CHAPTER 32

USE OF NANOTECHNOLOGY IN TREATING SOME IMPORTANT VIRAL ANIMAL DISEASES

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INTRODUCTION

Over the course of history, technology has been the best friend to all living creatures when it comes to their welfare as it has helped us find new ways to solve many problems that had never been solved before. When it comes to medicine and all related biological fields, technology has provided a gateway to solving hurdles that were in the way of solving health-related problems of all living beings. In this chapter we have reviewed the part that Nanotechnology has played in providing better answers to the questions regarding viral veterinary diseases over the course of years. There is no doubt in the fact that vaccination is the only solution to prevent viral diseases in living beings, but we can improve every technique and treatment with the aid of nanotechnology these days. Nanoparticles play the role of finer adjuvants with lesser cytotoxicity and even better results than any other alternatives. We will discuss different Virucidal Nanoparticles in this chapter along with the major work that has been done in successful trials to prepare nanoparticle-antigen conjugated vaccines.

Viruses are incredibly small pathogenic particles that can cause several kinds of diseases in both animals and humans. They cannot survive on their own. They are also called the "obligate intracellular parasites". They are only composed of coating proteins called the capsid and DNA or RNA. The simplicity of genetic material gives them a major property of rapid mutation. Some viruses also have an outer coating called an envelope. They cause significant mortality and morbidity in animals. Despite dumbfounding advancements in the pharmaceutical industry, no sure-fire antiviral drugs have been synthesized till now. Thus, viruses are a nuisance for both the sick and the doctors attempting to treat viral diseases (Ulmer et al. 2006).

Nanotechnology

The word "nano" here clearly exclaims the small size of the object that will be discussed here. Despite its small size, nanotechnology has found a wide range of uses in all kinds of industries and futuristic advancements. The United States' National Science and Technology Council has defined nanotechnology as the working being with particles of size ranging from 1-100nm. The term nanotechnology itself refers to the ability to measure, manipulate and rearrange matter at the nanoscale level. This nano scale level includes atomic, molecular and supra-molecular stages of matter where a man can perform experiments to achieve the desired reaction from the nanoparticles (Emerich and Thanos 2003).

Even the most primitive nanotechnology experiments have revealed that nanotechnology holds a promise of unmatched animal production, best animal welfare, long-lasting animal health, guaranteed animal safety and quickly effective animal medicine. This will serve as a booster for animal-related industries like the meat and milk industry. This will in turn also solve the issues of food shortage and balanced nutrients for humans (El-Sayed and Kamel 2020).

Nanotechnology will also help researchers to deal with minute quantities of materials, such as DNA and RNA, easily and precisely hence, making genetic material manipulation faster. This will quicken the genetic improvement programs by many folds. Problems like DNA loss during cloning or the inability to select proper genes within lesser generations of larger animals will be solved.

The main problem of losses in poultry is viral diseases that spread uncontrollably among flocks and kill hundreds of birds in a short time. The most disturbing factor here is that it cannot be controlled because we lack antiviral agents and have no hope of recovery once a viral outbreak begins. Thus, nanotechnology will be the almighty saviour for poultry farmers. Nanotechnology will defeat the arch-nemesis of the poultry industry for good.

Researchers all around the globe are also working on several types of other nanoparticles that instead of killing viruses deliver enzymes which can render viruses unable to reproduce. This will stop the progression of diseases even if the virus enters a host's body. Development of orally consumable drugs containing such nanoparticles is underway.

Nanobots or nanorobots are another attempt to begin a promising era in medicine related to cell repair technology. These bots will be programmed to help the natural healing system much like antibiotics.

In recent years, nanotechnologists have widely investigated the development of antiviral agents for the treatment of previously hard to fight viral diseases. Nanotechnology will not only improve the effectiveness of current medicinal options, but it will also provide the manufacturers with a whole new branch of remedies that will be a hundred times more effective than older ones.

