



The Perfect Disguise: Virus-Like mRNA Vaccines Turn Viral Mimicry into Immunity

By Dylan Allender* and JF Trembl*†

The rapid success of mRNA vaccines has transformed modern vaccinology, yet their limitations are becoming increasingly clear. Protection against rapidly evolving viral variants is not always complete, and immune responses can decline over time, suggesting that efficacy depends not only on the antigen itself but also on how that antigen is delivered and interpreted by the immune system. Writing in *Nature Nanotechnology*, Zhang and colleagues present a vaccine platform that seeks to address these challenges by combining antigen delivery, immune targeting, and structural mimicry into a single system¹. Their virus-like structure (VLS) platform represents a conceptual shift: rather than simply delivering mRNA, it attempts to reproduce key features of viral infection, thereby shaping a more coordinated and durable immune response.

This approach builds on decades of work in genetic vaccination. Early studies demonstrated that direct gene transfer into muscle tissue could result in protein expression within host cells, establishing that the body itself could act as a site of antigen production². Subsequent experiments showed that DNA encoding viral proteins could generate both antibody responses and cytotoxic T cell activity, leading to the concept of genetic immunization, in which nucleic acids serve as instructions for endogenous antigen synthesis.³⁻⁵ This marked a fundamental shift in vaccine design, moving away from the direct administration of proteins and toward programming host cells to produce antigens internally. Such strategies provided the basis for later advances in RNA-based vaccination, which offered similar benefits without the risks associated with genomic integration.

mRNA vaccines expanded this framework but introduced new challenges. Because mRNA functions in the cytoplasm, it avoids nuclear entry and integrates more safely into therapeutic strategies. Early work confirmed that mRNA could induce antigen-specific immune responses *in vivo*, yet these approaches were limited by the

innate immune system's ability to detect foreign RNA. Recognition by pattern recognition receptors such as Toll-like receptors can trigger inflammatory responses that reduce protein translation and limit vaccine effectiveness.⁶⁻⁸ This barrier was overcome through chemical modification of the RNA molecule itself. Incorporation of modified nucleosides, such as pseudouridine, reduces immune detection while increasing translational efficiency, a breakthrough that enabled the development of modern mRNA vaccines.⁹

At the same time, improvements in delivery systems played a critical role in advancing the field. Lipid nanoparticles were optimized to protect mRNA from degradation and facilitate

cellular uptake, particularly through mechanisms that promote endosomal escape.¹⁰ These innovations made it possible to deploy mRNA vaccines at scale, culminating in highly effective vaccines against SARS-CoV-2 that demonstrated strong antibody and T cell responses in both preclinical and clinical settings.^{11,12} However, despite these successes, current mRNA platforms rely largely on passive delivery into cells and do not fully replicate the spatial targeting and immune activation seen during natural viral infection.

Zhang and colleagues address this limitation by designing a delivery system that more closely resembles a virus. Their VLS platform consists of an mRNA-loaded lipid nanoparticle decorated with viral spike protein on its surface, creating a structure capable of engaging host receptors such as ACE2 and DC-SIGN.¹ This receptor-mediated interaction allows the particle to preferentially enter epithelial cells, dendritic cells, and macrophages, which are central to initiating immune responses. By targeting these cells directly, the VLS platform enhances mRNA delivery and antigen expression compared with conventional lipid nanoparticles, effectively shifting from passive distribution to active cellular targeting.

This targeted delivery has important con-

sequences for immune activation. Rather than relying on nonspecific uptake, the VLS system promotes interaction with antigen-presenting cells, leading to a more controlled and balanced activation of innate immune pathways. Experimental data show increased interferon signaling and immune regulator expression without the excessive inflammatory responses often associated with unmodified RNA delivery.

¹ This balance is critical, as excessive inflammation can impair antigen expression, while insufficient activation may fail to generate a robust adaptive response. By modulating this balance, the VLS platform creates a more favorable environment for immune priming.

The downstream effects of this improved targeting are evident *in vivo*. VLS immunization results in greater colocalization of antigen with dendritic cells and macrophages, along with increased activation of these cells. These early innate responses translate into stronger adaptive immunity, characterized by higher antibody titres, improved neutralization of multiple viral variants, and enhanced T cell responses. ¹

Notably, these immune responses are more durable than those generated by mRNA or protein alone, suggesting that the coordinated activation of multiple immune pathways contributes to long-term protection.

A key feature of the VLS platform is its ability to deliver both mRNA and protein simultaneously. This dual-delivery strategy allows the immune system to process antigen through multiple pathways. Endogenously produced antigen from mRNA supports presentation via major histocompatibility complex class I pathways, activating CD8⁺ T cells, while surface-displayed protein provides immediate antigen for uptake and presentation via class II pathways. This combination enhances communication between different arms of the immune system and may facilitate cross-presentation across diverse dendritic cell populations. In doing so, the VLS platform more closely mimics natural infection, where antigens are encountered in multiple forms and contexts.

