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Commentary

Modulating immunodominance through adjuvants and routes – A commentary on next-generation vaccine design for clinical trial

Zhuo Zhao[1*]

[1]Department of Microbiology and Biochemical Pharmacy College of Pharmacy and Laboratory Medicine Army Medical University Chongqing 400038, China

*Author for correspondence: Email: zhaozhuo198309@163.com

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Abstract

Immunodominance – the preferential recognition of certain epitopes – is a double-edged sword in vaccine development. While it enables strong responses against specific pathogens, it limits breadth and durability, especially against rapidly mutating viruses or bacteria. This commentary discusses how adjuvants and immunization routes actively reshape immunodominant epitope landscapes, based on recent preclinical findings. MRSA antigens (Hla,SEB,LuKG,IsdB and MntC), *Klebsiella pneumoniae* FimA, and SARS-CoV-2 RBD, showing that adjuvant choice can profoundly alter humoral immunity. These insights might have direct implications for clinical trial design, patient stratification, and the development of broadly protective vaccines. We argue that incorporating immunodominance modulation into early phase clinical evaluations may accelerate the path toward more effective and safer vaccines.

Introduction: The Immunodominance Dilemma in Recombinant Subunit Vaccines

Recombinant subunit vaccines are favored for their safety and manufacturability, but their efficacy hinges on the immunodominance of selected antigens. Immunodominance ensures that the immune system focuses on a limited set of epitopes, often leading to high-titer neutralizing antibodies. However, this narrow focus becomes a liability when strain heterogeneity exists (e.g., MRSA and *Klebsiella pneumoniae*) or when pathogens mutate (e.g., SARS-CoV-2 variants). The key challenge is no longer merely identifying protective antigens, but actively steering the immune response toward conserved, broadly protective epitopes while avoiding non-protective or variable regions. Adjuvants and immunization routes are emerging as powerful tools to achieve this redirection – not as passive enhancers, but as active determinants of epitope selection.

Immunodominant Epitopes as Diagnostic and Protective Targets

Immunodominance is defined by the hierarchical recognition of epitopes during an immune response. Although this prioritization is beneficial for clearing the primary infection, it often leads to strain-specific immunity that fails against divergent isolates. A compelling example comes from our recent work on MRSA [1]. By screening convalescent sera from MRSA-infected patients, previous study identified ten immunodominant B-cell epitopes from antigens currently in phase III trials (Hla, SEB, MntC, IsdB) and the newly described leukocidin LukG. Seven were novel. Five of these epitopes (Hla_{168_185}, $IsdB_{384\_401}$, $MntC_{55\_72}$, SEB_{37_54}, and $LukG_{235\_252}$) conferred protection in a murine sepsis model, and their combination showed broad efficacy against diverse clinical MRSA isolates. Intriguingly, these B-cell epitopes all contained predicted $CD4^+$ T-cell epitopes,

suggesting dual T-B cell stimulation. This finding not only supports a multi-epitope vaccine platform but also enabled a rapid (3-hour) diagnostic panel with 83.9% sensitivity and 82.6% specificity which outperforms culture. Thus, immunodominant epitopes can serve dual purposes, bridging diagnostics and therapeutics which could be integrated into clinical trial endpoints for infectious diseases.

Adjuvants Beyond Enhancement While Directing Epitope Selection

Adjuvants are emerging as modulators that can influence epitope selection. Traditional aluminum adjuvants are Th2-biased and offer limited capacity to broaden the epitope repertoire. Recent data, however, demonstrate that next-generation adjuvants might fundamentally reshape the immunodominance hierarchy. For example, one group compared four adjuvants (alum, AddaVax, diABZI, and ISCOMs) with OVA or RBD-Fc (receptor-binding domain–Fc fusion protein) given intramuscularly. All raised serum IgG and BALF (bronchoalveolar lavage fluid) IgG, but only ISCOMs significantly increased lung-resident $CD8^+$ T cells [2]. This indicates that certain adjuvants can redirect immunity toward cellular compartments and conserved intracellular epitopes, which may be critical for protection against intracellular pathogens or for long-term surveillance.