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Nanotherapeutics

The use of nanoparticles for the sake of treating a disease is termed nanotherapeutics making it a separate branch of nanotechnology medicine. This refers to the use of nanoparticles combined with antiviral drugs (Wang et al. 2012). Antiviral drugs can be encapsulated with nanoparticles which will protect it against viruses when given systemically. If given locally, the nanoparticles will form a surface coating that prevents further spread of the drug from the desired location. The nanoparticles have a long half-life in circulation and good drug loading characteristics. Such properties make it a good companion for hydrophobic chemicals. These drugs cannot be given directly in their free form because of their hydrophobic nature (Cojocaru et al. 2020).

Virucidal Nanoparticles

Nanoparticle researchers have tried to check the virucidal effects of various metal and sheet-based nanoparticles to determine their use against several diseases (Szunerits et al. 2015). Metal nanoparticles and graphene-based nanosheets were discovered to be naturally virucidal due to their unique physicochemical properties. Their simple mechanism of action is interacting with the envelope or capsid of viral proteins to disrupt structural integrity and inhibit infective behaviour. Some of these particles can also stop viral replication (Liu et al. 2017). Here are discussed different types of nanoparticles which have a virucidal effect and come in handy while fighting off a viral disease:

Nano-metals

Silver nanoparticles are the most widely exploited metal nanoparticles in terms of medicinal research (Rai et al. 2014). Experiments have shown that silver nanoparticles can inhibit a broad range of viruses with the least chances of developing resistance even in the case of highly mutative viruses. Silver nanoparticles have worked astonishingly both extracellularly to block entry of viruses and intracellularly to prevent replication of the virus (Figure 1). It has been used successfully in several experiments for treating human immuno-deficiency virus and influenza virus diseases (Singh and Laura 2012). Similarly, gold particles synthesized from seaweed *Sargassum wightii* were also found to be effective against the herpes virus in an experimental trial.

Nano-emulsions

A category of nanoparticles that has simple and low-cost synthesis but is still active for the treatment and prevention of several viral infections is nano-emulsions. Nano-emulsions can be produced by mixing a lipid phase and an aqueous in presence of a surfactant material. Like several other types of nanoparticles, its mode of action is also dependent upon interaction with the viral particles (Hamouda et al. 2001). Nano-emulsions have shown good efficacy against enveloped viruses like herpes, influenza and vaccinia viruses. An old example of nano-emulsion is 8N8 made from 8 volumes of tributyl phosphate, 64 volumes of soybean oil and 8 volumes of triton X-100. It was used to disrupt bacterial membranes.

Graphene-based Nanosheets

Graphene is a material with excellent thermal and electrical conductivity properties. In the medical industry, graphene has appeared as a novel anti-viral material that is especially helpful in disinfecting viruses. The two unique two-dimensional structure of graphene is the physiochemical property that gives it antiviral characteristics. Graphene has an exceptionally high surface volume ratio allowing it to intercept viruses effectively. Graphene oxide is negatively charged and carries sufficient reactive oxygen species on its surface to destroy viruses through redox reactions and forces of electrostatic attractions (Geim and Novoselov 2007). These interactions are especially effective if virus capsid proteins are positively charged (Figure 2). Some virus capsids have high arginine protein content making them positively charged.

Nano-decoys

Initially developed to bind and neutralize bacterial toxins, the nanodecoys soon found their application against viruses too (Rao et al. 2020). They can be designed to neutralize specific viruses through ligand-receptor interactions (Angsantikul et al. 2018). This use of nanodecoys against viral infections was recently reported. Nanodecoys can be broadly classified into two main types. The first type is invader nanodecoys that are specially designed to bind with a specific viral receptor (Figure 3). Virions encountering such particles are also captured and blocked by nanodecoys to prevent infection (Hu and Zhang 2014). The second type of nanodecoys is formed by coating purified cell membrane contents from a target around the nanoparticles to form nanosponges. These nanosponges can then carry antiviral drugs or antigens for the safe delivery of a vaccine into the body without compromising vaccine effectiveness.

