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Adjuvants in Modern Vaccine Design: Mechanistic Insights and Clinical Applications

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ABSTRACT

Adjuvants are crucial components of vaccines, enhancing immune responses and improving vaccine efficacy. Recent advances in immunology and vaccine development have led to the design of novel adjuvants with improved safety and efficacy profiles. This review examines the mechanistic insights and clinical applications of adjuvants in modern vaccine design, highlighting recent advances and future directions. Findings from this study show that adjuvants stimulate innate immune responses, enhancing antigen presentation and activation of adaptive immunity. Toll-like receptor agonists, squalene-based adjuvants, and particulate adjuvants are among the most promising classes of adjuvants. Clinical trials have demonstrated the safety and efficacy of adjuvanted vaccines against infectious diseases, such as influenza and human papillomavirus, and cancer. Adjuvants have also shown potential in improving vaccine responses in vulnerable populations, including the elderly and immunocompromised individuals.Adjuvants play a vital role in modern vaccine design, enabling the development of effective and safe vaccines. Mechanistic insights into adjuvant action have informed the rational design of novel adjuvants, with improved safety and efficacy profiles. Continued research into adjuvant development will be crucial for addressing emerging infectious diseases and improving global health outcomes.

Keywords: *Adjuvants, Vaccine, Immune response, Diseases, and Global health.*

1. Introduction

The development of vaccines has changed the course of infectious illnesses and world health in significant ways, making them a landmark achievement in medical history [20]. Modern immunisation procedures have their roots in the work of Edward Jenner, who proved in the late 18th century that inoculation with cowpox could protect against smallpox [14]. Recombinant proteins, viral vectors, and nucleic acid platforms are just a few of the ways that vaccines have progressed from simple preparations of live or attenuated viruses over the past few centuries. The urgent need to handle new and re-emerging infectious illnesses, along with developments in immunology, have driven this evolution. Not only did the COVID-19 pandemic show how important vaccines are for public health, but it also showed how important it is to optimize vaccine design for strong, long-lasting, and widespread immune protection [14, 29].

In this optimization, adjuvants play a crucial role. Adjuvants are components that are added to vaccines in order to increase the strength, efficiency, and longevity of the immune response [9]. A lack of immunogenicity is a common problem with modern subunit and recombinant vaccines, in contrast to older vaccinations that typically used entire viruses, which naturally induced immunity. To make up for this shortcoming, adjuvants guide adaptive immune responses toward protective immunity, activate innate immunological pathways, and enhance antigen presentation [28]. As an example, for many years, people have used aluminum salts (alum), the first commonly used adjuvant, to enhance antibody responses.

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Vaccines can now elicit cellular immunity in addition to humoral immunity, thanks to the expansion of the repertory of immune-enhancing methods made possible by modern adjuvants including emulsions, toll-like receptor (TLR) agonists, and saponin-based formulations [27, 28].

Adjuvants' molecular function goes beyond only stimulating the immune system. The adjuvants bring in the lymphocytes by binding to the pattern recognition receptors (PRRs) on the dendritic cells and macrophages, which set off a chain reaction of cytokines and chemokines [1]. This causes the immune system to better absorb antigens, display them more effectively through molecules of the major histocompatibility complex (MHC), and trigger responses that last a long time [2]. Crucially, adjuvants have the ability to alter the immune response's quality, steering it toward Th1, Th2, or balanced profiles based on the infection and the level of protection sought. Vaccines against complicated infections, such as HIV, malaria, and tuberculosis, require such customization because conventional formulations have failed to produce effective results in the past [3, 4].

The creation of current vaccines still faces a number of obstacles and challenges, notwithstanding recent advancements. Overstimulation of the immune system might result in negative effects; hence it is crucial to thoroughly assess the safety and tolerability of adjuvants. The variety of adjuvants accessible for clinical usage is consequently limited because to the careful and slow regulatory licensing of new adjuvants [5, 6]. Secondly, rational design and optimization are made more difficult because many adjuvants' action mechanisms are still not fully known. Third, there are concerns over the optimal way to customize vaccination formulations due to the fact that adjuvant efficacy is impacted by host genetic diversity, age, and comorbidities [7].