In a separate study, one team systematically compared three clinically relevant adjuvants (AddaS03, AddaVax, and $AlPO_4$) on the immunogenicity and protective efficacy of recombinant FimA, the principal structural subunit of type 1 pili in *Klebsiella pneumoniae* [3], among which, AddaS03 is for squalene-based oil-in-water nanoemulsion adjuvant (AS03-like); AddaVax is for squalene-based oil-in-water nanoemulsion adjuvant (MF59-like), $AlPO_4$ is for aluminum phosphate adjuvant. The findings were striking: FimA + AddaS03 conferred 100% protection against lethal hvKP YBQ challenge in a murine pneumonia model, whereas FimA + AddaVax yielded only 40% survival, and FimA alone provided merely 20% protection ($P = 0.0003$ for AddaS03 vs. FimA-only). Bacterial load quantification corroborated these results. Importantly, total IgG titers did not correlate with protection: AddaVax induced the highest antibody titers (geometric mean titer: 256,000) but conferred the lowest survival, whereas AddaS03 induced intermediate titers (geometric mean titer: 198,400) yet achieved 100% protection. This discrepancy underscores that antibody functional quality, rather than mere quantity, determines protective efficacy, which is a critical insight for clinical trial design where antibody titers alone may be misleading surrogates of protection.

In a separate study, one team systematically compared three different adjuvants ($Al(OH)_3$, ASO3, and AddaVax) on RBD immunodominance [4]. It was found that each adjuvant generated a distinct B-cell epitope fingerprint as different dominant and subdominant epitopes were recognized. This suggests that adjuvants are not mere "immune boosters" but "immune directors" that can be rationally selected to expose cryptic conserved epitopes or to mask variable ones. For clinical trials, this suggests that adjuvant selection should be guided not only by safety and overall immunogenicity, but also by the desired epitope profile, which can be assessed through epitope mapping in early-phase studies.

While our own studies have focused primarily on B-cell epitopes and humoral immunity, the principles of immunodominance modulation extend equally to T-cell responses. Recent work has provided mechanistic insight into how PRR ligand adjuvants—specifically MPLA (TLR4 agonist) and CpG (TLR9 agonist)—reshape $CD4^+$ T-cell epitope hierarchies [5]. Using MHC-II immunopeptidomics, they demonstrated that these adjuvants do not reveal cryptic epitopes, as previously hypothesized, but instead inhibit the presentation of high-stability peptides that would otherwise dominate the T-cell response. The low-stability peptides presented in adjuvant-treated groups nevertheless elicited robust T-cell responses and formed immune memory. This finding has fundamental implications: adjuvants may function not by expanding the epitope repertoire but by altering the competitive hierarchy of peptide–MHC (pMHC) stability on antigen-presenting cells.

For $CD8^+$ T-cell responses, squalene emulsion-based adjuvants such as MF59 and AddaVax have been shown to stimulate antigen-specific $CD8^+$ T-cell responses through a RIPK3-dependent pathway [6]. The RIPK3-dependence of the CD8 response but not the antibody response, which suggests that humoral and cellular immunodominance may be regulated through distinct adjuvant-sensing pathways. This differential regulation underscores the importance of evaluating both humoral and cellular epitope hierarchies when selecting adjuvants for vaccines intended to induce combined antibody and T-cell protection.

The capacity of adjuvants to modify pMHC stability and thereby reshape $CD4^+$ and $CD8^+$ T-cell immunodominant epitope responses provide a mechanistic framework for understanding why different adjuvants produce distinct T-cell response profiles. These findings collectively indicate that adjuvant-driven immunodominance modulation operates at multiple levels such as APC activation, pMHC stability, and downstream T-cell differentiation into effector and memory populations.

Therapeutic Potential of Epitope Which Could Induced Antibodies

In a passive immunization experiment, serum from Mix-peptides + $AlPO_4$-immunized mice combined with low-dose meropenem achieved 90% survival in hvKP-challenged mice (n = 10 per group), significantly outperforming meropenem alone (70% survival) and naive serum controls (0% survival). Bacterial loads were reduced by approximately 1–2 orders of magnitude in the combination therapy group compared with the PBS control ($P<0.0001$) [7]. This synergistic effect of antibody-mediated opsonophagocytosis enhancing bacterial clearance and reducing the antibiotic dose required which has significant implications for combating multidrug-resistant pathogens. This concept mirrors our previous findings in *Staphylococcus aureus* and supports the development of antibody-antibiotic combination therapies as a viable strategy for clinical translation [8].

