Chapter 40

Utilizing Nano Vaccines for Enhanced Immunization against Lumpy Skin Disease

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ABSTRACT

Significant economic losses have been caused by the infectious viral infection known as lumpy skin disease (LSD), which is afflicting livestock in Pakistan. Even while there are now vaccinations, they are not ideal because of certain constraints. This paper explores the exciting field of improved LSD immunization using vaccines based on nanoparticles. We examine how these sophisticated vaccines, equipped with their higher stability, tailored distribution, and immune response, may overcome the drawbacks of more conventional methods. In particular, we explore different kinds of nanoparticles, such as liposomes and polymer nanoparticles, explaining their benefits and mechanisms of action in promoting strong immune reactions against LSD. Although possible issues like toxicity from nanoparticles are acknowledged, we stress that thorough safety assessments are essential to responsible development. We describe current research efforts aimed at improving the design of nanovaccines and demonstrate how they could transform LSD control. Lastly, we stress that, in order to guarantee complete protection, more research into multi-epitope nanovaccines and combination approaches with additional control mechanisms is required. This research opens the door to protecting animals from LSD, enhancing Pakistan's economy, and releasing the Nano defense.

KEYWORDS		
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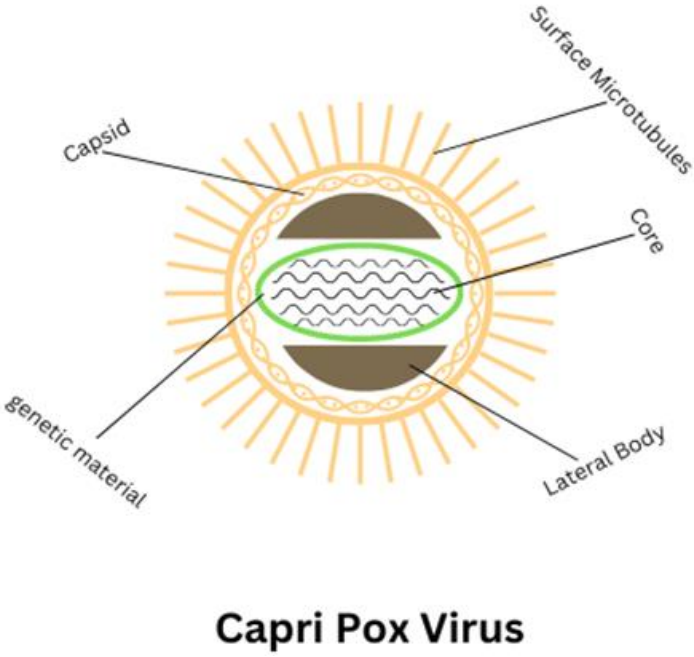
INTRODUCTION

The etiological agent of lumpy skin disease, the Lumpy skin disease virus (LSDV), is an infectious illness that is a member of the Poxviridae family, subfamily *Chordopoxvirniae* and genus *Capripoxvirus*. Some names for this illness include "Neethling virus disease," "exanthema nodularis bovis," "Pseudo-urticaria," and "knopvelsiekte," although "LSD" is the most often used (E.S.MTuppurainen et al., 2015). Lumpy skin disease is an illness spread by a transboundary vector. This illness is not zoonotic. It is believed that this disease's host range is quite restricted because it has mostly been documented in big ruminants, such as cattle and water buffalo. Among the most frequent carriers of this illness are ticks, mosquitoes, and biting flies (*Culicoides*) (S. Rouby et al., 2016). It has been demonstrated that caprine and ovine species can resist infection even while tied near diseased cattle and buffalo. But in certain experimental situations, skin lesions were created in a wide range of domestic and wild animals, including giraffes, impalas, sheep, and goats, in laboratory settings (H.G. Heine et al., 1999). LSD is linked to low death rates and high sickness rates. This illness's obvious symptoms are a high temperature, lymphadenitis, extreme thinness, bilateral epiphora, decreased milk supply, sterility, skin erythema, and nodules. The most significant financial consequences that farmers in LSD-endemic areas deal with include poor reproductive competence, loss of hide quality, decreased milk income, and persistent animal emaciation (Zheng, M. et al., 2007).

