Review



# Rethinking modRNA Immunogenicity: Toward a Human Genotype-Guided PRR/ISR Atlas

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# Rethinking modRNA Immunogenicity: Toward a Human Genotype-Guided PRR/ISR Atlas

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**Abstract**

In vitro-transcribed modified mRNA is a promising platform for transient protein replacement in regenerative medicine, including cardiomyocyte regeneration, but repeated dosing is limited by variable innate immune activation and ISR-mediated translation shutdown across individuals. We propose a Human-specific PRR/ISR Immunogenicity Atlas: a focused, genotype-aware computational framework linking patient genetic variation in pattern recognition receptors and ISR components to predict immune and translation responses for IVT modRNA. The Atlas generates individualized "genetic passports" that stratify responder risk, estimate cytokine and PKR/eIF2$\alpha$ activation, and prioritize clinically feasible temporary knockdown strategies (LNP-siRNA/ASO or small molecules). We outline a six-stage roadmap covering data integration, feature engineering, multi-modal modeling, uncertainty quantification, a knockdown prioritization module, and open deployment. Ethical, privacy, ancestry-representation, and regulatory considerations are discussed, along with a staged validation strategy. This Atlas provides a conceptual and practical framework to support safer, more consistent protein replacement in regenerative medicine by moving from one-size-fits-all to genotype-guided approaches.

**Keywords:** mRNA therapeutics; regenerative medicine; innate immunity; integrated stress response; personalized medicine; knockdown strategies

## 1. Introduction

The clinical success of mRNA vaccines has shown the potential of in vitro-transcribed (IVT) mRNA as a therapeutic tool. This technology has changed prophylactic and therapeutic immunization [1]. However, its use in non-immunotherapy settings, especially protein replacement and tissue regeneration, presents different biological and translational challenges [2].

In regenerative medicine, the goal is localized, repeatable, and transient expression of therapeutic proteins [3]. This requirement is especially clear in cardiac repair. For example, modified mRNA encoding VEGF-A can expand endogenous heart progenitor cells, promote vascular regeneration after myocardial infarction, and improve cardiac function [4]. Complementary approaches using human pluripotent stem cell-derived epicardial cells have further shown the ability to augment cardiomyocyte-driven heart regeneration and tissue repair [5]. At the same time, inflammation must remain sufficiently controlled to protect the injured tissue and support repair [3,6]. Cells recognize synthetic mRNA and other nucleic acid therapies as foreign through innate immune pathways [7], while cellular uptake mechanisms and intracellular processing further shape the balance between antigen expression and immune activation [8]. This sensing can trigger interferon and inflammatory responses, suppress translation, and reduce therapeutic benefit [7]. Considerable progress has been made to reduce these effects. Strategies include sequence optimization, nucleoside modification, removal of immunogenic byproducts such as double-stranded RNA contaminants, and pharmacological modulation of immune pathways [7,9]. In clinical settings, premedications such as dexamethasone and antihistamines have been used to regulate immune reactions associated with LNP-based RNA therapies [10,11]. In parallel, targeted approaches

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such as siRNA- or ASO-mediated knockdown of specific PRR and ISR components have been explored, alongside small-molecule inhibitors and other modulators [12,13]. These advances demonstrate that immune responses can be partially controlled, but they remain variable and context dependent.

Researchers have also made progress by developing strategies to temporarily suppress key immune pathways. These strategies include macromolecules, small molecules, short peptides and proteins, and siRNA- or ASO-mediated knockdown of specific PRR and ISR genes (see review [12]). Such siRNA or ASO approaches can be delivered via lipid nanoparticles, and some are already FDA approved for other indications [13]. A central limitation is that innate immune responses differ substantially across individuals. Genome-wide analyses show that genetic variation in PRR signaling pathways contributes to variability in innate immune activation, including response quantitative trait loci (reQTLs) that modulate PRR-driven gene expression[14]. Broader immunogenomic studies highlight that human genetic diversity, including PRR gene variants, shapes heterogeneous immune response profiles across populations [15]. Components of the integrated stress response, including PKR activation, also interact with antiviral signaling pathways and influence cellular responses to RNA stress [16]. Together, these factors contribute to variability in cytokine production, translation efficiency, and final protein yield.