In a mouse model of MRSA252 bacteremia, mice challenged with a lethal dose of MRSA252 were administered a cocktail of four immunodominant epitope-specific monoclonal antibodies (mAbs) targeting Hla_{48_65}, $IsdB_{432\_449}$, SEB_{78_95}, and SEB_{222_239}, combined with a low dose of vancomycin or linezolid. Survival analysis revealed that the mAb cocktail in combination with low-dose antibiotics significantly improved survival rates: in a lethal sepsis model, the combination achieved 80% survival (mAb cocktail + vancomycin) and 80% survival (mAb cocktail + linezolid), compared with only 20% survival for either antibiotic alone ($P<0.005$) and 30% for mAb cocktail alone ($P<0.05$) [8,9].

Clinical and Translational Perspectives

The findings reviewed here have several direct applications for clinical research:

Firstly, it might suggest applications for trial design. Phase I/II studies should incorporate epitope which mean that mapping assays to monitor how different adjuvants and routes shape the immunodominance hierarchy in humans, not just overall antibody titers. This would enable rational selection of lead candidates for phase III.

Secondly, it could advise applications for diagnostic Integration. The dual-function epitopes we identified for MRSA could be adapted as point-of-care tests to guide antibiotic stewardship and as correlates of protection in vaccine trials.

Thirdly, it might also provide regulatory considerations. Regulatory agencies may need to consider epitope breadth as a quality attribute, especially for vaccines intended against mutating pathogens. Standardization of epitope mapping methods would facilitate cross-trial comparisons.

Translational challenges and the preclinical-to-clinical gap

Firstly, a fundamental challenge in translating adjuvant-driven immunodominance modulation from preclinical models to human vaccine trials lies in the immunological discordance between inbred mice and outbred human populations. Mice with restricted MHC haplotypes exhibit predictable, narrow epitope hierarchies that can be readily mapped and manipulated; humans, by contrast, express up to six different HLA class I and class II molecules per individual, with extraordinary polymorphism across populations. An epitope that is immunodominant in one HLA context may be entirely silent in another.

Secondly, the route-dependent immunodominance differences observed in mice face substantial practical barriers in humans. Mucosal immunization, while immunologically attractive for respiratory pathogens, faces challenges including poor antigen retention, rapid mucociliary clearance, and the need for mucosal adjuvants that are safe and effective in humans. Few mucosal adjuvants have been approved for human use, and none have been systematically evaluated for their effects on epitope immunodominance hierarchies in clinical trials.

Thirdly, the preclinical-to-clinical failure rate for vaccines targeting complex bacterial pathogens such as *S. aureus* is sobering: despite over 30 Phase II/III trials, no vaccine has been approved. Whether adjuvant-driven epitope redirection can overcome this remains to be demonstrated.

Finally, the cost and feasibility of routine epitope mapping in early-phase trials must be considered. While peptide-based ELISA is relatively inexpensive, comprehensive epitope mapping using overlapping peptide libraries or MHC-associated peptide proteomics is resource-intensive and requires specialized expertise. Standardization across trials would be essential for meaningful cross-trial comparison.

Regulatory and ethical considerations

The integration of epitope mapping into clinical trial endpoints raises several regulatory and ethical considerations. From a regulatory perspective, epitope-based endpoints are not yet recognized by most regulatory agencies as validated correlates of protection. Establishing epitope breadth or epitope-specific antibody profiles as surrogate endpoints would require large-scale clinical validation studies. Moreover, the interpretation of epitope mapping data—particularly the distinction between "protective" and "non-protective" epitope responses which lacks standardized criteria. The development of standardized reference sera and validated epitope mapping protocols would be a prerequisite for regulatory acceptance.