Given that LSD is considered a transboundary illness, the World Health Organization (WHO) has decided that it should be reported to international forums because of the disease's severe and ongoing consequences on cattle occupation worldwide. The illness was previously believed to be common exclusively in African nations, but reports of cases have recently come from other parts of the world. LSD is widely used in practically every country on the African, Asian, and

European continents, according to the OIE (O. Mangana-Vougiouka et al., 1999). Given that LSD is considered a transboundary illness, the World Health Organization (WHO) has decided that it should be reported to international forums due to the disease's severe and ongoing consequences on cattle occupation worldwide. The illness was previously believed to be common exclusively in African nations, but reports of cases have recently come from other parts of the world. LSD is widely used in practically every country on the African, Asian, and European continents, according to the OIE (O. Mangana-Vougiouka et al., 1999). Considering that Pakistan has a lengthy land border with both China and India, this is probably one of the main causes of disease transfer into

Fig. 1: Structure of a Capri Pox Virus



Pakistan. Livestock travels across international borders within Pakistan. Given that LSD has lately been observed in Iran, China, and India, another explanation would be the seasonal migration of vectors into Pakistan from surrounding nations. As a result, careful planning and epidemiological analysis have become essential for managing diseases effectively when it comes to these exotic diseases. Fig.1 shows the structure of a *capri-pox* virus.

Nanotechnology

Nanotechnology is an emerging field of research and advanced technology that exploits the physicochemical properties of nanoparticles to precisely manage their size, surface area, and shape, facilitating the development of novel and enhanced functional characteristics. (Prasad, 2008). To create nanoparticles, a variety of components, including proteins, lipids, and inorganic elements, can be utilized. Nonetheless, the most intriguing and promising nanoparticles seem to be polymeric ones, as alginate NPs (Girija, 2019). The United States Food and Drug Administration (US FDA) has already granted clearance for the use of alginate NPs, an environmentally benign and biocompatible co-polymer of guluronic acid and mannuronic acid, for human use. It is typically given orally (Ahmad et al., 2006). Their ultra-small nanoparticles (NPs) increase bioavailability, minimize cytotoxic effects, and maximize tissue compatibility. Applying polymeric nanoparticles. According to Joshy et al. (2018), certain research has started to demonstrate that alginate NPs can be utilized as an efficient carrier for antiviral medicines against the majority of viruses, including the human immunodeficiency virus (HIV). The in-vitro cellular internalization experiments revealed a much higher internalization efficiency, and the nanoparticles were shown to be biocompatible (Albarqi, 2019). According to Silva-Carvalho et al. (2015), propolis is a natural substance that is frequently added to food and drink to enhance health, prevent sickness, and have immunomodulatory effects. According to several studies (Abd El-Hady et al., 2002; 2007; Hegazi et al., 2004; Hegazi and Abd El-Hady, 2008), it has a major potential as an antiviral agent.

Nano Technology in the Field of Medicine

The use of nanotechnology to improve human health and wellbeing is known as nanomedicine. The field of medicine has changed as a result of the application of nanotechnology in several therapeutic areas. Nanoparticles with sizes ranging from 1 to 100 nm are created and utilized for biomedical research instruments, treatments, and diagnostics. With the aid of these instruments, therapy may now be administered at the molecular level, treating the illness and advancing the understanding of its pathophysiology. Because of the non-specificity of their mechanism of action, conventional medications are severely restricted in their ability to cause undesirable effects (A. Surrendering, S. Sandhiya, 2008). Among the nanoparticles utilized for analysis are paramagnetic nanoparticles, quantum dots, nanoshells, and nanosomic particles.