Ligand Functionalized Nanoparticles

Understanding of cellular pathways involved in the destruction of viruses by nanoparticles is important to help us add supporting materials with nano-metals or other nanoparticles that can increase their effectivity. These supporting particles are called ligand functionalized nanoparticles (Baram-Pinto et al. 2009). As an example, it was seen in lab animals that the use of mercapto-ethane sulfonate along with silver nanoparticles inhibits entry of the herpes virus by competitively binding to cellular heparan sulfate.

Cellular Nanosponges

Ligand-functionalized nanoparticles may serve as good potentiating agents and effective materials for blocking viral entry, but they have a crippling disadvantage, that is the requirement of full knowledge relevant to receptor-ligand interaction before they can be put to effective use. Hence, a thorough study of the cell and target virus is required to use the ligand functionalized nanoparticles effectively. The ligands are very specific in their interaction. On other hand, viruses are rapidly undergoing mutations and may change the shape of receptors over time. These disadvantages can be covered by broadening the use of nano decoys by application of cell-like nano-platforms (Rao et al. 2020). These nanoparticles will serve as the basis for displaying the same surface receptor as

Table 1: List of different nanoparticles used for different veterinary viral diseases for various purposes like diagnostics, vaccination and treatment:

No.	Disease	Virus	Family	Nanoparticle	Purpose
1.	Foot & Mouth Disease	FMDV	*Picornaviridae*	AuNPs	Vaccine
2.	Newcastle	NDV	*Paramyxoviridae*	Ag@SiO2	Vaccine
3.	Rabies	Rabies virus	*Rhabdoviridae*	AgNPs	Vaccine
4.	Canine Distemper	CDV	*Paramyxoviridae*	H-Nanoparticles	Vaccine
5.	Canine Parvo	Parvovirus	*Parvoviridae*	PLGA	Vaccine
6.	Bluetongue	BTV	*Reoviridae*	Glycan Gold NPs	Vaccine
7.	Bovine Viral Diarrhoea	BVDV	*Flaviviridae*	AuNPs	Serological detection
8.	Marek's Disease	MDV	*Herpesviridae*	TLR-Ls	Impedes tumor development
9.	Infectious Laryngotracheitis	GaHV-1	*Herpesviridae*	SN-TiO2-PSP	Serological detection
10.	Hydropericardium syndrome	FAV-4	*Adenoviridae*	AuNPs	Serological detection
11.	Infectious Bronchitis	IBSV	*Coronaviridae*	AgNPs	Virucidal activity
12.	Egg Drop Syndrome	EDSV	*Adenoviridae*	AgNO3-NPs	Antiviral activity
13.	Fowlpox	FPV	*Poxviridae*	AMS	Antiviral activity
14.	Feline Panleukopenia	Parvovirus	*Parvoviridae*	AuNPs	Serological detection
15.	Infectious Bursal Disease	IBDV	*Birnaviridae*	AgNPs	Virucidal activity

FMDV= Foot & mouth disease virus; AuNPs=Gold-Nanoparticle; NDV=Newcastle disease virus; Ag@SiO2=Silica coated Silver Nanoparticles; AgNPs= Silver Nanoparticles; CDV= Canine distemper virus; PLGA=Poly (lactic-co-glycolic acid); BTV=Bluetongue virus; BVDV=Bovine viral diarrhoea virus; MDV= Marek's disease virus; TLR-Ls=Toll-like receptor ligands; GaHV-1=Gallid alphaherpesvirus-1; SN-TiO2-PSP=Spiky titanium dioxide nanoparticle-loaded plantains semen polysaccharide; FAV-4=Fowl adenovirus-4; IBSV=Infectious bronchitis virus; EDSV=Egg drop syndrome virus; AgNO3-NPs=silver nitrate nanoparticles; FPV=Fowlpox virus; AMS=Aluminium Magnesium Silicate; IBDV=Infectious bursal disease virus.