Thus, modern vaccine design encompasses not only the identification of potent antigens but also the rational choice of adjuvants and administration techniques with the goal of optimizing protective immunity. To ensure efficient antigen presentation and sustained immune activation, adjuvants are increasingly being employed in combination with delivery platforms such nanoparticles, viral vectors, and liposomes [9]. This technique of integrating antigen, adjuvant, and delivery technology represents the future of vaccinology since it allows for the creation of vaccines that are safer, more effective, and adaptable to different populations and pathogens.

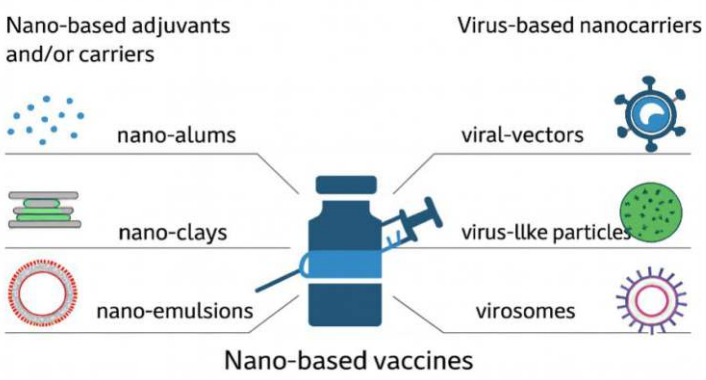

Figure 1. Schematic of vaccine components — antigen + adjuvant + delivery system
***Source**: [29]*

The above graphic shows the tripartite design of the vaccine's components: In order to stabilize antigens and promote innate immunity, nano-adjuvants including nano-alums, nano-clays, and nano-emulsions are developed [10, 11].

Examples of nano-structured materials include alums, which activate inflammasomes and boost antibody production, and clays, which provide immunomodulation and antigen stabilization due to their layered silicate structures. Respiratory vaccines can benefit from nano-emulsions, which are oil-in-water droplets that aid antigen uptake and stimulate mucosal immunity [12, 13].

In contrast, virus-based nanocarriers transport antigens in formats that elicit strong immune responses by imitating the structural and functional features of viruses. Genetically engineered viruses called viral vectors can elicit strong cellular immunity by transporting antigen-encoding genes [14]. While not infectious, virus-like particles (VLPs) mimic the structure and function of real viruses by presenting antigens in a multivalent, repeating pattern that stimulates B-cell activation. The immunostimulatory characteristics of viral components and the delivery efficiency of liposomes come together in virosomes, which are lipid-based vesicles that contain viral proteins and provide a flexible platform for therapeutic and preventative vaccinations [15, 16, 17].These advancements in nanotechnology are fundamental to the development of modern vaccines because they allow for exact regulation of immune activation, antigen stability, and the rate of delivery. Their incorporation into cancer immunotherapies and mRNA vaccines highlights their revolutionary potential to influence future world health. Researchers are working to improve the processes and safety profiles of nano-based vaccinations, which could lead to their increased use in fighting infectious diseases, chronic disorders, and cancers.

2. Clinical Applications Based on Mechanisms of Adjuvant Action

Pattern recognition receptors, which are essential for innate immune sensing, are called TLRs and NLRs. Recognition of pathogen-associated molecular patterns (PAMPs) including lipopolysaccharides, flagellin, and nucleic acids is facilitated by transient receptor potential pore (TLR) receptors, which are membrane-bound receptors found on cell surfaces or within endosomal compartments. One example is the synthetic adjuvant CpG oligodeoxynucleotides, which stimulates TLR9 and elicits robust Th1-biased responses [18, 19]. Similarly, licensed vaccines like Cervarix use monophosphoryl lipid A (MPL), a detoxified derivative of lipopolysaccharide, to activate TLR4 and improve humoral and cellular immunity [20]. On the other hand, NLRs are receptors located in the cytosol that are responsible for detecting signals within cells that indicate potential danger. Particulate adjuvants like alum activate NLRP3 inflammasomes, which in turn activate caspase-1 and release the cytokine interleukin-1β (IL-1β), which is essential for starting adaptive responses [21]. These receptor-mediated processes show how adjuvants activate the immune system by imitating infection cues that do not cause illness.

