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Advances, Limitations, and Future Directions of Subunit Vaccines Against FMD Disease

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Abstract Foot -and-mouth disease (FMD) is a transboundary viral disease that is highly contagious and seriously affects the livestock productivity, food security, and international trade. Even though the traditional inactivated vaccines have long been used over decades, their shortcomings such as relatively short immunity, biosecurity concerns during manufacturing, antigenic breakdown, and the lack of cross-serotype coverage limit their efficacy in the long term. The difficulties have led to the creation of subunit vaccines as the safer and more carefully designed alternatives.Subunit vaccines are, first of all, designed based on structural capsid proteins, in particular, VP1, or are prepared as virus-like particles (VLPs) to resemble the native virion structure, but without infectious genetic material. Immunogenicity has been significantly increased with the development of novel systems of recombinant expression, multi-epitope designing techniques based on immunoinformatics, nanoparticle delivery systems, and optimization of adjuvant.Though pre-clinical results have been encouraging, some problems have been noted including incomplete cross-protection and small scale field validation. Further development of multivalent design, antigen stabilisation, and new delivery methods is needed in order to attain sustainable and successful control of FMD.
Keywords: FMDvs, Subunit vaccine, VLPs, Multi-epitope vaccine

Introduction oot-and-mouth disease (FMD) is a transboundary pathology of great contagiousness that causes significant economic losses to the livestock enterprises, both domestic and wild, with cloven hooves [1]. Foot-and-Mouth disease virus (FMDV) is an etiologic agent which is a Picornaviridae Aphthovirus [2]. The serological screening has revealed seven serotypes namely: A, O, C, South African-Type 1 (SAT-1), SAT-2, SAT-3 and Asia 1. The viral genome consists of a linear and non-segmented and single-stranded RNA of around 8, 500 nucleotides inside an icosahedral capsid which is made up of the structural proteins, VP1, VP2, VP3 and VP4 [4]. VP1 serotype-specific residues are utilised in the demarcation of genetic variation, geographic distribution, phylogenetic connexion, and diversification among FMDV serotypes.[5]

Due to the high heterogeneity of the circulating strains, cross-protection between divergent serotypes is not possible and hence it complicates the prevention and control strategies. FMD has therefore remained a complex and highly challenging pathogen managerially[6]. The cross-immunity among the different subtypes of a given serotype is not high [7], and Genetic variability and polymorphism in the virus likewise complicate prophylaxis and

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control measures [8]. Recombinant adenovirus vectors containing the structural protein P12A and 3C gene of FMDV are under consideration [9]. different serotypes have been shown to elicit protective effects in preclinical research. Classical inactivated vaccines have many weaknesses, including being thermolabile, providing only short-term immunity, being costly to produce, facilitating wild-strain recombination, and readily reverting to pathogenic forms [7]. Although 90 years of research have been conducted, no vaccine has yet been developed that offers the degree of sterilizing, long-term immunity necessary to control FMD effectively, and the disease has remained enzootic across vast geographic areas. There have been numerous vaccine development programs that have been unable to elicit sterile immunity, adequate cross-serotype coverage, or long-term immunity[10] .

The current control measures implemented in countries free from FMD encompass the culling of infected and exposed animals, restrictions on animal movement, and, in certain cases, additional protocols countries, prophylaxis with ring vaccination using adjuvanted inactivated preparations [11]. The variety of host species, the numerous modes of transmission, the high infectivity, the rapid viral multiplication, and the heavy viral shedding, together with the accelerated global trade, the dynamism of the environment, and the anthropogenic effects, all increase the risk of FMDV re-emergence [12]. Having detected an outbreak, countries may be forced to reimburse vaccination efforts to limit the spread of the disease, but these measures are controversial and inevitably involve risks. Preemptive vaccination before an outbreak occurs is more likely to provide greater protection[13].

Preventive vaccination and containment policies are among the strategies that must be used to control diseases like FMD effectively, since this disease is mostly spread by inhalation of virus particles emitted by infected animals. Under certain environmental conditions, airborne transmission can occur, and viral particles can move outside the quarantine barriers[14]. Cattle are most often infected through respiratory or air routes, but swine may be infected through consumption of contaminated feed, water, or fomites. Environmental pollution is further indirect, allowing the virus to spread[15]. The pathogen's ability to survive under suitable conditions, including temperatures below 50 o C, humidity above 55 o C, and a neutral pH [16], makes FMD epidemiology and control a particularly complex issue, since there may be numerous sources of infection. Afflicted animals also excrete and secrete excretions and secretions, which serve as the medium of transmission as well as precious noninvasive diagnostic samples[17].

