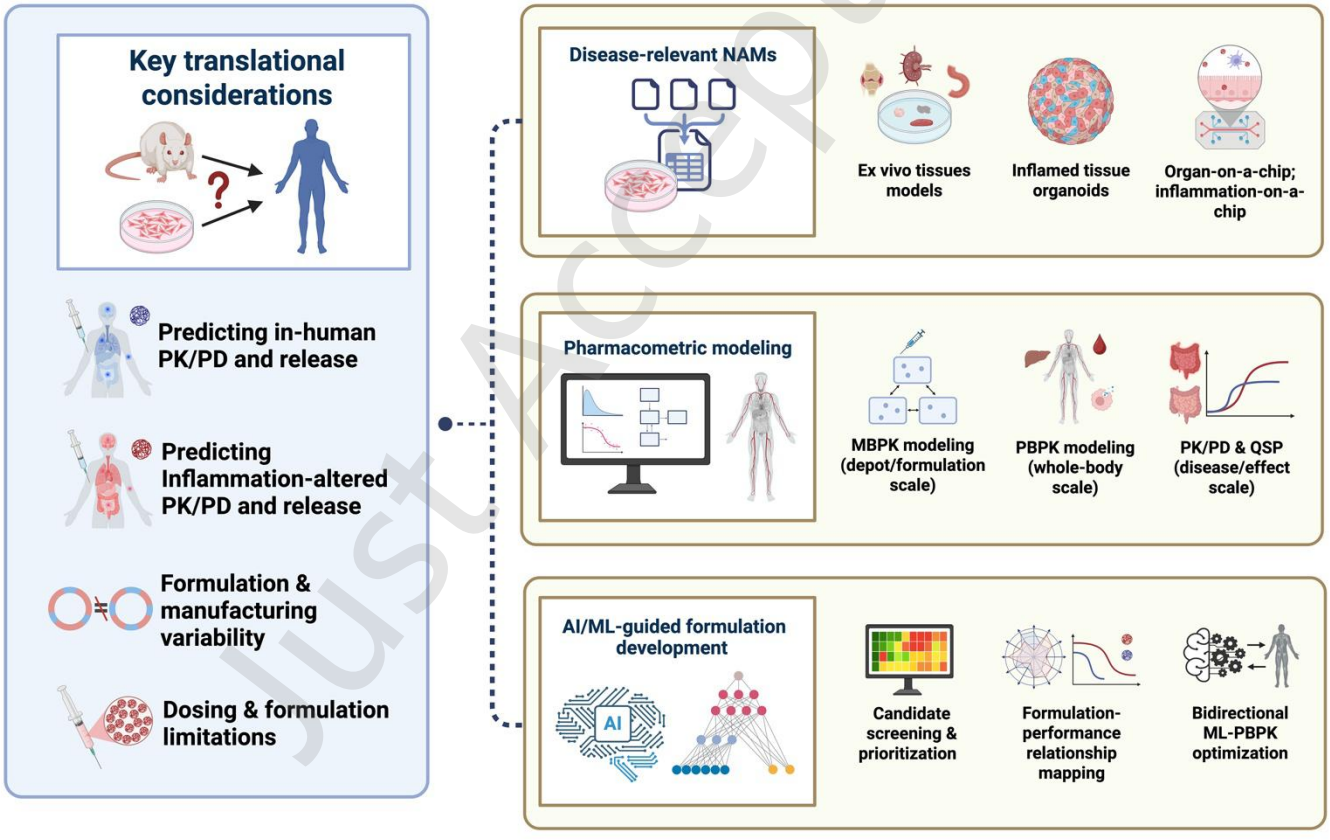


Figure 2. Translational roadmap for programmable long-acting injectable nanomedicine in chronic inflammation. Three interconnected frameworks are proposed to address key translational considerations in LAI nanomedicine development: disease-relevant NAMs as experimental data engines, multiscale pharmacometric modeling for human exposure and therapeutic response prediction, and AI/ML-guided formulation development for candidate prioritization and virtual optimization. Abbreviations: LAI, long-acting injectable; NAM, new approach methodology; MBPK, mechanism-based pharmacokinetic; PBPK, physiologically based pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; QSP, quantitative systems pharmacology; AI, artificial intelligence; ML, machine learning. Created with BioRender.com.