Important steps in the process of connecting innate and adaptive immunity are induced by adjuvants following PRR engagement, which in turn trigger cytokine synthesis and antigen presentation. Cytokines including IL-6, TNF-α, and type I interferons arrange for dendritic cells, macrophages, and lymphocytes to be recruited and activated [22]. Adjuvants enhance dendritic cells' capacity to deliver antigens to T cells by upregulating co-stimulatory molecules (CD80, CD86) and major histocompatibility complex (MHC) molecules [23]. In addition to recognizing vaccination antigens, this process processes and displays them in a way that promotes robust T-cell activation.

As an example, QS-21 and other saponin adjuvants drive cytotoxic T lymphocyte responses, which are crucial for cancer and intracellular pathogen vaccines [24]. How the immune response is biased toward antibody formation (Th2) or cellular immunity (Th1) is determined by the cytokine milieu that adjuvants produce, which in turn affects the polarization of helper T cells.

The activation of PRR initiates signaling cascades that support these actions at the molecular level. NF-κB, AP-1, and IRFs (interferon regulatory factors) are activated when TLRs signal through adaptor proteins like MyD88 and TRIF. An environment that is favorable to adaptive immunity is established when these transcription factors induce the expression of pro-inflammatory cytokines, chemokines, and interferons [25]. Amplifying inflammatory responses and improving antigen-specific immunity, NLR activation, especially through the NLRP3 inflammasome, causes the cleavage of pro-IL-1β and pro-IL-18 into their active forms [26, 27]. Critically, the immunological response quality is dictated by the timing and equilibrium of these signaling cascades. Reactogenicity occurs when activation is either too high or too low, while immunogenicity is compromised when activation is inadequate. Clinical adjuvant design aims to minimise side effects while maximizing efficacy by optimizing these mechanisms.

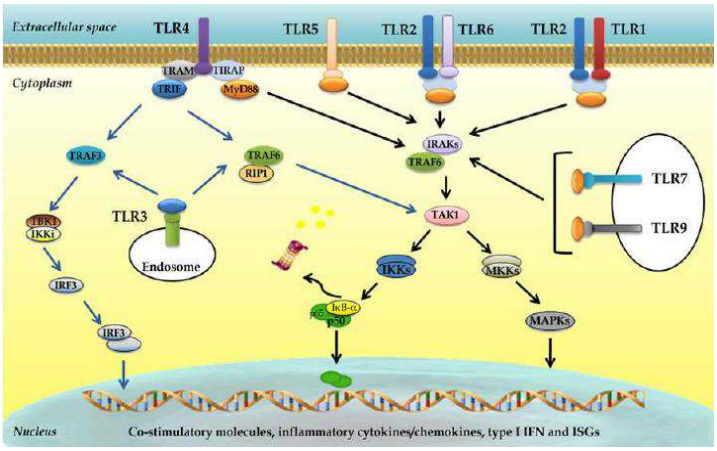

Figure 2. TLR-mediated immune activation pathway
***Sources**: [14, 25]*

Different Toll-like receptors (TLRs) trigger immunological responses via different intracellular signalling cascades, as shown in the schematic image. To identify pathogen-associated molecular patterns (PAMPs), surface TLRs (e.g., TLR1, TLR2, TLR4, TLR5, TLR6) and endosomal TLRs (e.g., TLR3, TLR7, TLR9) recruit adaptor proteins such MyD88, TRIF, TRAM, and TIRAP. Transcription factors such as NF-κB and IRF3 are stimulated when these adaptors activate molecules further down the chain, such as IRAKs, TRAFs, and RIP1. Important for the regulation of both innate and adaptive immunity, this process leads to the synthesis of inflammatory cytokines, co-stimulatory molecules, and type I interferons (IFNs) [14, 17, 21]. Many contemporary adjuvants, particularly those that aim to increase vaccine efficacy by targeting TLRs, rely on this route as their mechanism of action. For instance, CpG oligodeoxynucleotides have found use in cancer immunotherapy and hepatitis B vaccines because to their ability to imitate bacterial DNA, activate TLR9, and produce robust Th1-biased responses. Licensed vaccines like Cervarix use monophosphoryl lipid A (MPL), a detoxified form of lipopolysaccharide, to activate TLR4 and boost humoral and cellular immunity [29, 30, 31].

Adjuvants like these are the molecular foundation of next-gen vaccine design; they use Toll-like receptor signaling to boost antigen presentation, cytokine production, and memory formation.

