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NEW GENERATION VETERINARY VACCINES

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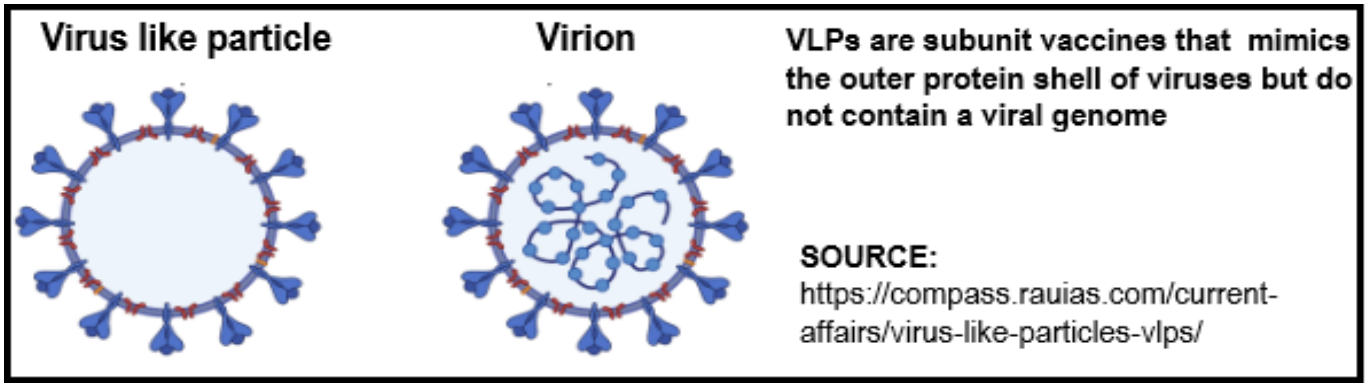
ABSTRACT

New generation vaccines such as Virus-like particles (VLPs), bacterial ghosts, Outer membrane vesicles (OMVs), and SRP technology have opened new vistas in vaccine development to curb infectious diseases in livestock. Unlike conventional vaccines, such as killed bacterial vaccines, bacterial ghosts are excellent alternatives because their antigenic components remain undenatured. VLPs act as modular vaccine platforms for several viral diseases since VLPs confer dense repeating protein arrays and conformational epitopes homogeneous to those of native viruses.

KEYWORDS: Artificial Seeds, CRISPR, Multi-Omics, Seed Enhancement Technologies, Seed Priming

VIRUS-LIKE PARTICLES (VLPs)

VLPs are subunit vaccines that closely imitate the outer protein shell of viruses. VLPs do not contain a viral genome and hence are non-infectious. VLPs possess the exact size and shape of native viruses. VLPs present the immune system with multiple viral epitopes in the precise conformation.



VLPs can activate helper T cells, can give rise to long-lived memory cells and induce a strong antibody response. VLPs stimulate dendritic cell activation and are efficiently taken up and processed by dendritic cells, and presentation of antigens is done using both MHC class I and class II molecules, which helps to prime both CD4+ and CD8+ T cells. This ability to target dendritic cells makes VLPs highly effective

immunogens, which helps to circumvent the requirement of using adjuvants and hence VLPs can act as self-adjuvanting vaccines. Because of their immunogenicity, VLPs are needed in smaller doses when compared with conventional subunit vaccines and this reduces vaccine costs.

VLPs are currently produced using different expression systems such as *E. coli*, yeasts, mammalian cells or insect cells. Among the various production systems, the most promising is the one involving the use of insect cells to grow baculoviruses, which helps to co-express multiple viral proteins that are then allowed to self-assemble into VLPs.

