A paradigm shift in mucosal vaccinology: NanoCF501 as a mechanistically grounded, clinically viable STING-targeting adjuvant

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Received: July 10, 2026; Accepted: July 20, 2026; Published Online: July 21, 2026; https://doi.org/10.59717/j.xinn-mater.2026.100233

Citation: Xi E., Sun F., Chen L., et al. (2026). A paradigm shift in mucosal vaccinology: NanoCF501 as a mechanistically grounded, clinically viable STING-targeting adjuvant. *The Innovation Materials* **4**:100233.

The persistent global threat posed by respiratory viruses—from SARS-CoV-2 variants to emerging zoonotic coronaviruses and seasonal influenza—underscores a fundamental gap in pandemic preparedness: the absence of safe, effective, and approved mucosal vaccines. Intramuscular platforms, while instrumental in controlling systemic disease, fail to elicit robust secretory IgA (sIgA) or tissue-resident memory T cells (TRM) at the primary site of infection—the respiratory mucosa. This limitation leaves the "front door" of immunity unguarded, permitting viral entry, replication, and transmission despite high serum neutralizing titres. In their landmark study published in Nature Nanotechnology, Liu, Zhou, Gao, and colleagues do not merely propose an incremental improvement; they deliver a rationally engineered, mechanistically validated, and translationally de-risked solution: NanoCF501, a nanoparticulate STING agonist that redefines the boundaries of mucosal adjuvant design.[1]

At its core, NanoCF501 is a triumph of precision nanomedicine. It addresses two critical, interlinked failures of first-generation STING agonists: poor mucosal bioavailability and systemic toxicity.[2] The authors encapsulate the potent small-molecule agonist CF501 within a biocompatible, self-assembling poly(2-ethyl-2-oxazoline) (PEOX) polymer. This simple yet profound formulation yields monodisperse ~18 nm nanoparticles—small enough to penetrate the dense glycoprotein mesh of respiratory mucus, yet large enough to avoid rapid systemic absorption. Pharmacokinetic data in rats confirm this design principle: NanoCF501 exhibits no detectable systemic exposure, remaining localized in the respiratory tract. This spatial confinement is not a compromise—it is the therapeutic imperative. By restricting STING activation to the lung and upper airways, NanoCF501 harnesses the pathway's potent immunostimulatory power for local immune education while sidestepping the cytokine storm and systemic inflammation

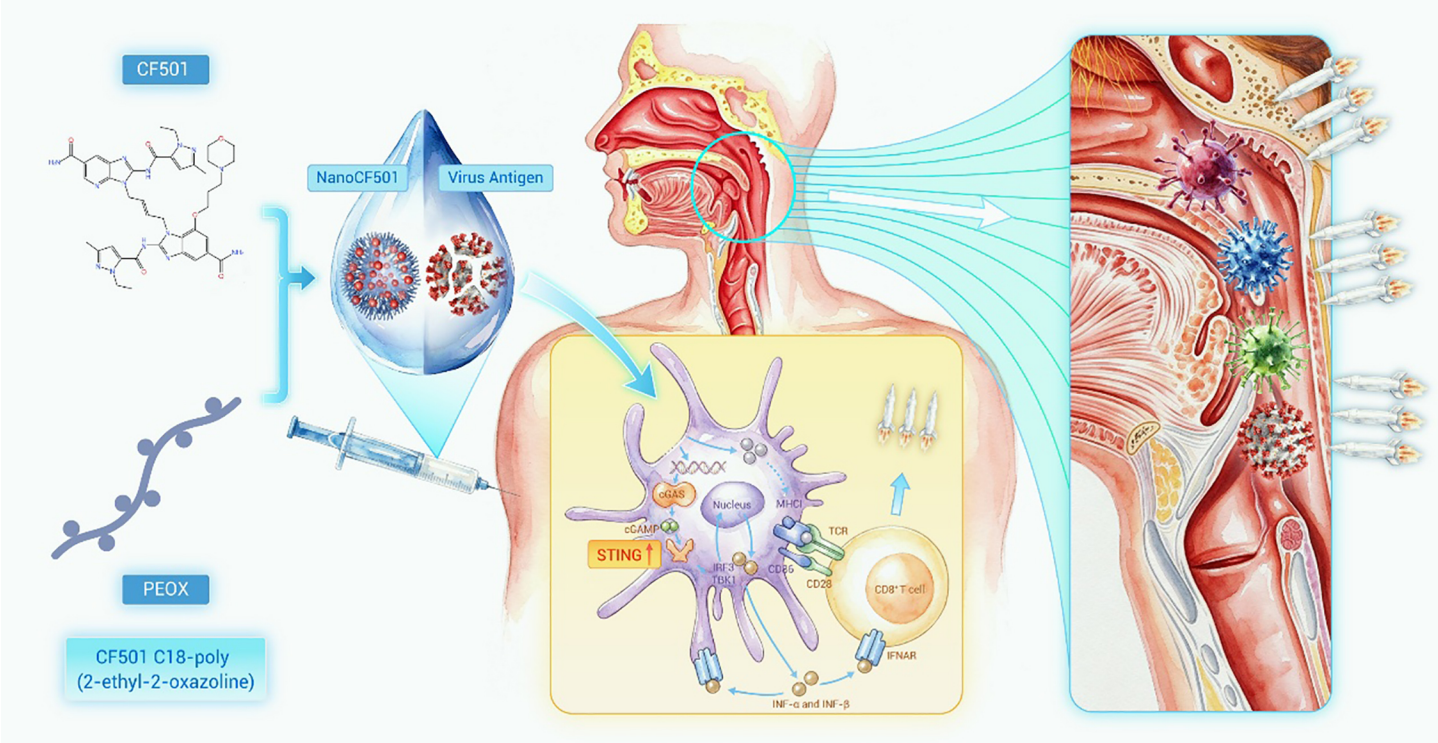

Figure 1. Schematic illustrations of NanoCF501 acted as a STING-Targeting Adjuvant in Mucosal Vaccinology.

that have plagued STING agonists in oncology (Figure 1).