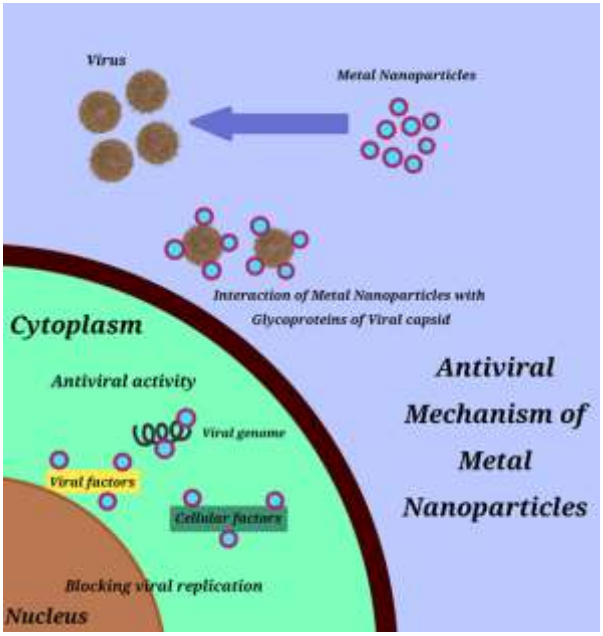

Fig. 1: Pathway adopted by metal nanoparticles to stop viral replication

the cell on the nanoparticles (Figure 4). Hence, cell membrane coating technology helped the researchers to broaden the use of nano decoys and ligand functionalized nanoparticles (Zhou et al. 2019).

An important use of cell membrane-derived nanoparticles is for detoxification. While displaying the same receptors as cells, the nano receptors will divert harmful toxins away from susceptible cells. The nanosponges will then react with the toxins and bind them rendering their toxicity harmless for other healthy cells of the host (Hu et al. 2013).

Nanoparticles for Different Veterinary Viral Diseases

Foot and Mouth Disease (FMD)

Foot and mouth disease (FMD) is a highly contagious viral disease of many domesticated and wild cloven-hoofed animals that is caused by foot and mouth disease virus (FMDV) which belongs to the family *Picornaviridae* (Martinez-Salas et al. 2008). FMDV is an RNA-containing and filterable *aphthovirus* of this family and it has seven different sero-types based on their antigenic structural characteristics which include about 80 total variants of this devious disease-causing virus. Vaccination has been the only tool to prevent this disease in domesticated cloven-hoofed animals for decades. Commercial vaccines are used for this purpose but many times over the course of the history of this disease, these vaccines have failed and caused enormous losses to the dairy business (Doel 1996).

Many times, the vaccination doesn't fail yet the disease appears in flocks because of the slow process of immunity development in the animals. But now a new hope has emerged regarding the prevention of this disease. Research studies have been held and experimental procedures have concluded that nanotechnology can not only provide the successful vaccination of FMD, but it can also make the immunity development process faster than the commercial vaccines available for this disease (Park 2013). Peptide antigen-nanoparticle combinations have been proposed to provide vaccinated-to-immuned status in flocks. For this purpose, gold nanoparticles (AuNPs) were conjugated with the antigen peptides in combination with CFA. This study suggested that vaccination with the conjugate of AuNPs and antigen peptides (VP1 of the native peptide) has shown a more immense immunity response in the animals against FMD as compared to the animals vaccinated with commercial FMD vaccines available in the market. Higher titre of the antibodies was observed in the test animals along with even more sensitivity shown against the antigen immunoassay. A considerable increase in the production of proinflammatory cytokines (especially IFN-γ) and the peritoneal macrophages was also observed. In short, this study laid the foundation to future research works regarding the vaccination of animals against FMD using gold nanoparticles (AuNPs) conjugated with antigen peptides (Moisa and Kolesanova 2010).