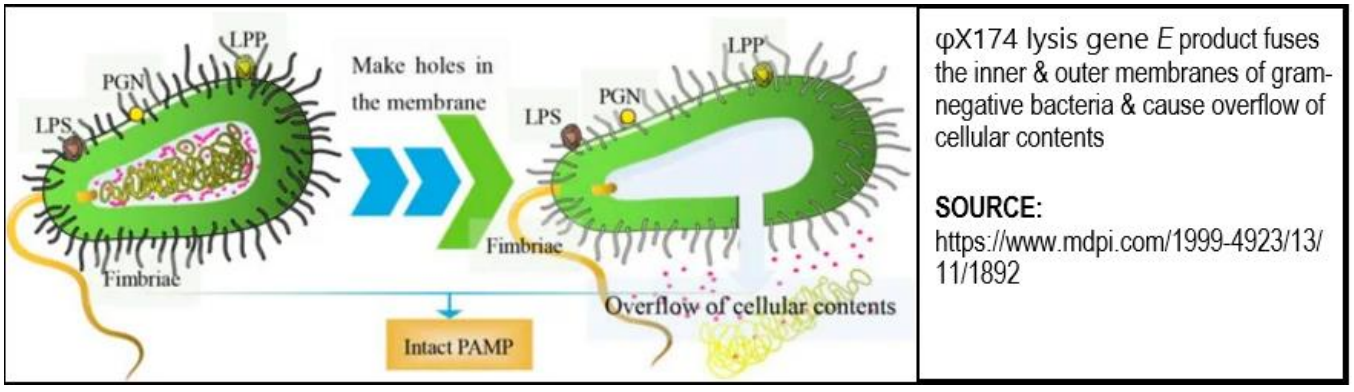
VLP-based vaccines have been produced against various veterinary virus pathogens such as caliciviruses, nodaviruses, and birnaviruses, all of which can form VLPs with just a single capsid protein. Nowadays, VLP-based vaccines have been developed against parvovirus, circovirus and Newcastle disease virus. Other noteworthy VLP-based veterinary vaccines include those against Avian Influenza and FMD virus.

Two VLP-based vaccines currently available for human use are hepatitis B VLPs and human papilloma VLPs. The hepatitis B VLPs utilise adjuvant system-4 to induce a Th1 response. This hepatitis B vaccine was the first human vaccine to use VLPs and is also credited as the first anticancer vaccine to utilise VLPs since hepatitis B can cause liver cancer.

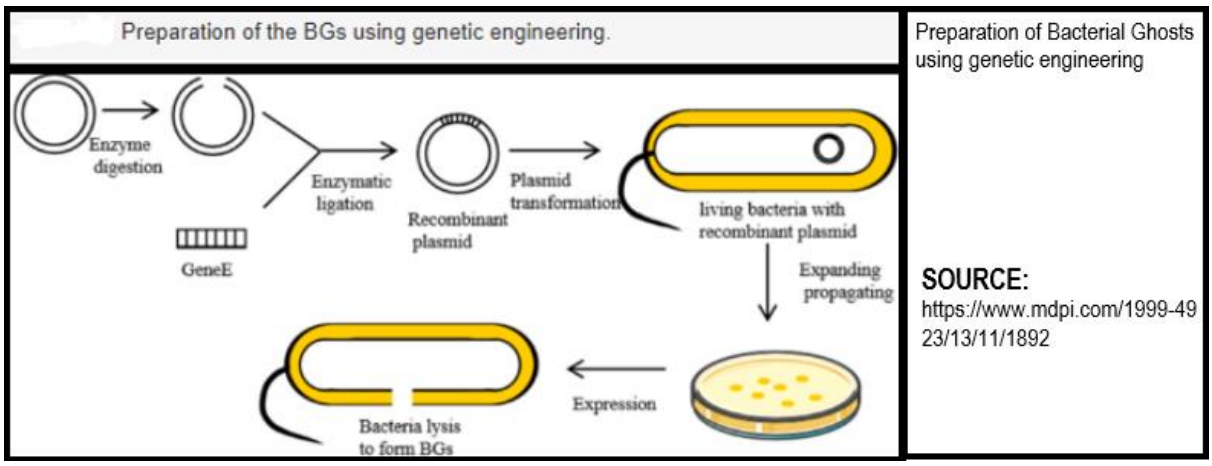
BACTERIAL GHOSTS

Bacterial “ghosts” emanate from gram-negative bacteria and are basically empty cell envelopes. Bacterial “ghosts” have no cytoplasm and no chromosomal or plasmid DNA. Bacterial “ghosts” from *E. coli* are constructed using controlled expression of the cloned bacteriophage φX174 lysis gene *E*. Gene *E* codes for a 91 amino acid protein, and this protein fuses the inner and outer membranes of gram-negative bacteria to form a transmembrane pore through which bacterial cytoplasm escapes.

