VACCIREVIEW

Mucosal vaccination in mice provides protection from diverse respiratory threats

Bibliography

Zhang H, Floyd K, Fang Z, Hoffmann FA, Lee A, Froggatt HM, Bharj G, Xie X, Eppler HB, Santagata JM, Wang Y, Hu M, Fox CB, Arunachalam PS, Baric R, Suthar MS, Pulendran B. Mucosal vaccination in mice provides protection from diverse respiratory threats. Science. 2026; eaea1260.

Summary

The authors address the need for broadly protective vaccines against diverse respiratory viruses and bacteria, motivated by the limitations of pathogen-specific vaccines in the face of sheer endless numbers and diversity of pathogens, antigenic drift, shift, and emerging pathogens. Building on epidemiologic and experimental evidence that live-attenuated vaccines (such as BCG, OPV, measles) induce heterologous protection via “trained immunity” and integrated organ immunity, they design a purely synthetic mucosal platform intended to harness similar principles without using live microbes. The candidate vaccine consists of an intranasal PEGylated liposomal formulation (GLA-3M-052-LS) combining a TLR4 agonist (GLA) and a TLR7/8 agonist (3M-052-LS) admixed with a model antigen, ovalbumin, delivered in four intranasal doses to mice.

In multiple challenge models, vaccinated mice showed broad and durable protection lasting at least three months against viral and bacterial respiratory pathogens and even a noninfectious allergen challenge. After intranasal SARS-CoV-2 B.1.351 challenge at 21, 42, and 90 days post-immunization, vaccinated mice had less weight loss, reduced lung viral titers, decreased subgenomic RNA, and attenuated histologic lung damage compared with controls. Cross-protection extended to mouse-adapted SARS-CoV MA15 and SCH014 MA15 coronaviruses, with lower lung viral titers and milder pathology. Vaccination also reduced lung bacterial loads after intranasal infection with *Staphylococcus aureus* and *Acinetobacter baumannii* and lowered kidney bacterial burden after intravenous *S. aureus*, suggesting protection beyond the respiratory tract. In influenza-experienced mice, the same vaccine further decreased bacterial loads, indicating efficacy in immunologically primed hosts.

Mechanistically, the vaccine induced persistent antigen-specific CD4+ and CD8+ tissue-resident memory T cells (TRM) in the lung capable of producing IFN-γ, IL-2, TNF-α, and IL-17A, along with sustained activation and antigen-presenting capacity in alveolar macrophages (AM) and other innate cells. Flow cytometry and single-cell RNA-seq/ATAC-seq demonstrated long-lasting upregulation of MHC-I/MHC-II and CD86 on AM, enrichment of antigen-presentation and interferon-response pathways, and

durable epigenetic remodeling with accessible chromatin at antigen-presentation and inflammatory-response loci for at least three months. Cytokine profiling showed a largely lung-localized, transient inflammatory burst with elevated CXCL10, CCL5, CCL2, IFN-γ, sRANKL, and BAFF in BAL fluid, while systemic cytokine levels remained comparatively low.

Depletion experiments revealed that long-term heterologous protection required both antigen and T cells: adjuvant alone produced only short-lived effects, and combined CD4/CD8 depletion abolished protection against SARS-CoV-2 and *S. aureus* and blunted persistent AM activation. Spatial transcriptomics and ligand–receptor analyses showed that vaccination re-organized lung tissue into an integrated immune network with enhanced communication between T cells, B cells, AM, and epithelial cells; this pattern was lost when T cells were depleted. Functionally, vaccinated mice formed tertiary lymphoid-like structures near airways within three days of heterologous infection, supporting rapid local T- and B-cell responses, higher pathogen-specific T-cell frequencies, increased virus-specific IgG/IgG2c in BAL, and reduced pro-inflammatory cytokines associated with cytokine storm.

The authors further demonstrate that AMs are critical effectors of non-specific protection. Intranasal clodronate liposome–mediated AM depletion abrogated protection against *S. aureus*. AM from vaccinated mice showed enhanced in vivo phagocytosis of labeled *S. aureus*, apoptotic/necrotic neutrophils, and virus-infected epithelial cells, upregulation of activation markers after infection, and transcriptomic signatures indicating improved antigen presentation, chemotaxis, tissue repair, and cell–cell adhesion. RANKL emerged as a key mediator linking T cells to trained AM; its depletion during immunization eliminated protective effects, whereas blocking CD40L, IFN-γ, or TNF-α did not.

Beyond infection, the authors tested a house dust mite–induced asthma model. Vaccinated mice displayed reduced eosinophils, ILC2 cells, Th2 cytokine-producing CD4+ T cells, serum IgE, and mucus hypersecretion, with these effects lasting at least three months. Protection against allergic airway disease was lost when CD4+ and CD8+ T cells were depleted and could be transferred with vaccine-primed T cells in an OVA–alum asthma model, indicating a central role of vaccine-induced T-cell memory in modulating allergic responses.

In the discussion, the authors propose that intranasal GLA-3M-052-LS plus antigen establishes “integrated organ immunity” in the lung by coupling robust TRM formation to RANKL-mediated, epigenetically imprinted AM training, yielding broad, antigen-agnostic

protection against respiratory viruses, bacteria, and allergens. They argue that, unlike live-attenuated vaccines with context-dependent heterologous effects, this synthetic platform offers a programmable, clinically translatable route to universal respiratory vaccines and early pandemic countermeasures, potentially using influenza or SARS-CoV-2 antigens to leverage pre-existing human T-cell memory.

Comment

The study presents an ambitious concept of a "universal" mucosal vaccine, but the same strong, unspecific activation and durable reprogramming of lung immunity that make it effective also raise safety questions. The formulation combines potent TLR4 and TLR7/8 agonists in a PEGylated liposomal system, given repeatedly intranasally, leading to broad innate and adaptive activation, persistent changes in chromatin accessibility, and long-lived TRM and alveolar macrophage phenotypes. Although inflammatory cytokine elevations are largely confined to the lung with lower systemic levels, this intense localized stimulation and durable "trained-immunity–like" state could, in principle, predispose to chronic inflammation, tissue remodeling, or autoimmunity, especially in susceptible individuals. The mouse experiments do not systematically assess autoantibodies, loss of tolerance, or tissue damage beyond approximately three months, and the authors acknowledge that human mucosal immunity, shaped by lifelong exposures, may respond differently.[ppl-ai-file-upload.s3.amazonaws]

Mechanistically, RANKL-dependent crosstalk between T cells and alveolar macrophages is central to long-term protection, yet this pathway also participates in bone and immune regulation, so chronic modulation in humans could have unforeseen systemic effects. Deliberate induction of tertiary lymphoid structures and enhanced antigen presentation in lung tissue, while advantageous for rapid pathogen control, might under other conditions favor ectopic lymphoid neogenesis and autoimmunity, as known from chronic inflammatory diseases. The platform's ability to suppress Th2-driven asthma is encouraging, but its capacity to amplify Th1/Th17 responses and remodel tissue microenvironments means that different antigenic or environmental contexts (for example, concurrent autoantigen exposure, pollutants, or latent infection) might tilt responses toward immunopathology. Because the work relies on a model antigen and controlled challenges in mice, careful, stepwise human evaluation with explicit autoimmunity and immune-dysregulation endpoints will be essential before broad application.

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