Vaccines against cancer and infectious disorders have been developed using these mechanistic findings. One example of how TLR4 agonists might safely increase immunogenicity in people is the incorporation of MPL into HPV and hepatitis B vaccinations [32]. In a similar vein, CpG adjuvants that target TLR9 are being studied for their potential to enhance anti-tumor T-cell responses in cancer immunotherapy [17]. The capacity of alum to activate NLRP3 inflammasomes and encourage robust antibody responses makes it an appropriate adjuvant for vaccines against extracellular infections, and this has led to its continued widespread usage despite its antiquity [20].

3. Types and Recent Advances in Vaccine Adjuvants

The evolution of vaccine adjuvants reflects the broader trajectory of vaccinology, moving from empirical formulations to rationally designed immunomodulators. Classical adjuvants such as aluminium salts (alum) have been used for nearly a century, providing safe and effective enhancement of antibody responses [14]. However, alum's limitations in inducing robust cellular immunity prompted the development of modern adjuvants, including oil-in-water emulsions (MF59, AS03), synthetic oligonucleotides (CpG), and nanoparticle-based systems. These innovations are grounded in mechanistic insights into innate immune activation, enabling vaccines to elicit tailored responses against diverse pathogens and even cancers [15].

Classical adjuvants: Alum, introduced in the 1920s, remains the most widely used adjuvant in licensed vaccines. Its mechanism of action was initially thought to rely on depot formation, whereby antigens were slowly released at the injection site. More recent studies have revealed that alum activates innate immunity by inducing local cell death and releasing danger-associated molecular patterns (DAMPs), which in turn stimulate the NLRP3 inflammasome [16]. This leads to caspase-1 activation and secretion of IL-1β, promoting strong humoral responses. Alum is particularly effective at driving Th2-biased immunity, making it suitable for vaccines against extracellular pathogens such as diphtheria, tetanus, and hepatitis B [17]. However, alum is less effective at inducing cytotoxic T lymphocyte (CTL) responses, limiting its utility in vaccines requiring robust cellular immunity.

Modern adjuvants: MF59 and AS03 Oil-in-water emulsions represent a major advance in adjuvant technology. MF59, composed of squalene droplets stabilised by surfactants, was the first emulsion adjuvant licensed for human use in influenza vaccines. MF59 enhances immune responses by recruiting monocytes and dendritic cells to the injection site, increasing antigen uptake and presentation [18]. Unlike alum, MF59 promotes both humoral and cellular immunity, with a balanced Th1/Th2 profile. Clinical studies have demonstrated that MF59-adjuvanted influenza vaccines provide superior protection in elderly populations, where immune responses are typically weaker [19].

AS03, another squalene-based emulsion containing α-tocopherol, was deployed during the H1N1 influenza pandemic. The inclusion of α-tocopherol enhances the immunostimulatory properties of the emulsion, leading to stronger cytokine induction and improved antibody titers [21].

As03 has been shown to broaden immune responses, increasing cross-reactivity against antigenic variants. Its use in pandemic preparedness highlights the importance of modern adjuvants in rapidly generating effective vaccines against emerging pathogens [22].

CpG oligodeoxynucleotides. Synthetic CpG motifs mimic bacterial DNA and activate TLR9, a receptor expressed in plasmacytoid dendritic cells and B cells. CpG adjuvants induce strong Th1-biased responses, characterised by IFN-α and IL-12 production, which promote CTL activity and IgG2a antibody responses [23]. CpG has been incorporated into vaccines against hepatitis B and is under investigation in cancer immunotherapy, where it enhances anti-tumour T-cell responses. Mechanistically, CpG differs from alum and emulsions by directly engaging PRRs, providing a defined molecular trigger for immune activation. Its ability to induce cellular immunity makes CpG particularly valuable for vaccines against intracellular pathogens and malignancies [24].

Nanoparticle-based adjuvants Nanoparticles represent the frontier of adjuvant innovation, offering precise control over antigen delivery and immune activation. Lipid nanoparticles (LNPs), used in mRNA vaccines against COVID-19, serve both as delivery vehicles and adjuvants by stimulating innate immunity through endosomal TLRs and cytosolic sensors [25].

Other nanoparticle systems, including polymeric nanoparticles and virus-like particles, enhance antigen stability, facilitate targeted delivery to dendritic cells, and enable co-delivery of antigens and immunostimulatory molecules. Mechanistically, nanoparticles combine depot effects with PRR activation, providing versatile platforms adaptable to diverse vaccine modalities [20]. Their success in COVID-19 vaccines underscores their transformative potential in vaccinology.