Protein E-specific lysis tunnel spans the inner (IM) and outer membrane (OM), which is located at membrane adhesion sites within the host cell. The bacterial ghosts contain no genetic information, since any remaining DNA is destroyed by the expression of cloned staphylococcal nuclease A in *E. coli*.



Because of their structure, they have intrinsic adjuvant activity and can induce both adaptive and innate immune responses.

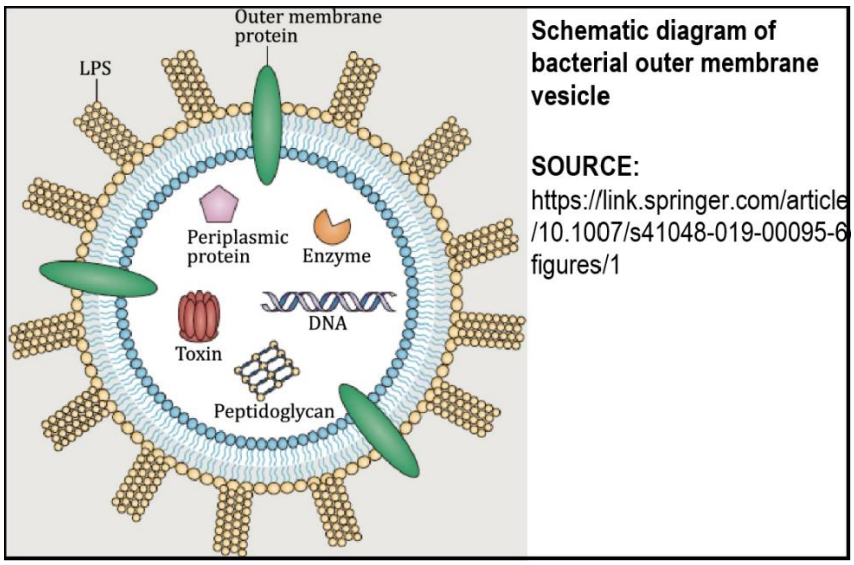


Bacterial ghost technology has been used against *Actinobacillus pleuropneumoniae*. When *Actinobacillus pleuropneumoniae* bacterial ghost was administered orally in pigs, it generated sterile immunity and cross-protection between serotypes. When given intramuscularly, it was protective, but did not induce sterile immunity. Bacterial Ghosts have also been generated successfully against *Pasteurella multocida* and *Mannheimia haemolytica*.

OUTER MEMBRANE VESICLES (OMVS)

Bacterial outer membrane vesicles are miniature membrane vesicles with huge vaccine potential. OMVs are globular particles having a diameter of 20-300 nm released by gram-negative bacteria. OMVs are generated by the budding out of the bacterial outer membrane and contain many bacterial outer membrane components. OMVs can induce strong immune responses as they are highly immunogenic. Bacteria can be engineered to increase vesicle production, reduce LPS toxicity and increase expression of protective antigens.

