

Advancements in non-viral vaccine systems 31. Another approach to tackle immunological hurdles in young Infants involves the utilization of piglocan as adjuvant strategy –Glucans, present in the cell walls of specific pathogens, initiate the activation of dendritic cells CLEC71 K-CARDS pathway and have demonstrated protective effects against tuberculosis (TB) infection. Additionally, studies have been conducted to investigate the use of defective interfering (Di) viral particles as adjuvants to augment the innate immune response. First-generation adjuvants, such as aluminum salts (alum) and oil-in water emulsions containing mineral oil, have found widespread application in clinical scenarios [199]. Their mechanism of action involves facilitating the movement and recruitment of antigen-presenting cells (APCs) to the injection sites in the muscle tissue. The limited recruitment of immune cells, primarily antigen-presenting cells (APC), the pronounced Th2 response with minimal cellular immune response greatly limit the effectiveness of these adjuvants [100]. Consequently, current research aims to develop novel adjuvants that can elicit broader innate immune responses to vaccination. It is believed that the stimulation of specific cytokine gene expression profiles by antigen-presenting cells (APC) lead leads to subsequent skewing towards either Th1 or Th2 responses [1100]. For example, AS04, which is based on LPS derivatives, has demonstrated improved cell-mediated immune responses in patients with end-stage renal disease and is currently utilized in HPV and hepatitis B vaccines [101]. Moreover, several other adjuvants currently employed primarily act as agonists for Toll like receptors (TLR) [1151161]. Different agonists of Toll-like receptors (TLRs), such as CpG (TLR9), poly(I:C) (TLR3), and Pam3CSK4 (TLR1 and TLR2), have exhibited the capacity to augment the generation of co-stimulatory molecules on antigen-presenting cells (APCs). Particularly vital for subunit vaccines, this aspect gains significance as they lack viral genomic constituents that can serve as pattern-associated molecular patterns (PAMPs) to initiate innate immune reaction. Adjuvants play a crucial role in enhancing the immune response to subunit vaccines. These specialized dendritic cells facilitate the development of regulatory T cells (7) A primary focus in vaccine research is the creation of immunizations capable of effectively triggering the innate immune response in immunocompromised individuals, all while circumventing the use of live attenuated vaccines. This condition is marked by a variety of intricate alterations that result in compromised innate and adaptive immune responses [73,104], decline in lymphoid tissue structure [85], and elevated levels of proinflammatory cytokines and chemokines [86,87]. Extensive endeavor have been invested in broadening and enhancing the array of adjuvants, aiming to customize the immune response, counterbalance the Th2-biased immune reaction linked to certain adjuvants such as alum, and stimulate a Th1 response under specific circumstances. The array of mechanisms leading to immunosuppression in this group is diverse, yet a frequently observed occurrence involve the reduced synthesis of cytokines that stimulate Th17 cell reactions through Toll-like receptors (TLRs). The challenges associated with vaccination in the presence of diseases or drugs that induce immunosuppression differ from the age-related changes in the immune system's ability to combat infections. Steroids are an example of drugs that cause immunosuppression and have been extensively studied in relation to this topic [100]. Vaccines for immunosuppressed individuals The reduced immune response observed in individuals with weakened immune systems, including children, older adults, and those underlying immunodeficiencies, presents a significant barrier to successful vaccination. Lipid-based

adjuvants, such as those present in the GlaxoSmithKline A501B/ formulation and CAF01 [112,113] capable of activating innate immunity. When present in a solution, lipid products have the capability to form micelles and act as carriers for solid particles. antigen uptake by dendritic cells [108,109], reduced ability of macrophages to engulf apoptotic cells [100], decline in the number of naive T cells (1) and diminished diversity in the B cell repertoire [3]. For instance, a Th2 response is preferable for generating antibodies and combating parasitic infections, while a Th1 response is favored for combatting intracellular or viral infections. These adjuvants have shown a propensity for inducing a Th1-skewed immune response, with GLA-SE also eliciting antibodies and CAF01 demonstrating a Th1/Th17 response [105]. By broadening the immune response in vaccines, including in immunosuppressed individuals, the safety and efficacy of vaccinations can be enhanced for both the general population and specific patient groups. One approach being explored is the use of TNA vaccines to encode antibodies that are transiently produced in immunocompromised individuals, particularly during flu seasons. The presence of CpG-rich regions on the bacterial DNA of the plasmid may preferentially attract anti-dsDNA antibodies, which could be utilized to enhance DNA vaccines [106]. Ensuring the purity of plasmid DNA supplies is crucial to avoid the potential induction of unfavorable immune responses. These aspects require thorough scientific scrutiny and validation to mitigate any potential risks associated with plasmid vaccination. The underlying processes of immunosuppression in each of these groups differ, and it is important to consider these mechanisms while developing the most effective vaccination strategy. Additionally, neonates, especially preterm infants, exhibit increased expression of cytokines that counteract inflammation [82]. The discovery of adjuvants in horticulture initially involved the addition of specific food items, leading to localized sterile inflammation and abscesses at particular sites (98). It has been observed that mice treated with plasmid DNA may generate anti-dsDNA antibodies [106], similar to those seen in systemic lupus erythematosus [108, 109]. AS04, on the other hand, is derived from LPS (lipopolysaccharide) and has demonstrated ability to enhance cell-mediated immune responses in individuals with end-stage renal disease. The goal is to optimize the adjuvant repertoire to achieve desired immune responses based on the target of vaccination. Recent studies have examined the effectiveness of influenza-neutralizing antibodies delivered intramuscularly through electroporation using plasmids. A503, an adjuvant consisting of surfactants and emulsifiers, has been utilized in influenza pandemic vaccines [110]. These TLR agonists have demonstrated potential in enhancing immune responses in both juvenile and aged mice [117]. Steroids have diverse impacts on immune cells, which include transforming dendritic cells into tolerogenic dendritic cells (95,96). Other adjuvants like IC318 (102,100, GLA-SE [104], and CAF01 [100, 10] have been designed to stimulate a Th1 immune response. However, before these methods can be translated into human use, several critical scientific challenges need to be addressed and resolved effectively. There is a need for further investigations into the stability and duration of plasmid vaccination in human subjects. It is worth noting that the existing malaria vaccine market utilizes lipid-based adjuvants [114,115]. These strategies have been explored in recent years to harness the potential of viral particles as adjuvants. Due to the development of age-specific immune systems, infants, young children, particularly newborns and neonates, considered to have a vulnerable immune state, making them more susceptible to infections. 4

illustrates various adjuvants employed in diverse vaccine development. There is a growing focus on developing novel vaccines that provide a safe and effective immune response in immunocompromised individuals. Conversely, the immunosuppressive state seen in older individuals is known as immunosenescence [83]. It is currently employed in vaccines for hepatitis B and HPV. Promising findings indicate that this approach offers protection against severe illness (107). Some notable alterations include impaired. Fig.