The functional impact of this engineering is extraordinary. When co-administered intranasally with a multivalent chimeric antigen (SSM2), NanoCF501 induces coordinated mucosal-systemic immunity—a dual-layered defence previously unattainable with subunit vaccines. In mice, it drives unprecedented levels of airway sIgA against SARS-CoV-2, SARS-CoV, and MERS-CoV, alongside durable, cross-reactive serum neutralizing antibodies. Crucially, it achieves systemic nAb titres equivalent to conventional intramuscular vaccination—yet at just 1/20th the dose, demonstrating remarkable potency and efficiency. This is not merely quantitative enhancement; it is qualitative reprogramming. Single-cell RNA sequencing reveals NanoCF501's mechanism: it triggers STING-dependent reprogramming of lung antigen-presenting cells (cDCs and macrophages), leading to enhanced antigen uptake, maturation (CD86/MHC-II upregulation), and migration to draining lymph nodes. This innate activation then orchestrates adaptive responses: expansion of germinal centre B cells, somatic hypermutation, class-switching to IgA, and the generation of long-lived plasma cells (LLPCs) in the bone marrow—all hallmarks of high-fidelity, durable humoral immunity.

Perhaps most clinically significant is NanoCF501's ability to generate robust TRM populations.[3] Unlike systemic vaccines, which poorly seed the

mucosa, NanoCF501 drives potent CD4+ and CD8+ TRM formation in both nasal tissue and lungs—a finding validated in non-human primates. These TRM cells are the frontline sentinels, capable of immediate cytolytic activity upon viral re-encounter. The study demonstrates that this TRM response persists for at least 12 months in mice, correlating with sterilizing protection against heterologous challenge with bat-derived sarbecoviruses (WIV1, RsSHC014) and the highly evasive SARS-CoV-2 BA.5.2 variant—even in aged mice, a population notoriously refractory to vaccination. This durability, coupled with efficacy in aged models, directly addresses two of vaccinology's most pressing challenges.[4]

Beyond coronaviruses, NanoCF501's platform flexibility is proven by its successful repurposing of a licensed intramuscular quadrivalent influenza vaccine for intranasal delivery—eliciting potent strain-specific mucosal IgA and systemic IgG. This "adjuvant retrofitting" strategy could rapidly accelerate the development of next-generation flu vaccines without requiring de novo antigen design.[5]

Critically, the authors rigorously de-risk NanoCF501 for clinical translation. Comprehensive safety studies in rats—including high-dose (18×) repeated administration—show no adverse effects on body weight, hematology, organ histopathology, or genotoxicity. While the paper rightly notes the need for first-in-human trials to assess rare events, the preclinical safety profile is exceptionally favorable.

Mucosal vaccine development has long been hindered by a critical challenge: inducing robust localized immunity without causing systemic toxicity. This innovative work from Nature Nanotechnology presents an elegant solution in NanoCF501, a precision-engineered nanoparticulate STING agonist that opens new avenues for pan-coronavirus protection.

The researchers designed NanoCF501 by encapsulating the potent STING agonist CF501 in a self-assembling 2-ethyl-2-oxazoline polymer, creating uniform ~18 nm nanoparticles ideal for mucus penetration. Preclinical results are striking: intranasal immunization with NanoCF501 plus a multivalent pan-β-coronavirus antigen induced robust mucosal immunity (marked by secretory IgA and tissue-resident memory T cells) and durable systemic broad-spectrum protection, even against heterologous bat-derived coronaviruses not included in the original antigen design. Notably, it achieved equivalent systemic neutralization with only 1/20th the systemic dose of intramuscular delivery, with minimal systemic exposure and a favourable safety profile validated in both mice and non-human primates.

This work stands out by solving longstanding limitations of current mucosal adjuvants, combining nanoscale rational design with innate immune targeting to create a potentially universal adjuvant platform. Beyond coronaviruses, its demonstrated compatibility with licensed influenza vaccines highlights its broad translational potential for pandemic preparedness and next-generation respiratory vaccine development.

In conclusion, Liu et al. have moved beyond empirical adjuvant discovery to mechanistic engineering. NanoCF501 is not just another nanoparticle; it is a spatially intelligent, STING-pathway-targeted immune conductor that transforms the respiratory mucosa from a passive barrier into an active immunological organ. By solving the twin problems of delivery and toxicity, it provides a universal, scalable, and clinically viable platform—not only for pan-coronavirus protection but for a broad spectrum of respiratory pathogens. This work represents a watershed moment, shifting the paradigm from "can we induce mucosal immunity?" to "how do we deploy it safely and effectively?"—and in doing so, it lays the definitive nanotechnological foundation for the next generation of pandemic-prepared vaccines.

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FUNDING AND ACKNOWLEDGMENTS

This research was funded by the National Key R&D Program of China (Grant No. 2022YFB3805902), the National Natural Science Foundation of China (Grant No. 22077118), the "111" project (No. B18012). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Enpeng Xi: conceptualization, investigation, writing original draft; Fanshu Sun and Licong Chen: conceptualization, writing-review; Nan Gao: supervision, writing-review, funding acquisition. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.