Nano Technology and Vaccine Development

Nanocarriers with a range of compositions, sizes, and surface characteristics are included in the nanotechnologies created for use in the vaccination industry (L.J. Peek, C.R. Middaugh, 2008). To encourage a protective immune response, a variety of vaccine nano carriers have been created and studied for their potential to transfer adjuvants and antigens to immune cells. Unfortunately, insufficient adjuvant activity may lead to restricted immunogenicity even though antigens may be taken up by immune cells. Certain strategies have involved designing nanocarriers to co-deliver an adjuvant and an antigen (A. Dunkle, 2013). Antigens or adjuvants can be targeted to antigen-presenting cells and/or released continuously with the help of nanocarriers. The effectiveness of nanocarriers in vaccine fields is supported by the working mechanisms of vaccine formulations based on nanotechnology. Dendritic cells and macrophages are examples of phagocytic cells that readily take up particles smaller than 10µm. This characteristic has been utilized to boost antigen absorption into cells, which has increased antigen recognition and presentation efficiency (M.O. Oyewumi, A. Kumar, 2010). In order to make protein-based antigen vaccines suitable for oral or mucosal distribution, solid nanocarriers can protect them from depletion and allow access to the gut-associated lymphoid tissue and mucosa-associated lymphoid tissues. Nano carriers with altered surfaces could help distribute antigens in a targeted manner. Along with the mannose, scavenger, and toll-like receptors (TLR) (V. Apostolopoulos, T. Thalhammer, 2013), immune cells express a number of surface receptors. Targeting these overexpressed receptors using nano carriers coated in immune cell-targeting compounds including peptides, antibodies, and carbohydrates may improve the effectiveness of antigen and adjuvant delivery and raise the production of particular and selective immune responses in preventive vaccinations (M. Masuyama and S. Misumi, 2009).

Composition of Nano Vaccines

Although the contents of nano vaccines might vary greatly, they usually consist of certain vaccine components and nanocarriers. Typical elements could be:

Nanocarriers: Polymeric or lipid-based nanoparticles, liposomes, micelles, and other nanoscale objects are utilized for antigenic or genetic information.

2. Antigens: The elements of the pathogen (or related proteins) that elicit an immune response are known as antigens. Antigens are frequently linked to or encapsulated within the nano carrier in nanovaccines.

3. Adjuvants: These could include substances that strengthen the immune response. Adjuvants can be given individually or integrated into the nanocarrier to increase the vaccine's efficacy.

4. Stabilizers: Stabilizers are frequently added to vaccines in order to preserve their structural integrity and efficacy.These could consist of proteins, carbohydrates, or other stabilizing agents.

5. Surface modifications: Coatings or other surface alterations on the nano-carrier can be used to increase stability, target certain cells, or boost the vaccine's overall effectiveness.

Nano Particles used in Nano Vaccines

To improve cow vaccinations, chitosan nanoparticles (CNP), silica nanoparticles, and polylactic acid-glycolic acid (PLGA) nanoparticles are employed as adjuvants or vaccine carriers. The bovine respiratory syncytial virus (BRSV) vaccine, for example, produced condensed clinical signs and viral loads matched to controls after BRSV challenge because recombinant cyclic nanoparticles, used as an adjuvant, induced the production of specific antibodies and specific cellular immunity in vaccinated calves (Riffault S, Meyer G and Deplanche M, 2010). Cattle developed a strong T-cell immunological response to the p67 antigen when the sporozoite surface antigen, p67C, was loaded into silica capsules (Lacasta A, Mody KT and De Goeyse I 2021). Furthermore, calf nasal mucus containing BPI3V-specific IgA antibodies was much higher when the bovine parainfluenza virus (BPI3V) vaccine was encapsulated in PLGA nanoparticles than it was in commercial vaccinations (Mansoor F, Earley B, Cassidy JP 2015). Chitosan-coated PLGA FMD DNA nanoparticle vaccine (Chi-PLGA-DNA) produced almost three times the amount of sIgA compared to conventional vaccines and increased mucosal, systemic, and cell immunity in cattle. It reduces the severity of the disease, slows the removal of the virus, and postpones the beginning of clinical symptoms, even though it does not offer total clinical protection (Pan L, Zhang Z, Lv J 2014).As innovative vaccine carriers, nanoparticles are safe, well-organized, and effective at delivering antigens to immune cells and boosting cellular and humoral immune responses. Furthermore, nanoparticles can stimulate mucosal immunity, offering fresh perspectives on the creation of vaccines. Because of these advantages, adjuvants and carriers of nanoparticles are highly sought after in the field of vaccine development.