Vaccination is one of the main strategies for managing viral infections, with the aim of enhancing host immune responses and reducing inter-host transmission[18]. However, this is not the case because antigenic variation is a constant phenomenon in numerous viruses, implying the need to develop vaccines to keep them effective.

Early in the 20th century, formulations of inactivated viruses were used to begin the development of the FMD vaccine. This development offered optimism that this economically significant illness may be controlled. Numerous issues plagued inactivated vaccines, including the need for numerous doses and the absence of cross-serotype protection. These difficulties shift the emphasis to the development of live attenuated vaccines, which provide a more robust immune response and long-lasting protection. They had the potential to revert to virulence despite their advantages over inactivated vaccinations. The creation of virus-like particles, peptide-based vaccines, and nucleic acid vaccines in the late 20th and early 21st centuries has signaled a change in the paradigm of FMD vaccine development. Since then, those vaccines have been in continuous development till now; however, there is very limited field data on their efficacy [12].

2. Principles of Subunit Vaccines Against FMD

Modern studies have focused on the creation of new vaccines which include the subunits that are

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genetically engineered, empty capsids, and recombinant proteins [19]. Advances in the bioinformatics and genomics domains have redefined the paradigm of vaccine development to focus on current design modalities, which place efficacy and reduction of the risk factors associated with the development in the forefront. Recent developments in immunoinformatics have precipitated the development of a dedicated science focused on the development of multi-epitope-based vaccines (MEBVs) (20).

Therefore, an in-depth study of the four structural proteins (FP134) of the foot-and-mouth disease virus (FMDV) was conducted with the objective of developing a multi-epitope-based vaccine. After infection of the host cell with the virus, the long open reading frame is largely con-co-translated into four major polypeptides, i.e. L, P1, P2 and P3. P1 is cleaved into structural proteins VP1, VP2, VP3 and VP4 by the process of proteolytic processing. Whereas VP4 is a part of the internal structure of the viral particle, VP1 to VP3 are comprised of the capsid surface. Besides, the virus capsid has 60 capsomeres that contain one molecule of VP1, VP2, VP3, and VP4 [21]. It is anticipated that the expression of these structural proteins will positively influence vaccine efficacy and this will provide protection against a wide range of FMDV strains.

2.1 Antigen Selection

The genome of foot-and-mouth disease virus has one large and open reading frame that forms one polyprotein precursor. It is further broken down to the functional viral proteins, which are the structural VP0, VP1, VP3, and a succession of the non-structural proteins. In the process of maturation, VP0 is further broken down to VP2 and VP4. Although VP1, VP2, VP3 are shown on the virion surface, the rest VP4 is an intra-capsomeric protein, as described in the literature (22).

This large ORF is enclosed in the viral RNA by a large 5' untranslated region of some 1,300 nucleotides and a smaller 3' untranslated region of nearly 90 nucleotides, as well as a poly(A) tail [23]. The virus proteases L and 3C cleave the polyprotein into the P1, P2, and P3 modules to produce fifteen mature proteins. P1 module codes the structural proteins VP1 (1D), VP2 (1B), VP3 (1C) and VP4 (1A). The non-structural proteins, which consist 2A, 2B, 2C; 3A; 3B (viral protein genome-linked, VPg); 3C protease; and 3D RNA-dependent RNA polymerase, are based on the P2 and P3 modules, respectively. Proteins synthesis is closely linked with RNA replication and immune resistance, which is mostly facilitated by non-structural proteins (24).

VP1 is the most divergent of these serotypes with a sequence variance of 3050 percent. Such a variability plays a crucial role in serotype differentiation and thus is a major marker in serological studies (25).

The antigenic determinants of the virus are major and are located in separate looping segments of the structural proteins, especially N terminal, BC loop, EF loop, FG loop, GH loop and C terminal segments. One of them is the high-conservation of the RGD (argumentine-glycine-aspartic acid) motif, which is found in GH loop of VP1. This motif is a dominant determinant of cell host-entry, which facilitates integrin receptor binding. Integrins are a variable family of 24 heterodimers characterised by high affinity to the RGD sequence of native ligands [26]. In addition, the GH loop contains a hyperreactive zone (HV) a regulatory domain that regulates immune evasion and antibody binding. As a result, full virions and virions that express VP1 GH loop, in particular, stimulate a strong immunogenic response [27].