From an ethical standpoint, human epitope mapping studies require careful consideration of participant consent, particularly when stored serum samples are used for epitope profiling beyond the original study scope. Additionally, patient stratification based on epitope-specific immune responses raises questions about equitable access to vaccine candidates. If certain epitope profiles correlate with vaccine responsiveness, could this create disparities in vaccine efficacy across genetically diverse populations? Proactive consideration of population-level HLA diversity in clinical trial design is essential to avoid exacerbating health inequities.

Future Rational Design of Vaccine

In future, we propose three pillars for rational design. Firstly, precision adjuvant selection might be necessary. It could guide by mechanistic understanding of each adjuvant's effect on epitope hierarchy, coupled with human in vitro models to predict clinical responses. Secondly, it involves innovative immunogen engineering such as epitope "resurfacing" to shield immunodominant but variable regions, thereby focusing responses on conserved domains, while using appropriate adjuvants to enhance those specificities. Thirdly, we should choose the optimal immunization regimen, as combining systemic and mucosal delivery in heterologous prime and boost schedules, and evaluating their safety and efficacy in diverse populations, including those with pre-existing immunity.

Ultimately, the goal is to develop vaccines that are "ready for all changes" which is capable of inducing broad, durable protection against evolving pathogens, where immunodominance is a controllable parameter.

Current Limitations and Unresolved Questions

Despite the compelling preclinical evidence that adjuvants and routes can modulate epitope immunodominance, several critical limitations and uncertainties must be acknowledged.

Firstly, nearly all current evidence derives from inbred mouse strains with defined MHC haplotypes (H-2d or H-2b), which do not recapitulate the extraordinary HLA diversity of human populations. In humans, up to six different HLA class I and class II molecules are expressed per individual, with extensive polymorphism across populations. An epitope that is immunodominant in one HLA context may be entirely silent in another. Thus, the extent to which adjuvant-driven epitope hierarchy modulation observed in mice predicts outcomes in outbred humans remains unproven.

Secondly, the correlative nature of most studies cannot definitively establish causation. While we observe that AddaS03, but not AddaVax, reshapes FimA epitope hierarchy and confers higher protection, formal proof that epitope redistribution is the mechanistic driver of differential protection awaits experiments using epitope-specific responses blocking strategies.

Thirdly, conflicting evidence exists regarding the mechanism by which adjuvants modulate epitope hierarchies. Previous study demonstrated that PRR adjuvants restrain high-stability peptide presentation on APCs, thereby altering the competitive hierarchy of peptide–MHC complexes, rather than actively "revealing" cryptic epitopes [5]. This suggests that the mechanistic basis of adjuvant-driven immunodominance modulation may be adjuvant-class specific may operate through fundamentally different mechanisms that are not universally generalizable.

Fourthly, the durability of epitope-focused immune responses and their capacity to be recalled upon boosting remain poorly characterized. Most murine studies have evaluated protection only at short intervals (7–14 days after the final immunization), leaving open questions about long-lived plasma cell generation and memory B-cell formation targeting specific epitopes.

Finally, the human vaccine development landscape is complicated by pre-existing immunity both from prior natural infection and previous vaccination, which can substantially alter the baseline immunodominance hierarchy through a phenomenon known as "original antigenic sin" or immune imprinting. Pre-existing immunity may either synergize with or antagonize adjuvant-mediated epitope redirection, an interaction that is currently unpredictable from preclinical models alone.

Concluding Remarks

A summary of adjuvant and route effects on immunodominance is shown in **Table 1**. Adjuvants and immunization routes are no longer auxiliary factors; they are central to sculpting the immune response. By actively modulating immunodominance, we can design vaccines that overcome strain specificity and provide cross-protective coverage. The integration of diagnostic epitope discovery with vaccine development, as demonstrated for MRSA, offers a blueprint for future infectious disease management. We call upon the clinical trial community to embrace immunodominance as a key endpoint and to explore novel adjuvant-epitope combinations in well-controlled human studies. Such efforts may not only accelerate the development of next generation vaccines but also improve our ability to respond swiftly to emerging threats.