Despite existing strategies to suppress innate immune activation, their efficacy remains inconsistent across models, species, and patients [12,17]. Recent reviews consistently identify ISR-mediated translation shutdown and human-specific immunogenicity as key barriers to safe repeated dosing in regenerative applications [12,18–22]. Preclinical animal models do not fully capture this human genetic heterogeneity, which further limits clinical translation [23].

These observations point to a specific gap. The field has developed multiple tools to modify therapeutic RNA and modulate immune pathways, but it lacks a structured approach to account for patient-specific genetic variation in PRR and ISR signaling. This gap is particularly relevant for modRNA-based cardiac regeneration, where repeated dosing and controlled protein expression are essential. In this Perspective, we propose a Human-specific PRR/ISR Immunogenicity Atlas as a focused, genotype-guided framework for modRNA therapies. The Atlas is designed to integrate patient genetic data with therapy-specific features to predict immune activation and translation outcomes. It aims to generate individualized “genetic passports” and to prioritize a small set of candidate genes for temporary knockdown to reduce unwanted immune responses.

This work is presented as a staged and testable framework. The initial implementation is intended for a single platform and biological context, with emphasis on defining minimal datasets, measurable outputs, and validation strategies. We also outline a practical technical roadmap for its development, together with key limitations that must be addressed before clinical application.

## 2. The Problem: Human Genetic Variability in PRR and ISR Pathways

Pattern recognition receptors and the integrated stress response form the central machinery that cells use to detect foreign nucleic acids and control translation. Key PRRs include TLR3, TLR7, TLR8, RIG-I, MDA5, NLRP3, and TLR9 [24]. These receptors recognize specific features in therapeutic nucleic acids, and RNA delivery itself can actively engage antiviral defense programs through innate immune sensing pathways [25]. The ISR, particularly through the PKR kinase, acts as a downstream regulatory brake [21]. When activated, PKR phosphorylates eIF2$\alpha$ and reduces global protein synthesis.

In the context of modRNA therapies, sensing is primarily mediated by endosomal TLR7/8 and cytosolic sensors such as PKR, which can phosphorylate eIF2$\alpha$ and inhibit translation. These pathways are directly relevant for transient protein replacement strategies, where both magnitude and duration of expression are critical. Other platforms such as saRNA and AAV engage additional sensing pathways, including RIG-I/MDA5 or TLR9 and cGAS-STING, and may trigger stronger or more sustained immune responses [26]. However, the present bottleneck can already be observed in conventional modRNA systems used for regenerative applications.

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Human genetic studies show that individuals differ widely in how strongly these pathways respond. Common and rare variants in PRR and ISR genes can influence receptor sensitivity, expression levels, and downstream signaling. Evidence from eQTL studies, GWAS, and rare-variant analyses indicates that these differences contribute to variability in cytokine production, interferon signaling, PKR activation, and downstream translation efficiency [14,15]. Components of the ISR further interact with antiviral signaling pathways and modulate cellular responses to RNA stress [16]. A large body of work has focused on reducing innate immune activation through sequence design and pharmacological modulation, yet translation into consistent clinical outcomes remains limited (see review [12]). One major reason is inter-individual genetic variability and the resulting heterogeneity in innate immune responses to foreign mRNA. Animal models do not fully capture this variability. Mice and non-human primates often show lower or qualitatively different immune responses to the same constructs, which complicates translation to human patients [2]. As a result, promising preclinical findings do not consistently translate into predictable effects in clinical settings.

This limitation is particularly relevant for regenerative medicine, where repeated dosing over time is often required. Recent reviews consistently identify ISR-mediated translation shutdown and human-specific immunogenicity as key barriers to safe and reproducible repeated dosing [12,18–22]. At the same time, current booster or inhibitor strategies lack standardization and show variable efficacy across studies and patient populations [12,17]. Recent literature highlights a consistent pattern. The field has developed multiple approaches to optimize the therapeutic molecule itself, yet it lacks a structured framework to account for patient-specific genetic differences that influence response [27,28]. This gap becomes evident in emerging clinical studies. For example, Phase 2a testing of AZD8601 VEGF-A modRNA (EPICCURE; NCT03370887) showed favorable safety and early efficacy signals in a limited cohort [29]. However, transient expression and PRR/ISR-mediated translation shutdown, particularly through TLR7/8 and PKR/eIF2$\alpha$, remain constraints for repeated dosing required for durable cardiac repair [20–22].