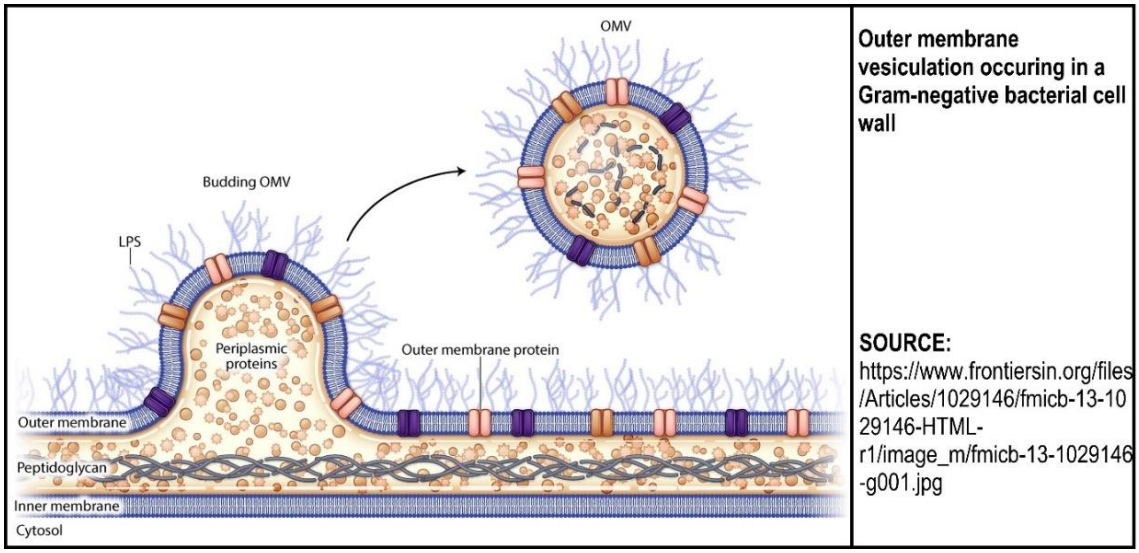
OMVs are readily phagocytosed by Antigen Processing Cells (APCs) and carry many Pathogen-Associated Molecular Patterns (PAMPs) including LPS, lipoproteins and peptidoglycans. OMVs induce a potent cell-mediated immune response (type 1 effector response). OMVs can be readily obtained in large quantities from culture supernatants. The main limitation of OMVs is their strain specificity.



Schematic diagram of bacterial outer membrane vesicle

SOURCE:
https://link.springer.com/article/10.1007/s41048-019-00095-6/figures/1

An anti-Neisseria based OMV vaccine is commercially available for humans. Heterologous proteins of other species may be incorporated into OMVs. For example, *Leishmania* antigens have been incorporated into *E. coli* OMVs.

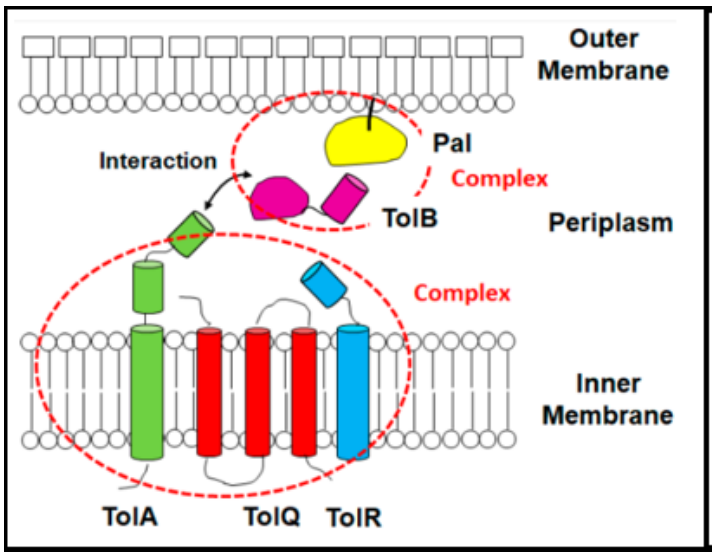


Outer membrane vesiculation occuring in a Gram-negative bacterial cell wall

SOURCE:
https://www.frontiersin.org/files/Articles/1029146/fmicb-13-1029146-HTML-r1/image_m/fmicb-13-1029146-g001.jpg

GENETIC ENGINEERING IN INCREASING THE PRODUCTION OF OMVS

Tol-Pal system functioning affects the OMV production. TolR, TolQ and TolA proteins form an inner membrane complex. The C-terminal domain of the periplasmic TolB protein is associated with the outer membrane-associated Pal protein, while the N-terminal domain of TolB interacts with the C-terminal domain present on the TolA protein. The *tolB* mutant shows increased OMV release in several bacteria such as *S. typhimurium*, *E. coli*, and *H. pylori*.