-mulation and *in vitro* experimental inputs [44]. In the context of chronic inflammation, Rafiei et al. connected LNP formulation parameters to microglial phenotype shifts, enabling selection of candidates that drive anti-inflammatory repolarization in disease-relevant immune cells [89], illustrating how ML can bridge formulation design and disease-specific biological outcomes.

The third and most integrative role is to combine AI/ML with disease-relevant experimental systems and mechanistic pharmacometrics models [90, 91]. PBPK-predicted tissue exposure profiles, organ-on-chip-derived transport parameters, and disease-relevant release kinetics can serve as training inputs for ML models to explore large virtual design spaces before additional experimental testing [90, 92]. Conversely, ML can

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assist PBPK frameworks by estimating poorly characterized parameters, lymphatic transport rates, disease-state-dependent enzyme activity, and immune cell uptake kinetics from *in vitro* data, using PBPK model structure to constrain predictions within physiologically plausible bounds [92]. For example, Chou et al. employed a deep neural network to predict hard-to-measure cellular uptake kinetic parameters from easily measurable physicochemical properties across diverse nanoparticle types, which were then fed into a mechanistic PBPK model to accurately predict tumor delivery efficiency without requiring new animal experiments [45]. Extending this paradigm to LAI nanomedicines, ML models could learn inflammation-altered immune cell uptake kinetics and depot release profiles from *in vitro* systems and PBPK outputs, enabling virtual optimization across thousands of formulation candidates [92].

Although such bidirectional integration between ML and PBPK modeling remains limited and platform-specific, it represents an important future direction for the development of complex LAI nanomedicine.

Overall, current AI/ML tools are largely limited to LNPs, PLGA-based polymeric nanoparticles, and co-assembled systems, and they remain highly platform-specific, which restricts their generalizability to emerging multicomponent platforms. In addition, small and species-limited *in vivo* datasets constrain predictive accuracy and translational potential, and large-scale models for guiding *in vivo* efficacy for different disease contexts remain lacking.

4 Outlook: Toward a Predictive Translation Framework

The future of programmable LAI nanomedicines for chronic inflammation will depend less on adding more platform features than on connecting each feature to a measurable translational purpose. This requires an integrated framework that links formulation design, disease-relevant data generation, mechanistic modeling, and iterative optimization.

The LAI nanoformulations should be evaluated based on the specific translational question they are designed to address, such as depot retention, lymphatic transport, inflamed-tissue accumulation, controlled release, immune cell uptake, or sustained immunomodulation. Several trade-offs are particularly important. A months-long depot is valuable only if prolonged exposure remains safe and if excessive immunosuppression can be avoided or managed. Second, retention must be balanced against tissue access. Lar-

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Table 2. Integrated tools for predictive translation of long-acting nanomedicines for chronic inflammation. Abbreviations: NAM, new approach methodology; MBPK, mechanism-based pharmacokinetic; NP, nanoparticle; PBPK, physiologically based pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; QSP, quantitative systems pharmacology; AI, artificial intelligence; ML, machine learning.