2.2 Virus-Like Particles (VLPs)

Taking into account the fact that they maintain epitope conformations without the use of live viruses to create the vaccine, empty capsid virus-like particles (VLPs) represent an interesting alternative to traditional subunit vaccines, showing superior structural complexity [28]. VLPs assemble themselves to form well-defined structures with numerous copies of viral structural proteins, which is similar to the composition of a virion in nature [29]. These

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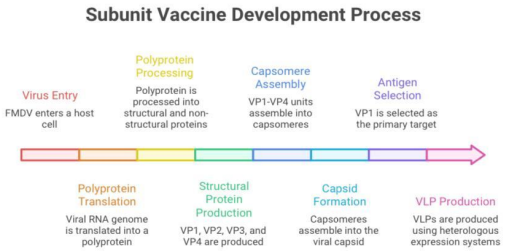
particles include particles all of the repertoire of immunogenic epitopes of native virus particles, but exclude the infectious genetic material required to stimulate the synthesis, processing, and assembly of structural proteins into viable viral capsids (30).

Though spontaneous in-vitro assembly of VLPs may happen in cell culture systems, they are normally produced by heterologous expression of single capsid subunits, and then assembled. Various viral gene delivery systems such as bacterial systems, baculoviruses-infected insect larvae, mammalian cell line, and plant expression systems have been explored as possible hosts of the recombinant expression of Foot-and-Mouth Disease Virus (FMDV) VLPs [31].

Figure1: Subunit Vaccine Development Preocess



3. Advances in Subunit Vaccine Development

Advances in bioinformatics and genomics have transformed traditional vaccine development into modern design approaches that prioritize efficacy while reducing risk. Recently, advances in immunoinformatic have highlighted a dedicated sub-discipline focused on the rational design of multi-epitope-based vaccines (MEBVs) [20]. The efficacy of an MEBV depends on the selected epitopes, which should also be capable of generating both humoral and cell-mediated immune responses. B-cell epitopes are required to activate antibody-mediated immunity, and T-cell epitopes are required to stimulate cytotoxic T lymphocytes (CTLs) to clear infected cells [32].

3.1 Recombinant Expression Systems

Among the viral attachment proteins, VP1 has been used to generate vaccines, and this vaccination has been significant as an immunogen [33]. Most recently, it has been firmly established as an excellent vaccine target through epitope mapping and recombinant expression methods [34].

It has been described by Chathuranga and others that recombinant VP1 vaccines can offer mice the highest levels of protection possible against either serotype of FMDV (O and A) due to their ability to target individual epitopes. Furthermore, this platform based on peptide has several advantages as compared to traditional whole-virus vaccines, which are improved safety and scalability[35]

Patricia de León and others have explored new dendrimer peptide scaffolds which are molecules that have many copies of FMDV epitopes on branch molecules. These vaccines induced strong responses in swine to IFN -G when administered with neutralizing antibodies in high dosages and showed that multivalent antigen display could be an efficient means of boosting immunity [36]. The researchers also extended the investigation to the enhancement of vaccine efficacy by co-delivery of RNA transcripts that are based on non-coding regions of FMDV that have been associated to trigger immune pathways [37].

Giselle Rangel and her collaborators constructed virus-like particles using a chimeric Rabbit Hemorrhagic Disease Virus expressing major FMDV epitopes, such as T -cell epitope 3A 2135 and B -cell epitope 140158. The resultant immunogen was both serotype O protective in pigs, and potent neutralizing monkey antibodies in murine models. Though not all animals were fully protected, the vaccinated group had significantly better safety results as compared to those of the controls, with a single pig having attained full immunity [38].

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Li and colleagues transduced FMDV VLPs in the yeast Pichia pastoris by co-expressing the P1 capsid precursor with optimized 3C protease using an N -helix loop helix motif. One intramuscular dose of 50 µg in mice and swine induced a significant response in FMDV-specific immunoglobulin and neutralizing antibody, robust cellular activity with IFN- 7, and 80-86 per cent protection in swine after challenge using the same dose- no protection was observed with PBS-treated controls. These findings confirm the immunogenicity of VLP strategy and its ability to provide a protection of at least partial immunity in a cost-effective yeast system. In order to achieve total immunity, the further development of work should focus on improving epitope selection and design of particles. To sum up, these articles all point out the need to further research VLP platforms to vaccinate against FMDV[39].