The efficacy of this approach is particularly striking. In viral challenge experiments, animals immunized with the VLS platform show minimal viral replication across tissues and are protected against multiple SARS-CoV-2 variants.¹ This suggests that the immune response generated is not only stronger but also more functionally effective.



tive. By integrating innate and adaptive responses, the platform achieves a level of protection that approaches that of natural infection while avoiding its associated risks.

Despite these promising findings, several questions remain. The authors note that the precise physicochemical structure of the VLS particles and the mechanisms governing their interactions with receptors such as DC-SIGN are not yet fully understood[†]. Further investigation will be needed to determine how these interactions influence immune signaling and how they can be optimized. In addition, the complexity of the system may present challenges for large-scale manufacturing and clinical translation, factors that will be critical for its broader application.

More broadly, this work reflects a shift in vaccine design from simple delivery systems to platforms that actively shape immune responses. Early genetic vaccines demonstrated that immunity could be programmed, while later advances refined delivery and molecular stability. The VLS platform builds on these developments by incorporating structural and functional elements of viral infection, enabling more precise control over how the immune system is engaged. This approach has implications beyond infectious disease, particularly in areas such as cancer immunotherapy, where targeted and coordinated immune activation is essential.

Zhang and colleagues therefore offer more than a technical innovation. Their work highlights how combining insights from immunology, virology, and nanotechnology can lead to vaccines that better replicate natural immune processes. As the field continues to evolve, platforms that integrate delivery, targeting, and immune modulation may define the next generation of vaccines, moving closer to the goal of fully engineered immunity.

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*University of Kansas, Edwards Campus, Biotechnology

†Corresponding Author jtreml@ku.edu

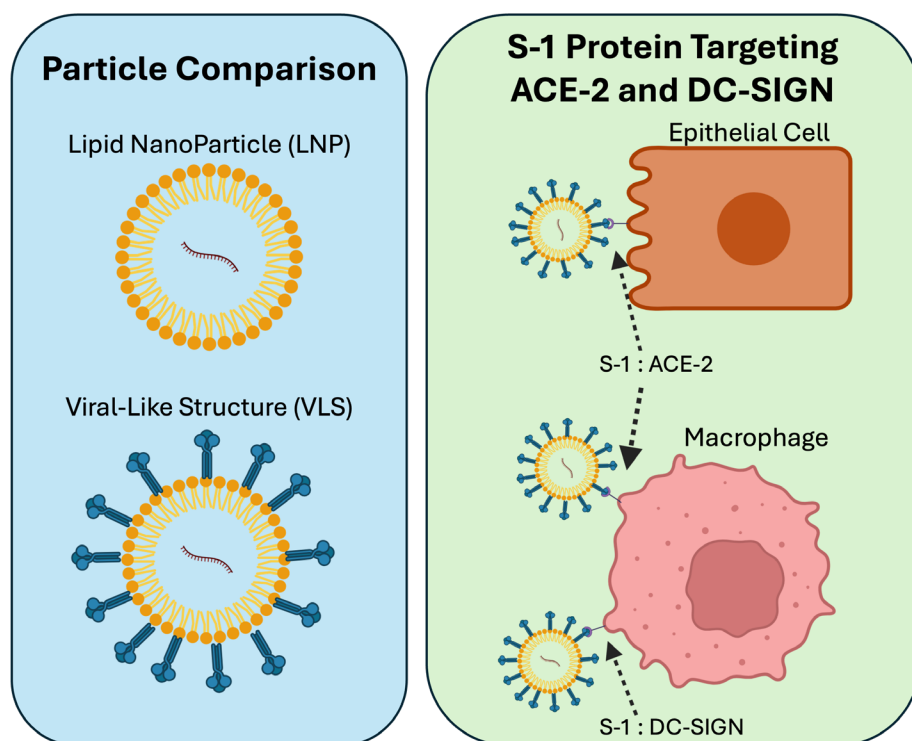


Figure 1 | Viral-Like Structure Interaction with Host Cells. Lipid nanoparticles (LNP) and a viral-like structures (VLS) carrying mRNA. On the left, the LNP is shown as a simple lipid sphere containing mRNA, while the VLS has spike-like S-1 proteins on its surface. The right side shows the S-1 protein on the VLS binding to ACE-2 receptors on epithelial cells and the ability to bind to both the ACE-2 and DC-SIGN receptors on macrophages, allowing the particle to target these cells more specifically. Created in BioRender. Allender, D & Trembl, J. (2026) <https://BioRender.com/hpspami>