Limitation of Conventional Vaccines for LSD

Recounts of LSD vaccination disappointment have been made in a number of Ethiopia's constituent nations. 11% of RM65 (Ramayer strain)-vaccinated cattle (4.2% in dairy and 33.7% in feedlot cattle) contracted the infection during the 2006 outbreak in Israel (Brenner et al., 2009). According to Abu Tarbush, (2014), cow populations inoculated with RM65 (Jovivac®) and an unnamed LSD vaccine in Jordan had a general LSD morbidity of 4.7%. According to Kumar, (2011), Oman saw an ongoing LSD outbreak for over three months following the immunization of cattle herds with the Kenyan sheep and goat pox vaccine. Since 1993, reports of LSD vaccination failure have been made in Ethiopia (Carn, 1993). According to Ayelet et. al, (2013), following vaccination with the KS1 O-180 virus strain vaccine, the expected morbidity in the cattle population of central Ethiopia would be 23.8%. Nonetheless, a tenfold increase in the dose of the RM65 vaccine (1.85% morbidity) and the Neethling vaccine (1.11% morbidity) were found to provide superior protection (Ben-Gera et al., 2015). In general, vaccines may either protect a portion of the population (leaky vaccines) or only protect some people (all-or-nothing) (Smith et al., 1984). Furthermore, poor vaccination coverage or host-related or vaccination-quality-related issues resulting from vaccine handling, reconstitution, or administration may cause additional immunization failure (Quinn et al., 1999).

Immunized animals receive only partial protection from the KS1 O-180 vaccination. The degree of protection and how it affects the severity of the illness, however, have not been well studied in the field. In Ethiopia, the KS1 O-180 vaccine remains the only effective way to combat LSD. Therefore, the purpose of this study was to determine the impact of the KS1 O-180 viral strain vaccination on the transmission and severity of natural LSD infections below field circumstances. Traditional vaccinations have limitations despite being widely employed in clinical application and bovine vaccine enhancement because of their easy basis and high safety profile. For instance, inactivated vaccines need to be stored under controlled conditions, require multiple injections, and have a limited vaccination time. Moreover, live attenuated vaccines contain antigens that may persist within the host for an extended duration, potentially causing vaccinated animals to become long-term carriers of the virus. Additionally, conventional vaccinations could not offer adequate immune protection because of the virus's ongoing mutation and development. In conclusion, practicing supervision of pastures requires a thorough understanding of bovine vaccinations and adjuvants.

Mode of Action of Nanovaccines for LSD

Antibodies produced by plasma B cells in response to an antigen (foreign material) cause the generation of a specific antibody response, also known as antigenicity. Antibodies produced against both the combined antigen and the nanoparticle itself may be part of the immune response to nanovaccines. Even when generated, immunization with nanoscale gold colloidal systems, cationic dendrimers, and nanoparticles made entirely of carbon (fullerene) did not reveal any immune response specific to the nanoparticles.

Adjuvants function to improve and increase the immune system's reaction to antigens. Nanoparticles as adjuvants have been documented in numerous investigations. Nanoparticles elicited immunological responses that were either comparable to or greater than those caused by aluminum-containing adjuvants, such as alum, which are the most commonly employed in human medicine (E.J. Park et al., 2010; W. Zeng et al., 2012). Additionally, compared to an adjuvant based on alum, cobalt oxide nanoparticles promoted reduced generation of allergic antibodies and in-vivo inflammation at various injection locations (W. Zeng et al., 2012).

The immune system's cells secreting cytokines in reaction to foreign substances is known as an inflammatory response. In most cases, this sets off and attracts effector immune cells, which results in the foreign material being sanctioned. Numerous nanoparticles stimulate the immune system by producing inflammatory cytokines (A. Caputo et al., 2009). It has been shown that a variety of nanoparticles, including polymers, dendrimers, gold colloids, and others, might cause inflammatory cytokines (A. Caputo et al., 2009). A particular endocytosis route is used by cells to take up nanoparticles when they bind to their surface (J.J. Moon et al., 2011). Particle size, surface charge, surface modification, and hydrophobicity are some of the factors that can affect a nanoparticle's ability to absorb other materials (J.J. Moon et al., 2011). The way in which nanoparticles interact with cell membranes and go over physiological barriers is largely dependent on their size and distribution.