3.2 Nanoparticle and Delivery Strategies

In addition to antigen selection, vaccination delivery techniques have changed. Novel delivery technologies, including oral vaccination formulations, VLPs, and nanoliposomes, are currently being added to conventional injectable vaccines[40].

These developments reduce the need for repeated booster doses by improving ease of administration and the durability of immune responses. Farmers in isolated or resource-constrained areas, where maintaining regular immunization schedules can be difficult, could greatly benefit from such developments. Cattle and pigs continue to be the most pertinent species for assessing vaccination performance, even though early immunogenicity research employed small animal models like mice and guinea pigs. Interestingly, pigs are typically harder to immunize with traditional vaccines than cattle, so each species requires a different strategy [41].

Heshmati et al. created nanoliposomes using cholesterol (Chol), 1,2-dimyristoyl-sn-glycerol-3-phospho (DMPG), and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) lipids (5:4:16 molar ratio) to encapsulate synthetic FMDV peptides (VP1 141–161 and 198–211 from serotype O/2016).

Slow antigen release (less than 2% in 24 hours; full over 7 days) was observed with the particles (~130 nm, 67% encapsulation efficiency). Intramuscular immunization (100 µg/dose, administered in three doses separated by two weeks) produced FMDV-specific IgG responses in guinea pigs. Freund's adjuvant produced the strongest response when compared to conventional adjuvants, followed by alum and nanoliposomes. According to the study, nanoliposomes enhance peptide stability and controlled release; nevertheless, potency tuning is still necessary[42], according to the study, nanoliposomes enhance peptide stability and controlled release; nevertheless, potency tuning is still necessary.

For the administration of FMD vaccines, extracellular vesicles (EVs) have shown great promise. In a groundbreaking in vitro investigation, Menay et al. found that dendritic cells pulsed with inactivated FMDV (O1 Campos, 10 µg/mL for 16 hours) released EVs with a diameter of about 155 nm. Viral proteins, immunoregulatory molecules such as MHC-II and CD86, and traditional EV markers such as CD9, CD63, and CD81 were all expressed on these vesicles.

Crucially, these EVs indirectly boosted T-cell responses in splenocytes from vaccinated mice and led to a notable proliferation of FMDV-specific B cells, including follicular and marginal-zone B cells. The results imply that EVs may serve as organic carriers of antigens that might stimulate humoral and cellular immunity[43]. As a result, EV-based systems show continued advancement in the creation of sophisticated vaccine delivery tactics for FMD and offer a novel and possibly more stable substitute for traditional antigen and peptide delivery techniques[44].

4. Limitations and Challenges

Numerous attempts to develop a vaccine to prevent FMD have not succeeded in producing sterile immunity, with insufficient duration of

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immunity and limited cross-serotype protection [10].

4.1 Limited Immunogenicity

It is now clear that the period of immunity induced by currently available strategies is not adequate, cross- serotype immunity is not extensive yet, and sterile immunity has not been reached in the endeavour to come up with a vaccine against foot-and mouth disease (FMD) [10]. Traditional vaccine manufacturing processes, including serial passage of the virus in cell culture [45], in non-permissible animals and in its natural host have however been successful in attenuating the pathogen. This attenuation is caused by the selective concentration of mutations around antigenic and binding sites [46]. However, the quasi-species swarm method and agent reversion through positive selection cannot be used in non-endemic areas(47).

A negative finding can be observed even when the virus is alive in the case of a plaque assay performed in BHK -21 cells; this can be explained by the fact that the production of the FMD vaccine in non-permissive hosts can force the virus to use alternative cellular receptors other than the canonical Arg -Gly -Asp (RGD) motif [48]. Furthermore, in addition to the quasi species swarm and positive selection, the vaccine strain still has the possibility of returning to the pathogenic form [47].

4.2 Short Duration of Immunity

Short duration of immunity remains a major limitation of traditional inactivated foot-and-mouth disease (FMD) vaccines. These vaccines present several drawbacks, including thermal instability, transient immune responses, high production costs, and potential risks, including recombination with wild strains and pathogen reversion [7].
Despite nine decades of research, Sterile immunity is rarely achieved firm and sterile immunity for

Protective antibody titers often decline within months after vaccination, necessitating frequent booster doses to maintain adequate herd immunity, particularly in endemic regions where continuous viral circulation requires sustained immune protection.