Therefore, variability in PRR and ISR pathway activity across individuals limits the predictability and consistency of modRNA-based therapies. Addressing this bottleneck requires moving beyond uniform strategies toward approaches that incorporate patient-specific genetic information. The next section introduces a framework designed to address this gap in a testable and staged manner.

## 3. The Proposed Solution: A Human-Specific PRR/ISR Immunogenicity Atlas

We propose the development of a Human-specific PRR/ISR Immunogenicity Atlas as a genotype-guided computational framework focused on modRNA therapies. This resource is intended to link patient genetic variation to predicted innate immune activation and translation outcomes in a defined therapeutic context. The framework is designed as a staged and testable system rather than a complete solution at this stage. In its initial implementation, the atlas focuses on a single platform and biological context, such as modRNA delivery in human-derived cardiomyocytes. It takes two primary inputs: the patient's genetic data and the sequence features of the therapeutic modRNA. Based on these inputs, it estimates which innate immune pathways are most likely to be activated and how strongly they may influence translation efficiency. It then prioritizes a limited set of candidate genes whose temporary modulation could reduce unwanted immune activation.

The knockdown recommendations are restricted to clinically feasible strategies. These include LNP-deliverable siRNA or ASO approaches and approved small-molecule inhibitors targeting PRR or ISR components [12,13].

The framework is designed to prioritize minimal interventions, typically a single gene or a small combination, to reduce complexity and improve translational relevance. For each patient–therapy pair, the atlas is designed to produce three outputs. First, a simplified "Genetic Passport" that classifies individuals into low, medium, or high responder categories based on predicted immune activation. Second, quantitative estimates of biological responses, including cytokine and interferon levels, PKR activation probability, eIF2$\alpha$ phosphorylation, and expected protein expression profiles.

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Third, a ranked list of candidate knockdown targets tailored to the patient's genetic background and the specific modRNA construct( Figure 1).

At present, no framework systematically integrates patient genetic variation with modRNA-specific features to generate such predictions in a unified manner. However, this proposal should be interpreted with caution. The current limitation is the scarcity of datasets directly linking genotype to functional immune and translation responses following modRNA delivery. Therefore, the atlas is best viewed as a structured hypothesis and engineering framework that requires iterative validation.Instead of applying uniform modulation strategies across all patients, this approach aims to enable stratified and testable intervention strategies. By focusing on a clearly defined use case and measurable outputs, the atlas provides a basis for evaluating whether genotype-guided modulation can improve the safety and consistency of repeated-dose modRNA therapies in regenerative medicine.