Type of Tools	Function	Key Data Generated	Translational Value	Limitations
Disease-relevant NAMs	Generate disease-relevant experimental data for downstream pharmacometric modeling	Release kinetics, transport, retention, permeability, immune-cell uptake, cytokine response, toxicity	Provides human-relevant parameters under controlled inflammatory conditions	Still under exploration; limited throughput; not all biological processes fully recapitulated
MBPK	Capture depot- or mechanism-specific behavior in selected compartments	Depot degradation, lymphatic uptake, local retention, NP-associated vs. released drug	Useful when full physiological parameterization is not available	Reduced physiological detail may limit direct interspecies extrapolation
PBPK	Predict drug disposition and tissue exposure; interspecies scaling	Organ distribution, clearance, route-dependent exposure, tissue partitioning	Supports human exposure prediction and dosing-regimen design	Interspecies scaling less established in nanomedicines than in small molecules
PK/PD and QSP	Link exposure to biological effect	Biomarker dynamics, immune cell response, efficacy	Connects formulation behavior to therapeutic response	Requires extensive biological parameterization; limited application for chronic inflammation
AI/ML-guided design and optimization	Accelerate candidate selection; learn and integrate across datasets	Formulation descriptors, release profiles, characterization data, biological outcomes, model	Prioritizes candidates, identifies nonlinear relationships, and accelerates design iteration	Platform-specific and limited generalizability; *in vivo* training datasets small and species-restricted

		simulations		

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-ger or adhesive depots may remain at the injection site but fail to reach diseased matrix or target cells, whereas smaller particles may penetrate tissue but clear too rapidly. Third, responsiveness must be balanced against reproducibility. Logic-gated or multi-trigger systems can improve specificity, but each additional trigger increases synthetic and analytical complexity. Fourth, biomimicry complexity must be balanced against manufacturability. Cell-membrane-coated and EV-inspired systems are conceptually powerful, but batch-to-batch consistency, source material control, sterilization, and immunogenicity will determine whether they can move beyond preclinical proof-of-concept.

This perspective also argues for a closed-loop development paradigm. Disease-relevant *in vitro* and *ex vivo* systems can generate mechanistic parameters that standard assays and healthy-animal studies often miss, while MBPK, PBPK, PK/PD, and QSP models can translate these parameters into human-relevant predictions of tissue exposure, dosing interval, biomarker response, and therapeutic effect. AI/ML tools can further refine formulation by identifying nonlinear relationships between formulation variables, release behavior, and biological outcomes. The choice of tools should also be driven by the formulation and translational objective. Depot-forming systems may benefit most from release assays and MBPK models; lymphoid-targeted nanoparticles require lymphatic transport models and PBPK frameworks; inflammation-responsive platforms require disease-relevant tissue models and PK/PD or QSP approaches; and complex multicomponent systems may benefit from AI/ML-guided screening before experimental validation.

Several practical barriers deserve particular attention. Human dose and injection volume may be the defining constraints for many LAI nanomedicines, especially for biologics or low-potency payloads that require high drug mass. Concentrated formulations must preserve stability, injectability, and release control without creating unacceptable viscosity or burst release. Long-term local biocompatibility, foreign-body response, biodegradation, and repeat-dose feasibility need to be evaluated early, not after efficacy has been demonstrated. Chemistry, manufacturing, and controls (CMC) considerations are equally important because many responsive, biomimetic, or multi-payload systems are difficult to characterize, sterilize, and reproduce at scale.

Finally, chronic inflammation remains underrepresented relative to oncology in many areas of nanomedicine development. This creates both a challenge and an opportunity. Inflammatory diseases are biologically diverse, clinically chronic, and often relapsing-remitting, but they also provide unusually clear design problems: control duration, localize therapy, minimize systemic immunosuppression, and adapt treatment to disease activity. Programmable LAI nanomedicines will be most impactful when they move beyond the language of "smart" delivery and demonstrate disease-informed, predictable, manufacturable, and clinically feasible control of inflammation over time.

Data availability

Not applicable.

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Declaration of competing interest

All the contributing authors report no conflicts of interest in this work.

Author contribution statement

Y.G. and R.J. wrote the manuscript. Y.G. prepared all figures. S.C. conceptualized the manuscript and supervised the project. All authors participated in critical revision and approved the final version.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

Grammarly, ChatGPT, and Claude were used to assist with grammar and language editing. ChatGPT was additionally used to help draft descriptive figure-planning templates for BioRender. The authors take full responsibility for the accuracy and integrity of the manuscript..

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