Despite more than nine decades of vaccine research, achieving firm and sterile immunity against FMD has remained elusive, and the disease continues to persist in many parts of the world. Numerous vaccine development efforts have failed to induce long-lasting protection, frequently resulting in insufficient duration of immunity and limited cross-serotype coverage[10]. This challenge is largely attributed to the selective accumulation of mutations within viral binding and antigenic regions, which can reduce vaccine effectiveness over time [46].
Although such evolutionary mechanisms may drive viral reversion through positive selection, their relevance is considered less critical in non-endemic regions where viral circulation is tightly controlled [49].

4.3 Antigenic Diversity of Foot-and-Mouth Disease Virus

The huge antigenic variation of the foot and mouth disease virus (FMDV) mainly arises due to the selective forces of the host and the dynamism of the evolutionary process of the virus. The large number of hosts and the rapid evolution of the virus make it possible to stay constantly genetically modified, which can change the antigenic characteristics, which adds to the complex epidemiology of FMD [50]. Amino -acid analysis has provided valuable information on protein changes in FMDV capsid region. Although the rate of site-specific mutations with time is measured using analyses of selection pressure, comparisons of amino-acid sequences make it possible to recognize the changes at the protein level (51).

Most of the studies have found out that some of the surface antigenic sites undergo diversifying selection but the P1 region (coding the structural capsid proteins) is predominantly under purifying selection (52).

This pattern implies that the mutations would be concentrated in the uncovered antigenic-binding areas, increasing viral adaptation to the host

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immunity and immune interventions including vaccination, although the general capsid framework would be comparatively preserved [53]. Moreover, the dynamic FMDV development has been traced by the variations of the selection pressure observed in various hosts, infection stages, and temporally clustering information [52].

5. Veterinary Applications and Experimental Evidence

Subunit vaccines, particularly those based on Virus-Like Particles (VLPs), have demonstrated in preclinical studies their capacity to induce neutralizing antibodies and offer partial protection against homologous viral challenges in cattle, pigs, and small ruminants. However, comparative data on field-level efficacy relative to traditional vaccines remains limited. A replication-defective adenovirus type 5 vector, encoding the P1 structural region and the 3C protease of serotype A Foot-and-Mouth Disease Virus (FMDV) (Ad5A24), elicited robust neutralizing antibody responses and conferred protective immunity in swine following a single immunization [11]. A potent humoral response and a high concentration of perforin and IFN -7 in CD8 + T-cells populations were observed in mice immunised with a plasmid encoding VP1 concomitant with IL -9, used as a genetic adjuvant, and concomitantly using anti-apoptotic pathways, but IL -17 was not detected. IL -9 served the objective of inhibiting T-cell apoptosis and increasing Becl following the Becl gene (54) .

In a different investigation, IL 2 was used as a genetic adjuvant in a plasmid vaccine with two different VP1 epitope of the foot-and-mouth disease virus (amino-acid residues 141-160 and 200-213), which form several antigenic determinants. This method was able to induce the T-cell growth and generation of neutralising antibodies to foot-and-mouth disease in swine. In addition, intranasal delivery of a DNA vaccine using a chitosan carrier, which included IL -2 in genetic adjuvant and IL -15 in molecular adjuvant, elicited mucosal and systemic immunity. The immunological characterisation was an amplified cell-mediated immunity, T-cell proliferation, increased cytotoxic T- lymphocyte activity and increased IFN-7 expression both in the CD4+ T- cell and CD8+ T- cell subsets (45) .[

The re-examination of the mice with the VP1 expressing plasmid and IL-9 adjuvant, in combination with the activated anti-apoptotic mechanisms also verified the production of a robust humoral response, as well as elevated levels of IFN-g and perforin in the CD8+ T-cells but not IL-17. In line with this, IL -9 stimulated the expression of Beclin genes and played a role in the prevention of T-cell apoptosis (54) .

All these observations point towards the fact that the subunit vaccines produced by means of genetic manipulation have significant potentials when it comes to being used as an alternative to standard vaccine platforms. However, it is necessary to rigorously test in livestock to prove the protective efficacy, define the persistence of the induced immunity and consider the possibility of such vaccines to be implemented into the routine veterinary practice.