Newcastle Disease

A highly virulent disease of domestic and wild poultry birds caused by Newcastle disease virus (vNDV) which belongs to the family *Paramyxoviridae* (Davis 2001). The higher susceptibility and higher mortality rates caused by this disease mostly lead to epidemics in avian flocks and wild poultry populations. Just like any viral disease, vaccination is the only way to prevent enormous losses caused by NDV in the poultry business industry (Chen et al. 2007). DNA vaccines are a great option for vaccination but there are still some obstacles to delivering it into the bird's body through traditional ways (Steel et al. 2008). As the traditional methods of vaccination include injecting it via intramuscular route, this way doesn't help much when the antigen wouldn't be able to reach the target APCs which then leads to vaccination failure (Romer-Oberdorfer et al. 2003). This necessity raised many questions in mind which led to the suggestion of considering the use of better adjuvants for delivering ND vaccines to the APCs effectively. Previous studies (Wang et al. 2011) have shown that all the disadvantages brought to light using DNA vaccines can be prevented by using nanoparticles by the aid of nanotechnology by building a mucosa delivery system using metal nanoparticles. Silver and silica nanoparticles were used in combination to deliver the DNA vaccine right where it should've been delivered in the first place (to antigen presenting cells APCs). The Ag@SiO2 hollow nanoparticles were used for this purpose. The beneficial properties manifested by these Ag@SiO2 hollow nanoparticles included safest delivery of plasmid DNA, lower chances of cytotoxicity, uniformity in the structure along with higher stability even in fluctuating temperatures (Alexander 1990).

Rabies

Rabies virus belongs to the *Rhabdoviridae* family, and it causes acute encephalomyelitis in both animals as well as humans (Finke and Conzelmann 2005). Annually more than sixty thousand people die of Rabies worldwide, of which 99% of the cases are from Asia and Africa. No doubt that Rabies is a preventable disease with the aid of vaccination tools these days. The World Health Organisation (WHO) has recommended a control strategy for this disease through vaccination worldwide (Bahloul et al. 2005). Vaccinating humans, dogs and other domesticated animals as well can help in limiting the invading ways of this virus into living bodies. Commercially prepared vaccines are available in the market for this purpose, most of which are alum-based (Wang and Singh 2011). Alum is used in vaccine manufacturing against many diseases these days. Along with many advantages, there are certain disadvantages of using vaccines that are alum-based. Recently trials have been manifested in search of better adjuvants than alum in the industry of vaccine manufacture (Zhao et al. 2014).

Many have used metal-based nanoparticles for this purpose like silver and gold nanoparticles (AgNPs & AuNPs) (Dykman et al. 2010). Green synthesis of nanoparticles has made their production way easier and cheaper these days (Sivakumar 2011). AgNPs have been used as adjuvant to deliver DNA/RNA of many viruses to produce immunity in animals. A study (Lindblad 2004) was held to test green synthesized AgNPs to deliver the Rabies vaccine as adjuvant against the commercially prepared alum-based Rabies vaccines. The results showed immense improvement in the successful vaccination along with lesser time taken to build immunity against the disease (Asgary et al. 2016). An increased humoral response to the antigen of the Rabies virus was also observed. As the search for better adjuvants in aids of vaccination against viral diseases continues, we see promising assistance in vaccine formulation from nanotechnology and metal nanoparticles. Yet there are still some limitations in their clinical application because of the higher cost in their production and public's access. As the work goes on, we'll tackle these hurdles as well (Asgary et al. 2016).

Canine Distemper

Canine distemper is a highly contagious and fatal disease of dogs, ferrets and giant pandas, caused by Canine Distemper Virus (CDV) which is an enveloped and single stranded-RNA virus that belongs to the family *Paramyxoviridae* (Plattet et al. 2016). Available means of getting rid of this disease include inactivated vaccines, subunit vaccines, DNA vaccines along with attenuated vaccines of CDV (Avota et al. 2013). Some studies regarding CDV also suggested that utilizing fusion (F) proteins along with purified hemagglutinin (H) proteins have shown great immune responses in dogs. While other studies also found that DNA vaccines containing H protein of CDV also come in handy in immunizing minks against Morbillivirus infections (Ge et al. 2015). Vector vaccines also show great immune response in subjects as compared to that of attenuated vaccines (Jensen et al. 2015). While inactivated or killed vaccines show poor immunization response and require multiple doses to keep the animal immunized. Some studies reported that animals that got vaccinated with attenuated vaccines of CDV developed leukocytopenia and typical erythematous rash of distemper. Some studies have shown that nanoparticle-based antigens are better adjuvants for immunizing animals against CDV as these vaccines show multiple advantages over inactivated, attenuated and subunit vaccines of CDV (Wang et al. 2013). These advantages include higher immunogenicity, more stimulation to antigen presenting cells (APCs) and better adjuvant effects to express better innate and adaptive immune responses (Cheng et al. 2010).