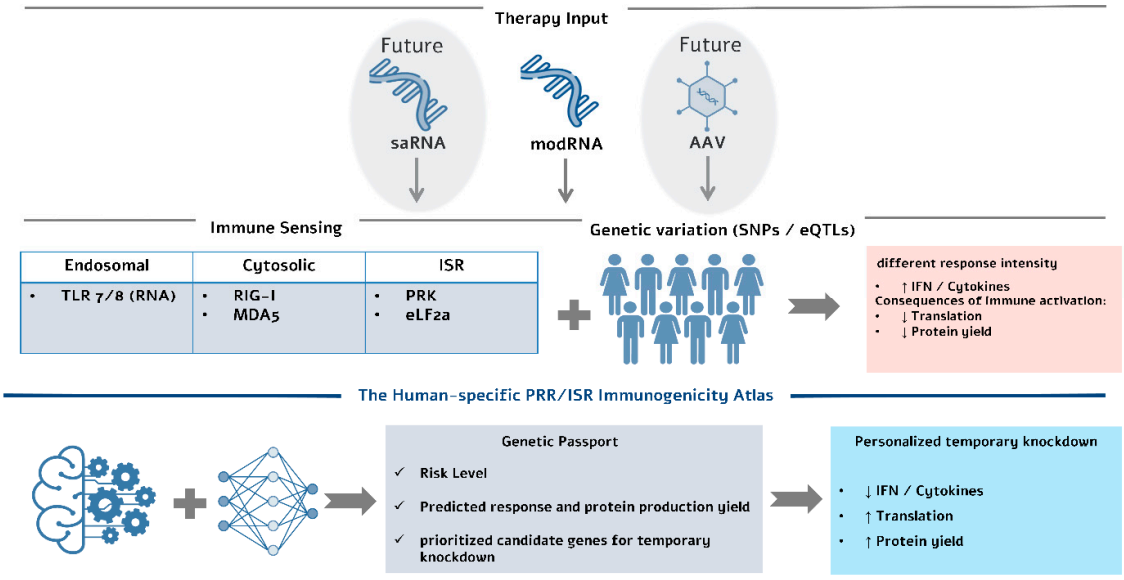


**Figure 1.** Schematic overview of the Human-specific PRR/ISR Immunogenicity Atlas. Therapy inputs (modRNA) are sensed by platform-specific innate immune pathways. Genetic variation (SNPs / eQTLs) modulates response intensity, leading to increased cytokines, reduced translation, and lower protein yield. The atlas integrates these inputs in a multi-modal model and outputs a Genetic Passport with a ranked list of the single best gene or small minimal synergistic combination for temporary knockdown.

## 4. Technical Roadmap for Atlas Construction

The proposed atlas is designed as a staged and testable framework with a clearly defined initial scope. Rather than attempting a multi-platform implementation, the first phase focuses on modRNA delivery in human-derived systems relevant to cardiac regeneration. The roadmap below outlines the key components required to build and evaluate a minimal viable version of the atlas.

### *4.1. Data Layer*

The atlas begins with integrating genetic and functional response data in a unified structure. Genetic data can be obtained from large-scale public resources such as gnomAD, GTEx eQTL datasets, and the 1000 Genomes Project, with focus on variants within PRR and ISR pathway genes. These include TLR7, TLR8, RIG-I, MDA5, PKR, MAVS, and related downstream signaling components [14,15]. The critical limitation at this stage is the availability of functional datasets that directly link donor genotype to response following modRNA exposure. Public datasets from GEO or

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ArrayExpress provide transcriptomic and cytokine response profiles in human cells exposed to nucleic acids, but they often lack matched genotype information. Therefore, a minimal proof-of-concept dataset is required. This could consist of a small panel of genotyped human iPSC-derived cardiomyocytes or primary cells exposed to a standardized modRNA construct, with readouts including cytokine levels, interferon response, and protein expression.

All data are harmonized into a structured database, with standardized variant annotation, gene expression normalization, and metadata curation. This step is essential to ensure that downstream modeling reflects biological signal rather than technical variability (Figure 2).

### *4.2. Feature Engineering*

Two main feature groups are constructed. The first includes genetic features derived from PRR and ISR pathway variation. These may include SNP-level encodings, haplotype information, and eQTL effect sizes that reflect gene expression regulation [14,15]. Where appropriate, aggregated features such as pathway-level scores can be included to reduce dimensionality. The second feature group captures properties of the modRNA construct. These include sequence-derived embeddings, nucleotide composition, and structural features known to influence immunogenicity and translation efficiency [2,7]. Pretrained models such as RNA language models may be used to extract embeddings, but they should remain fixed in the initial implementation to limit model complexity. The final input representation combines genetic and sequence features into a single vector for each patient–therapy pair. Feature selection or dimensionality reduction should be applied to avoid overfitting, particularly given the expected small size of early datasets.

### *4.3. Model Architecture*

The model is designed as a multi-modal and multi-task framework with constrained complexity. A simple architecture, such as a multi-layer perceptron with separate branches for genetic and sequence features, is sufficient for the initial implementation. More complex models, such as graph neural networks or transformers, can be considered only after sufficient data are available. The model predicts a limited set of outputs that can be experimentally validated. These include responder category, quantitative cytokine or interferon levels, markers of ISR activation such as PKR or eIF2$\alpha$ phosphorylation, and relative protein expression yield. In addition, the model includes a ranking component that prioritizes candidate genes for temporary knockdown. Importantly, the prioritization module should be constrained to single-gene or small combinations to maintain interpretability and translational feasibility. This reduces the risk of generating biologically unrealistic or clinically impractical recommendations.

### *4.4. Training, Validation & Uncertainty Quantification*

Given the limited size of early datasets, careful training and validation strategies are required. Data should be split into training, validation, and test sets with attention to donor-level separation to avoid information leakage. Where possible, cross-validation should be stratified by genetic background to assess robustness across different populations. Model performance is evaluated using appropriate metrics for each output. These include $R^2$ for continuous predictions, classification metrics such as AUC-ROC for responder categories, and ranking metrics for knockdown prioritization. However, performance should be interpreted cautiously given the small sample size. Uncertainty quantification is a critical component. Techniques such as Monte Carlo dropout or ensemble models can be used to estimate prediction confidence. Outputs with high uncertainty should be flagged explicitly, as they may not be suitable for downstream interpretation or experimental validation.