Mechanistic comparisonsin Table 1 summarisethe mechanistic differences among adjuvants and highlight their complementary roles in vaccine design. Alum primarily activates the NLRP3 inflammasome, driving antibody responses but limited cellular immunity. MF59 and AS03 recruit immune cells and enhance antigen uptake, promoting balanced humoral and cellular responses. CpG directly engages TLR9, inducing strong Th1 and CTL responses [8]. Nanoparticles integrate delivery and adjuvant functions, activating multiple innate pathways while ensuring efficient antigen presentation. These distinctions enable rational selection of adjuvants based on the pathogen, desired immune profile, and target population. For example, alum remains suitable for routine childhood vaccines, while CpG and nanoparticles are better suited for cancer vaccines and emerging infectious diseases requiring cellular immunity [23].

Table 1. Adjuvant type, composition, mechanism, and approved vaccines

Adjuvant	Composition	Mechanism of Action	Approved Vaccines
Alum	Aluminumsalts (aluminum hydroxide, aluminum phosphate)	Activates NLRP3 inflammasome; promotes Th2-biased antibody responses	Diphtheria, tetanus, hepatitis B, HPV
MF59	Squalene oil-in-water emulsion	Recruits monocytes/dendritic cells; enhances antigen uptake; balanced Th1/Th2	Influenza (Fluad)
AS03	Squalene emulsion + α-tocopherol	Enhances cytokine induction; broadens antibody responses	H1N1 pandemic influenza vaccines
CpG ODNs	Synthetic unmethylated CpG motifs	Activates TLR9; induces Th1-biased cellular immunity	Hepatitis B (Heplisav-B)
Nanoparticles (LNPs)	Lipid nanoparticles, polymeric nanoparticles, virus-like particles	Facilitate antigen delivery; activate endosomal TLRs and cytosolic sensors	COVID-19 mRNA vaccines (Pfizer-BioNTech, Moderna)

Sources: *[8, 23]*

4. Clinical Applications

4.1 COVID-19 mRNA Vaccines and Cancer Immunotherapy

The COVID-19 pandemic accelerated innovation in vaccine platforms, with mRNA vaccines such as Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273 becoming the first widely deployed nucleic acid vaccines. While these vaccines rely primarily on lipid nanoparticles (LNPs) for delivery, the LNPs themselves act as adjuvants, stimulating innate immunity through endosomal Toll-like receptors (TLRs) and cytosolic sensors [21]. This dual role—delivery vehicle and immune enhancerwas critical for generating robust antibody and T-cell responses against SARS-CoV-2.Recent reviews emphasise that adjuvants are essential for next-generation COVID-19 vaccines, particularly those designed to broaden protection against variants. For example, saponin-based adjuvants and CpG oligonucleotides are being investigated to enhance cellular immunity and cross-reactivity [8]. Clinical trials have shown that adjuvanted protein subunit vaccines, such as Novavax's NVX-CoV2373 formulated with Matrix-M (a saponin-based adjuvant), elicit strong neutralising antibody titers and durable protection, underscoring the importance of adjuvant selection in pandemic preparedness [23].

4.2 Cancer Immunotherapy

Adjuvants are also central to the rapidly expanding field of cancer immunotherapy, where the goal is to overcome tumour-induced immune suppression and generate durable anti-tumour responses.

CpG oligonucleotides, which activate TLR9, have been tested in clinical trials as adjuvants for therapeutic cancer vaccines, enhancing cytotoxic T lymphocyte activity and promoting Th1-biased immunity [32]. Similarly, saponin-based adjuvants such as QS-21 are incorporated into cancer vaccines to stimulate dendritic cell activation and IL-12 production, driving potent cellular responses [12].

Nanoparticle-based adjuvants are particularly promising in oncology. Virus-like particles and polymeric nanoparticles can co-deliver tumour antigens and immunostimulatory molecules, ensuring efficient antigen presentation and immune activation. Clinical studies highlight their potential in melanoma and prostate cancer vaccines, where nanoparticle formulations improve antigen stability and enhance T-cell priming [4].