6. Future Directions

As we explore the genetic composition of the various FMDV strains, it is possible to come up with vaccines that have a variety of serotypes- or even attempt to develop universal vaccines that have a broader spectrum[55]. The virus is mutating at an extremely rapid rate, and all its serotypes and subtypes continue to shift in their antigenicity, which complicates vaccine development and makes it more challenging[56]. An animal can be saved with one serotype, yet it can still be susceptible to others; thus, we always find ourselves going round and round, creating new vaccines[57]. Once more, an angle is examining viral genetics to develop broad or universal vaccines that would offer broader protection .The molecular design can also reveal stabilisers or modifications that make vaccine preparations solid, helping maintain their efficacy in storage and during application [58]. This is because the molecular structure of the vaccine is known, allowing scientists to select or develop adjuvants that complement it

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effectively .Exosome technology promises to advance vaccine design a notch higher, particularly against viruses that are more difficult to control, such as FMDV. Recent investigations used dendritic-cell-derived EVs based on an inactivated FMD shot .The EV epitopes bind to both B and T cells, triggering a distinct B-cell response to FMDV and an indirect kick-on effect by T cells .[43] Computational biology collaborates with AI when assembling shots. Such developments enable improved data acquisition, more precise model predictions, and aid the fine-tuning of vaccine candidates .By targeting these future directions, researchers will increase the usefulness of FMDV vaccination procedures, which will, in the future, help cope with and eliminate this large-scale economic monster of livestock worldwide. The FMDV issue will be addressed by staying on top of the ongoing innovation and collaboration that will increase animal output and well-being[59].

6. Conclusion

Due to its high infectivity, swift transmission, and remarkable antigenic diversity,FMDv continues to be among the most economically impactful livestock diseases. damaging transboundary animal diseases globally. The necessity for improved vaccination strategies is underscored by the inherent limitations associated with conventional inactivated vaccines, despite their substantial role in disease management. These limitations encompass a brief duration of immunity, biosafety concerns during the manufacturing process, limited cross-serotype protection, and the necessity for frequent administrations boosters.

Subunit vaccines, especially those based on VP1 epitopes, recombinant capsid proteins, and virus-like particles (VLPs), have become attractive next-generation substitutes. These systems provide improved safety profiles, flexibility in antigen design, and compatibility with DIVA methods. Developments in recombinant expression systems, immunoinformatics-driven multi-epitope vaccine design, nanoparticle-based delivery systems, and innovative adjuvant technologies have greatly enhanced the immunogenic potential of subunit vaccines. By eliciting neutralizing antibodies and cellular immune responses, VLPs and dendrimer peptide structures, in particular, have shown promising results in preclinical cattle models.

Even with these developments, a number of problems still exist. Widespread adoption remains hampered by short immunity duration, limited large-scale field validation, and limited cross-serotype protection. Furthermore, FMDV's high mutation rate and antigenic drift necessitate frequent vaccine updates and the development of broader-spectrum protection techniques.

Multivalent and universal vaccine design, adjuvant optimization, structural stability of antigens, AI-assisted antigen prediction, and novel delivery methods, such as extracellular vesicles, should be the main focus of future research. Subunit vaccines could greatly improve global disease management if incorporated into comprehensive FMD control efforts within a One Health framework.

In conclusion, subunit vaccines provide a scientifically sound and strategically significant platform for the future management and potential eradication of FMD, even though they have not yet completely replaced conventional immunizations. Large-scale livestock trials, ongoing interdisciplinary cooperation, and technological advances will be necessary to translate successful experiments into practical veterinary applications.

Table 1: Key Scientists and Their Discoveries in FMD Subunit Vaccine Development

Scientist(s) Vaccine Platform	Year	Discovery / Contribution	
Abrams et al.	1995	Assembly of FMDV empty capsids using the vaccinia expression system	Empty capsid / VLP precursor
Rodriguez & Grubman	2009	Comprehensive review on FMDV vaccine strategies and VLP concepts	Vaccine strategy foundation
Guo et al.	2013	Production of FMDV VLPs in E. coli, inducing protection in	Recombinant VLP

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		livestock	
de León et al.	2021	Dendrimeric peptide vaccines inducing strong neutralizing antibodies and IFN-γ in pigs	Multi-epitope dendrimer vaccine
Rangel et al.	2021	Chimeric RHDV VLPs displaying FMDV epitopes provide partial protection in pigs	Chimeric VLP
Heshmati et al.	2021	Nanoliposomal peptide vaccine with controlled antigen release	Nanoparticle delivery system
Menay et al.	2024	Extracellular vesicles as antigen carriers stimulating B and T cell responses	EV-based delivery
Zaher et al.	2024	Integration of emerging technologies and AI in FMD vaccine development	Advanced vaccine innovation
Li et al.	2025	Yeast-expressed FMDV VLPs inducing 80–86% protection in pigs	Pichia pastoris VLP system

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