### *4.5. Genetic Passport and Knockdown Recommendation Module*

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The model outputs are translated into a simplified and interpretable report. For each patient–therapy pair, the system generates a "Genetic Passport" that summarizes predicted immune activation risk and expected translation efficiency (Figure 3). This includes both point estimates and uncertainty ranges. The knockdown recommendation module provides a ranked list of candidate targets, limited to clinically feasible interventions such as siRNA, ASO, or small-molecule inhibitors [12,13]. Each recommendation is accompanied by a confidence score and supporting rationale derived from model features and known pathway biology. At this stage, the output should be considered a hypothesis-generating tool rather than a clinical decision system. Its primary purpose is to guide experimental validation and to test whether genotype-guided modulation improves outcomes in controlled settings.

### *4.6. Deployment and Open-Source Strategy*

The initial implementation should prioritize reproducibility and transparency over scalability. The atlas can be deployed as a lightweight computational tool using accessible frameworks, with all code and documentation made openly available. To facilitate validation, the system should support standardized input formats for genetic data and modRNA sequences and generate reproducible outputs across environments. Containerization and version control are recommended to ensure consistency. Importantly, deployment should not be framed as a clinical application at this stage. Instead, the focus should be on enabling collaborative development, data sharing, and iterative refinement as new datasets become available.

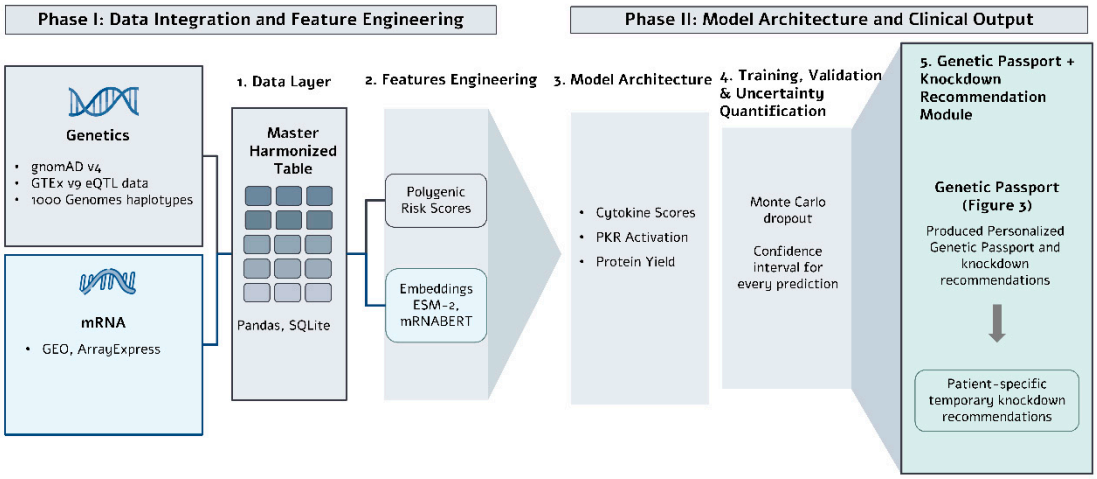


**Figure 2.** Two-phase technical pipeline for building the PRR/ISR Immunogenicity Atlas. Phase I shows data integration and feature engineering. Phase II shows the multi-modal model, training with uncertainty quantification, and the final clinical output (Genetic Passport + ranked knockdown recommendations).

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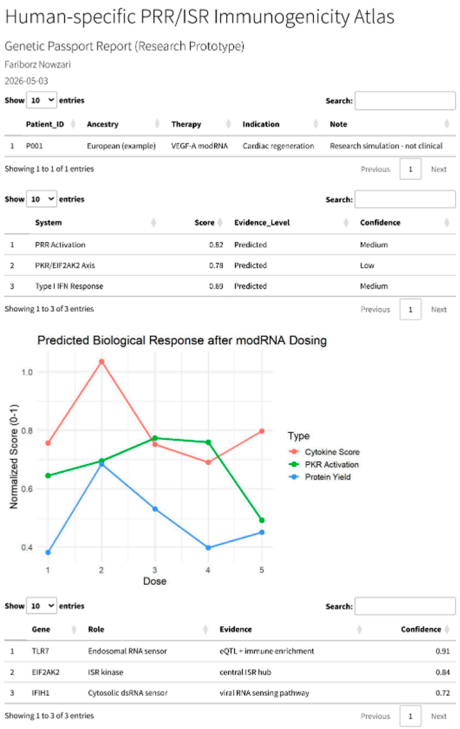


**Figure 3.** a mock "Genetic Passport" report (risk profile + predicted cytokine/ISR curves + top 1–2 knockdown recommendations with confidence scores). https://rpubs.com/fznvet/1429254.