Parvovirus

Parvovirus causes enteric and myocardial diseases in dogs worldwide. Canine parvovirus is a single stranded DNA virus. It is a small self-replicating virus. Parvovirus infection has a high mortality rate of about 90% of cases ending in the fatality of the animal (Derman et al. 2014). Absence of any kind of treatment leads to a mortality rate going even above 90%. The use of a vaccine against parvovirus has not been very successful. The attenuated virus or dead viral particle used as a vaccine is phagocytized by the protease enzymes present in the cell, rendering it useless for production of immunity (Prittie et al. 2004). Due to the failure of the traditionally used vaccines, a synthetically prepared peptide-based vaccine for the treatment of canine parvovirus soon emerged. To overcome the problem of the phagocytosis of live or attenuated vaccine antigens by the protease enzymes, the synthetically prepared peptide-based vaccine was introduced into the cell in a nanoparticle-based delivery system (Casal et al. 1995). Poly (DL,lactic-co-glycolic acid) (PLGA) is a widely

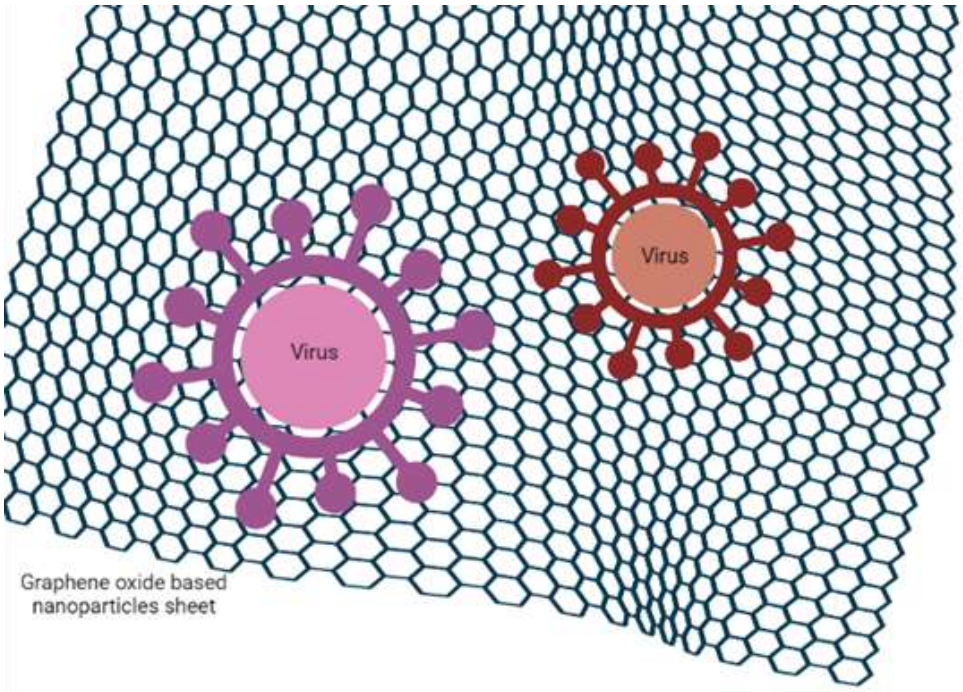

Fig. 2: Negatively charged Graphene oxide-based sheet attracts and entraps viral particles with positively charged protein coating. This entrapment renders the viral particles disabled preventing their attachment with healthy cell membranes.