References

1. Chen L, Yan P, Duan L, Ming G, Wang X, Zhang J, et al. Integrated immunodominant epitope discovery for dual-purpose rapid and economical diagnostic and immunoprotective applications against MRSA. Front Immunol. 2025 Oct 20;16:1697829.
2. Jiang J, Hong J, Yang H, Yang H, Chen Y, Yu W, et al. Adjuvants orchestrate cross-organ induction of mucosal CD8+ T cell immune responses in respiratory tracts. J Immunol. 2026 Jun 7;215(6):vkag117.
3. Ming G, Chen L, Yan P, Wang X, Chen Z, Gou Q, et al. Adjuvant-driven epitope hierarchy correlates with the protective efficacy of FimA vaccine against Klebsiella pneumoniae. Front Immunol. 2026 Jun 22;17:1796753.
4. Li S, Duan L, Zhang X, Yang R, Chen L, Chen Z, et al. (2023) The Effect of Adjuvants and Immune Routes on the Immunodominance of Epitopes and Protection Efficacy of SARS-CoV-2 RBD Antigen. Immunotherapy. 2023;9(1):1000211.
5. Li B, Zhang J, He T, Yuan H, Wu H, Wang P, et al. PRR adjuvants restrain high stability peptides presentation on APCs. Elife. 2024 Oct 30;13:RP99173.
6. Kim EH, Woodruff MC, Grigoryan L, Maier B, Lee SH, Mandal P, et al. Squalene emulsion-based vaccine adjuvants stimulate CD8 T cell, but not antibody responses, through a RIPK3-dependent pathway. Elife. 2020 Jun 9;9:e52687.
7. Yan P, Chen L, Ming G, Chen Z, Gou Q, Yuan Y, et al. Fine-Mapping and Protective Analysis of Immunodominant Linear B-Cell Epitopes of FimA Antigen of Klebsiella Pneumoniae. Vaccines (Basel). 2026 Apr 15;14(4):347.
8. Duan L, Zhang J, Chen Z, Gou Q, Xiong Q, Yuan Y, et al. Antibiotic Combined with Epitope-Specific Monoclonal Antibody Cocktail Protects Mice Against Bacteremia and Acute Pneumonia from Methicillin-Resistant Staphylococcus aureus Infection. J Inflamm Res. 2021 Aug 30;14:4267–82.
9. Zeng H, Zhang J, Song X, Zeng J, Yuan Y, Chen Z, Xu L, Gou Q, Yang F, Zeng N, Zhang Y, Peng L, Zhao L, Zhu J, Liu Y, Luo P, Zou Q, Zhao Z. An Immunodominant Epitope-Specific Monoclonal Antibody Cocktail Improves Survival in a Mouse Model of Staphylococcus aureus Bacteremia. J Infect Dis. 2021 May 28;223(10):1743–52.

Table 1. Summary of adjuvant and route effects on immunodominance — implications for clinical trial design.

Parameter	Effect on Immunodominance	Mechanistic Basis	Clinical Trial Implication
Adjuvant selection	Alters B-cell and T-cell epitope hierarchies	APC activation; pMHC stability modulation; MyD88-dependent DC maturation; RIPK3-dependent $CD8^+$ T-cell responses	Epitope mapping should be an early-phase endpoint; adjuvant choice determines epitope profile
Immunization route	i.m. (intramuscular) vs i.n. (intranasal) reveals different dominant epitopes	Differential antigen uptake and DC trafficking; mucosal vs systemic immune induction	Route selection should be guided by desired epitope profile and target tissue immunity
Adjuvant–antigen pairing	Suboptimal pairing yields high titers but poor protection	Antibody functional quality dissociates from total IgG titer	Total IgG is insufficient; functional antibody assays are essential correlates
Epitope-based diagnostics	Immunodominant epitopes enable 3-hour serodiagnosis	Natural infection sera identify clinically relevant epitopes	Same epitopes can serve as diagnostic biomarkers and vaccine targets
Multi-epitope vaccines	"Less is more"—few protective dominant epitopes may outperform many mixtures	Epitope interference or competition for MHC presentation	Empirical evaluation of epitope combinations is essential; more epitopes ≠ better protection