Research Work on Clinical application of Nano Technology

Treatment Protocol: During the summer of 2018, when the lumpy skin disease virus (LSDV) was spreading in Upper Egypt, a total of 35 clinically sick animals were collected from Beni-Suef Governorate, Egypt. They were split up into the two groups (Aand B) shown in Table 1. Group (A): Orally administered ALg-Propolis NPs at a dose of 300µl/animal for three consecutive days to twenty afflicted animals. Group (B): 15 diseased animals were given intramuscular injections of tetracycline (10%) at a dose of 1CC/10 kg per animal body weight over the course of three days. In certain circumstances, tetracycline ointment was used topically. (Babiuk et al., 2008): Clinical Examination of Animals: Clinical observations were made of infected cattle raised in the Bani-Suef Governorate, Egypt, between May and July 2018. These cattle suffered from depression, ocular-nasal discharges, appetence, salivation, and biphasic fever (40–41.5°C). Particularly the pre-scapular and precrural lymph nodes, there was a noticeable enlargement of the superficial lymph nodes. Getting Animal Samples Ready: From locally raised, diseased cattle raised in the Beni-Suef Governorate of Egypt, skin biopsies were taken, encompassing the epidermis, dermis, and subcutis of the nodular skin lesions. The same samples as in our earlier study by Allam et al. (2020) were utilized for separation and molecular investigations.

Toxicity and immune Response of Nano Vaccines

In addition to their amazing potential and range of uses, nanoparticles (NPs) have certain physicochemical qualities that make them unusually and unexpectedly harmful. By better understanding these traits and how they interact with cells, safer NPs can be developed. Numerous factors, including composition, size, charge, shape, hydrophobicity, and disclosure route, influence the harmful effects and immunological responses that the NPs elicit.

Therefore, it is crucial to look into the toxicity, immunological reaction, and long-term excretion of NPs before usage. Different cytotoxic features that make some NPs more toxic than others have been identified by several investigations

(Almeida JPM and Chen AL, 2011). This review [Hirsch C, Roesslein M, Krug HF 2011] addressed the current dependability of in vitro toxicity assays and suggested a number of controls to enhance experimental quality, which will eventually result in the safe and long-term usage of NPs. Numerous researchers looked into and concentrated on different facets of NPs (Fubini B and Fenoglio I, 2011). A number of other researchers have concentrated on enhancing NPs' biocompatibility and reducing their toxicity. It is advised that more research be done in order to fully comprehend the physicochemical properties and nanotoxicological standards of innovative nanomaterials, as well as their potential impact on human health.

Table 1: Research Work on Clinical application of Nano Technology (Allam et al., 2020).

Treatment	Number of Animals			Total
	Eye lesions	Skin lesion	wound lesions	
Group(A) ALg-Propolis NPs	1	16	3	20
Group(B) Tetracycline: (10%)	0	12	3	15

Conclusion

Finally, the development of vaccine tactiscs against lumpy skin disease appears to be enabled by the use of nano vaccines. Improved immunogenicity, tailored delivery, and increased efficacy are all provided by the nanotechnology-driven strategy. In addition to improving the health of our animals, adopting these creative approaches highlights the possibility of game-changing discoveries in the area of veterinary care as we traverse the complexities of livestock health.

Finally, the development of vaccine tactics against lumpy skin disease appears to be enabled by the use of nano vaccines. Improved immunogenicity, tailored delivery, and increased efficacy are all provided by the nanotechnology-driven strategy. In addition to improving the health of our animals, adopting these creative approaches highlights the possibility of game-changing discoveries in the area of veterinary care as we traverse the complexities of livestock health. As we adopt these innovative approaches, it becomes clear that nano-vaccines represent a significant advancement in veterinary medicine as well as a critical step in preserving the health of livestock. This novel strategy has the potential to completely rewrite vaccination guidelines and provide a glimmer of hope in the ongoing fight against lumpy skin disease.

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