4.3 Emerging Adjuvant-Based Therapies

Beyond infectious diseases and cancer, emerging adjuvant-based therapies are being developed to address chronic infections, antimicrobial resistance, and even autoimmune modulation. Novel adjuvants such as nanoparticle emulsions, TLR agonists, and STING (stimulator of interferon genes) agonists are under investigation for their ability to induce broad and durable immunity [23]. For example, nanoparticle-based adjuvants are being explored in tuberculosis vaccines to enhance cellular immunity, while STING agonists are being tested in combination with checkpoint inhibitors to boost anti-tumour responses.

Recent studies highlighted the synergy between adjuvanted protein vaccines and RNA-based platforms, showing that combining adjuvants with mRNA vaccines can broaden immune responses and improve durability [11]. Similarly, nanoparticle-based adjuvants are being for mucosal delivery, offering protection against respiratory pathogens by stimulating local immunity [9]. These innovations expand the scope of adjuvant applications beyond traditional systemic vaccines, opening new avenues for targeted and tissue-specific immunisation strategies.

5. Challenges and Future Perspectives

Despite the remarkable progress in adjuvant science, several challenges continue to shape itsclinical application and future development. One of the most pressing issues is reactogenicity, the short-term inflammatory responses that accompany adjuvant use. While mild local reactions such as pain, swelling, and fever are often acceptable, excessive reactogenicity can reduce vaccine acceptance and complicate regulatory approval. For example, saponin-based adjuvants such as QS-21 remain highly potent but can cause significant local irritation, limiting their widespread use. Balancing potency with tolerability remains a central challenge in adjuvant design, requiring careful optimisation of dose, formulation, and delivery systems [24].

Closely related to reactogenicity are broader safety concerns. Because adjuvants stimulate innate immunity, there is a risk of unintended immune activation, including autoimmunity or systemic inflammation. Regulatory agencies, therefore, demand extensive preclinical and clinical evaluation of novel adjuvants, which slows their introduction into licensed vaccines. Moreover, the mechanisms of many adjuvants remain incompletely understood, complicating risk assessment [19]. Advances in systems immunology and multi-omics profiling are beginning to clarify these mechanisms, enabling more rational safety evaluations. Nonetheless, ensuring long-term safety while maintaining efficacy is a critical priority for future adjuvant development [20].

Another frontier is the development of personalised adjuvants, tailored to individual genetic, immunological, and demographic profiles. Evidence suggests that host factors such as age, sex, and genetic polymorphisms influence adjuvant efficacy and tolerability [30]. For instance, elderly individuals often exhibit reduced responses to alum-adjuvanted vaccines, while MF59 formulations provide superior protection in this population. Personalised adjuvant strategies could involve selecting adjuvants based on pharmacogenomic and immunogenomic data, thereby optimising immune responses while minimising adverse effects. This approach aligns with the broader vision of precision medicine, where interventions are tailored to the unique molecular and immunological landscape of each patient [30].

Looking forward, several future perspectives are emerging. Nanoparticle-based adjuvants, which combine delivery and immunostimulatory functions, are expected to play a central role in next-generation vaccines, particularly for mRNA and DNA platforms. Lipid nanoparticles (LNPs), used in COVID-19 mRNA vaccines, not only deliver antigens but also act as adjuvants by stimulating innate immunity through endosomal TLRs and cytosolic sensors [31]. Novel adjuvants targeting pathways such as STING (stimulator of interferon genes) and RIG-I are under investigation, offering opportunities to induce broad antiviral and anti-tumour immunity [6, 32]. Furthermore, the integration of artificial intelligence and multi-omics data promises to accelerate adjuvant discovery, enabling predictive modelling of efficacy and safety. Finally, equitable access remains a global challenge: ensuring that advanced adjuvant technologies are affordable and available in resource-limited settings will be essential for maximising their public health impact.

Conclusion

Adjuvants have evolved from simple enhancers of antibody responses to sophisticated modulators of innate and adaptive immunity. Their clinical applications in COVID-19 mRNA vaccines, cancer immunotherapy, and emerging therapies underscore their indispensable role in modern vaccinology. Yet challenges such as reactogenicity, safety concerns, and variability in host responses highlight the need for continued innovation.

Future directions emphasise the promise of personalised adjuvants, nanoparticle-based systems, and novel innate immune agonists, supported by advances in systems biology and artificial intelligence. These innovations will not only improve vaccine efficacy but also expand their scope to address complex pathogens, chronic infections, and malignancies.

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