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 agaiast 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.Fint-generation adjuvants, such aluminum salts (slum) and oil-in water emulsions containing mineral oil, have found widespread appli cation in clinical scenarios 1991 Theit mechanism of action involves facilitating the movement anvement of antigen-presenting cells (APCA) to the in jection sites in the muscle tissue.The limited recruitment of inumune cells, primarily antigen-presenting cells (APC), the pronounced Th2 response with minimal cellular iminune response greatly limit the effectiveness of these adjuvants [00], Consequently, current research aims to develop novel adjuvants that can elirit broader innate immune responses to vaccination.It is believed that the stimulation of specific cytokine gene expression profiles by antigen-presenting cella (APC) lead leads to subsequent skewing towards either Thi or Th2 xmponses [1100], For example, AS04, which is based on LPS de rivatives, has demonstrated improved cell-mediated inumane 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 agoniats for Toll like receptors (TLR) [1151161 Different agonists of Tall-like receptors (TLJia), such as OpG (TLR9), poly(C) (LR3), and pum3CSK4 (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 im emune reactio 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 immunications capable of effectively triggering the innate immune response in immu nocompromised individuals, all while circumventing the we the use of live attenuated vaccines. This condition is marked by a variety of intricate alterations that result in compromised imate and adaptive immune responses [73,041, decline in lymphoid tissue structure [85), and elevated levels of proinflammatory tory cytolunes and chemokines [86,87].Extensive endeavom have been invested in fbroadening and enhancing the array of adjuvants, siming in customize the immune response, counterbalance the Th2-biased immune reaction linked to certain adjuvants such as alum, and stimulate a Thl response under specific circumstances.The array of mechanisms leading to imatismosuppression in this group is divene, yet a frequently observed accurrence involve the reduced synthesis of cytokines that stiralate 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 immunusuppression and have been extensively studied in relation to this tople 1001.Vaccines for immunosuppressed individuala The reduced immune response observed in individuals with weak ened immune systems, including children, older adults, and those underlying immunodeficiencies, presents a significam barrier cessful vaccination. Lipid-based

adjuvants, such as those present in the Glax ofmithKline 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 cartiers for solid particles.antigen uptake by dendritic cells [08,561, reduerd ability of inacro phages to engulf apoptotic cells [00], decline in the number of naive T cells (1) and diminished diversity in the B cell repertoire [3].For instance, a Th2 respome is preferable for generating antibodies and combating parasitic infections, while a Thi response is favered for combatting intracellular or viral infections.These adjuvants have shown a propensity for inducing a Thi-skewed immune response, with GLA-SE also eliciting antibodies and CAF01 demonstrating a Thi/Th17 response [1051..By hroadening the immune response in vaccines, including in immuno suppressed individuals, the safety and efficacy of vaccinations can be enhanced for both the general population and specific patient groups.One approach heing explored is the use of TNA vaccines to encode antibodies that he transiently produced in Immunocom promised individuals, particularly during flu seasons.The presence of CpG-rich regions on the bacterial DNA of the plaunid may preferentially attract anti-daDNA antibodies, which could be utilized to enhance DNA vacelnes [106].Ensuring the purity of y of plasmid DNA supphes is crucial to avoid the po tential induction of undavorable immune responses.These aspects require thorough scientific scrutiny and validation to mitigate any po tential risks associated with plasmid vaccination.The underlying processes of immunosuppression in ench of these groups differ, and it is important to consider these mech anisms while developing the most effective varcination strategy.Additionally, neonates, especially preterm infants, exhibit increased expression of cytokines that coun teract inflammation [82].The discovery of adjovants in hor cinations initially involved the addition of specific food items, leading to localized sterile inflammation and abscesses at particular sites (98).It has has been been observed obser t that mice treated with plasmid DNA may generate anti-dsDNA antibodies [106], similar to those seen in systemic Inpus erythematosas [108, 109).AS04, on the other hand, is derived from LPS (lipopolysaccharide) and has demonstrated ability to enhance cell-mediated immune responses in individuals end-stage renal disease.The goal is to optimize the adjuvant repertoire to achieve desired immune responses hased 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 p enza pandemic vaccines [1101.These TUJI sgonists have demonstrated potential in enhancing immune responses in in both juvenile and aged mice [117].Sterolds have diverse impacts on immune cells, which include transforming dendritic cells into tolerngenic dendritic cella (95,961.Other adjuvants like IC318 (102,100, GLA-SE [104], and CAF01 [100, 10 have been designed to stimmilate a Thi immune response.However, before these methods can be translated into human use, several eritied scientific challenges need to be addressed and resolved effertive.There is a need for further laves tigatice 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 hansess the potential of nt viral particles adjuvantsDue to the he development of age-specific immune systems, tems, young children, particularly newborns and neonates, considered to have a vulnerable immune state, making them more susceptible to infections .4

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