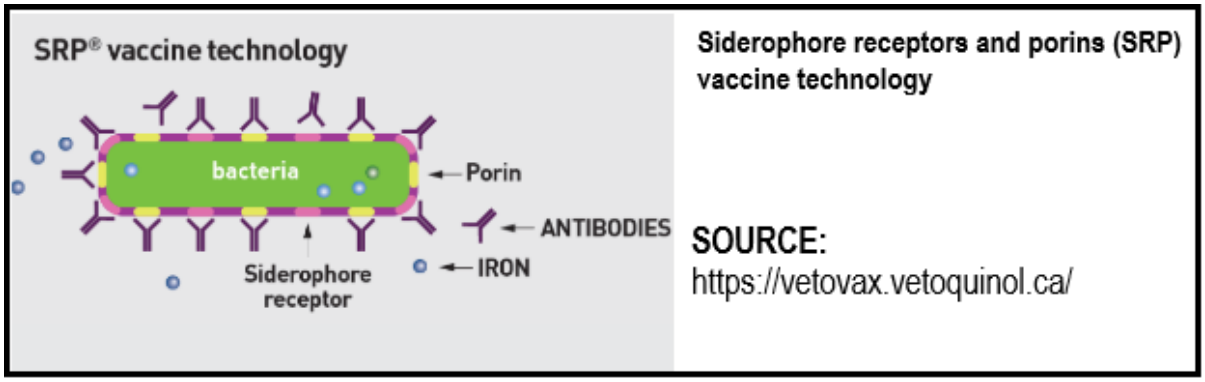


Structural representation of the Tol/Pal Protein complexes

SOURCE:
https://www.mdpi.com/2076-393X/10/3/422

SRP VACCINE TECHNOLOGY

Iron is an essential growth factor for many pathogenic bacteria. Bacteria take up iron from their environment by the use of iron-binding proteins called Siderophores. Siderophores such as Enterobactin (Enterochelin) have such a high affinity for ferric iron that they can take it from the host's iron-binding proteins. Bacteria have a siderophore receptor (Porins) on their outer membrane that facilitates the transfer of this iron into the cell. Antibodies directed specifically against these siderophores or their cell surface receptors (porins) will effectively block bacterial iron acquisition and thus inhibit bacterial growth.



Siderophore receptors and porins (SRP) vaccine technology

SOURCE:
https://vetovax.vetoquinol.ca/

If bacteria are cultured in a low-iron environment, they express increased quantities of their iron acquisition proteins. These can be harvested, and the siderophore receptors and porins (SRP) can be purified, and these purified proteins can be used in vaccines.

VETERINARY VACCINES BASED ON SRP VACCINE TECHNOLOGY

E. Coli bacterial extract, made with SRP technology, is the only USDA-licensed vaccine approved to reduce *E. coli* O157 prevalence in cattle. This vaccine is effective for vaccination of healthy cattle, ≥ 5 months of age, against *E. coli* O157.

Salmonellosis is responsible for acute diarrhoea in calves and multisystemic illness in adult cattle. Salmonellae are transmitted to humans through meat/milk products. Therefore, it is important to control Salmonella-mediated disease in addition to the shedding of these organisms in cattle. SRP vaccine licensed by USDA reduces shedding of serotype Newport in dairy cattle and is available in USA/Canada for vaccination of cattle at ≥ six months of age.

SRP vaccination of cattle at ≥ 22 months against mastitis caused by *Klebsiella pneumoniae* has been shown to reduce mastitis prevalence in the vaccinated herd. SRP vaccination of layer/broiler breeder chickens is an innovative option for Fowl Cholera as it protects poultry against mortality and improves livability in flocks affected by fowl cholera.

CONCLUSION

Novel vaccine technologies, such as SRP vaccine technology, hold promise against several egregious diseases in livestock and poultry. Nowadays, refinement in Outer Membrane Vesicles, such as the knock-out of *msbB* and *lpxL1* genes, has significantly decreased the level of LPS endotoxin in OMVs, which has led to the generation of OMVs with low toxicity and high safety.

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