## 5. Ethics, Privacy, Ancestry and Regulatory Considerations

The Human-specific PRR/ISR Immunogenicity Atlas integrates genomic data with functional predictions of immune and translation responses. As such, it operates on sensitive personal data and must be developed within a strict ethical and regulatory framework.

Genomic data are inherently identifiable and require robust protection strategies. The atlas should adopt a privacy-preserving architecture, such as local or federated data processing, to minimize the transfer and storage of raw genetic information. Explicit informed consent is required for all datasets used in model development and validation, together with a Data Protection Impact Assessment to identify and mitigate risks associated with data handling. These requirements are particularly relevant when combining genomic and functional response data across multiple sources ([14]; gnomAD; GTEx). A second critical issue is ancestry representation. Current genomic reference datasets are disproportionately derived from populations of European ancestry, which can introduce systematic bias in predictive models [14,15]. If not addressed, this imbalance may reduce model performance in underrepresented populations and lead to unequal predictive accuracy. Therefore, the atlas must report ancestry-stratified performance metrics and explicitly acknowledge limitations in generalizability.

The proposed framework also raises biological safety considerations. Temporary suppression of PRR or ISR pathways may reduce unwanted immune activation, but these pathways play essential roles in antiviral defense and cellular stress responses [16]. Even transient modulation may increase susceptibility to infection or alter normal cellular function. As a result, any predicted intervention should be interpreted cautiously and evaluated within controlled experimental or clinical settings.

From a regulatory perspective, the atlas is best positioned as a research and hypothesis-generating tool in its initial form. Depending on its future use, it may fall under the category of clinical decision support software, which is subject to regulatory oversight by agencies such as the U.S. Food and Drug Administration [30].

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## 6. Challenges and Future Directions

The development of a Human-specific PRR/ISR Immunogenicity Atlas faces several practical and conceptual challenges that must be addressed before broader application. The most immediate limitation is data availability. There is a lack of datasets that directly link donor genotype to functional immune and translation responses following modRNA delivery. While public transcriptomic datasets exist, they often lack matched genetic information, which limits their utility for genotype-guided modeling. This gap represents a primary bottleneck and defines the need for small, well-controlled proof-of-concept studies in genotyped human-derived systems [20]. A second challenge is model generalizability. Early implementations will likely rely on small datasets with limited diversity, increasing the risk of overfitting and reducing robustness across populations. Even with careful validation, model predictions should be interpreted as probabilistic and context-dependent rather than definitive. A third limitation relates to biological complexity. PRR and ISR pathways interact with broader immune and stress-response networks, including feedback loops and cell-type-specific effects [16]. Simplified models may not fully capture these interactions, particularly when predicting the effects of gene knockdown or pathway modulation. This limitation reinforces the need for iterative validation and integration of experimental data.

Delivery constraints also remain important. Although LNP-based systems enable delivery of both modRNA and siRNA/ASO, tissue specificity and efficiency vary across organs and conditions. These factors may influence the feasibility and effectiveness of the recommended knockdown strategies in practice. Clinical integration presents additional challenges. For the atlas to be useful, outputs must be interpretable, reproducible, and actionable within realistic timeframes. At the same time, uncertainty must be clearly communicated, especially in cases where predictions are based on limited data or extrapolation. Despite these limitations, the framework provides a structured path forward. Initial efforts should focus on generating minimal datasets, validating key predictions, and refining model components in a controlled setting. If successful, the approach could be extended to additional cell types, delivery platforms, and therapeutic contexts. In the longer term, integrating higher-resolution data such as single-cell transcriptomics or spatial profiling may improve the ability to capture cell-specific responses and refine predictions. However, these extensions should follow, rather than precede, validation of the core framework.

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