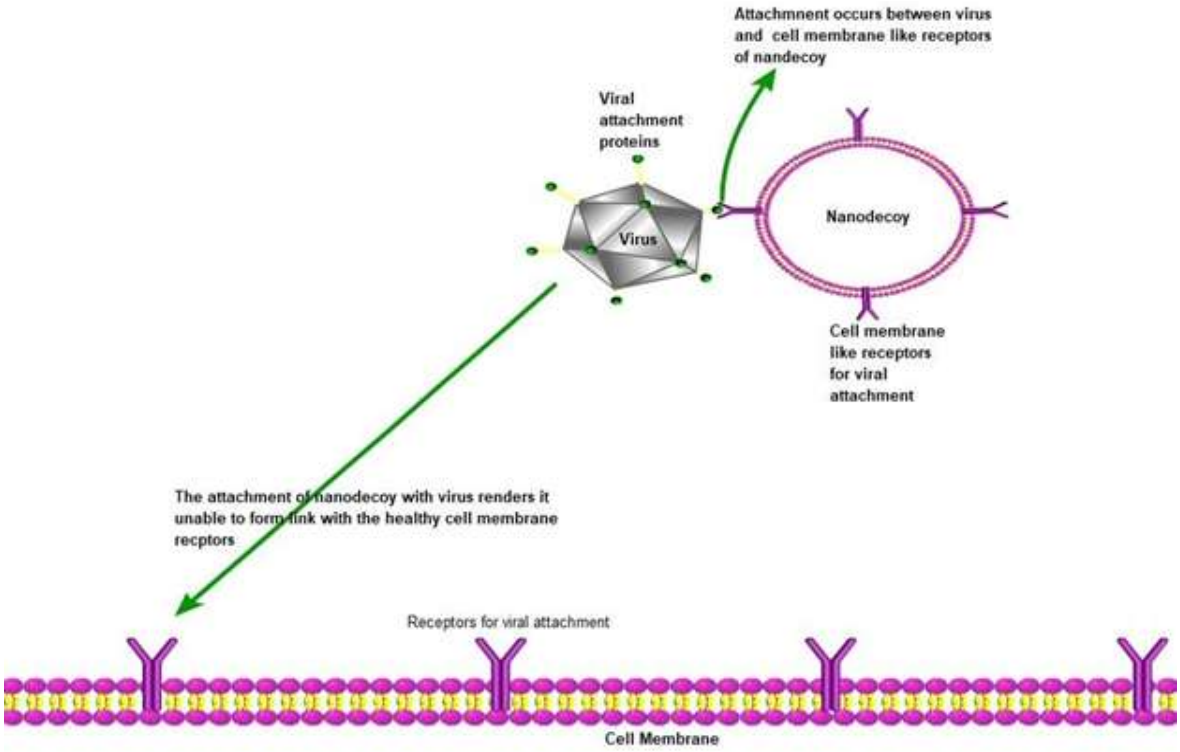

Fig. 3: A nanodecoy attaches itself to a viral particle to prevent it from linking with the receptors of a healthy cell membrane.

used nanoparticle-based carrier system. The nanoparticle delivery system might be a protein or a polymer. It can also be a nanoparticle (Langeveld et al. 1994). During the preparation of the carrier system, the following steps were followed as standard protocol. The W-1 L19 peptide of the canine parvovirus is encapsulated in the PLGA delivery system in the presence of oil or double water emulsion as a solvent. The uniformity of the size and smooth, spherical surface of the nanoparticles play an important role in the functioning of the carrier systems. The application of the peptide-based vaccine in a nanoparticle delivery system proved to be more advantageous as compared to the introduction of the vaccine directly into the cell. For instance, the release of antigen (vaccine) can be controlled over time if required. The nanoparticle delivery system also provides protection against the cell proteases. The surface area for absorption is increased. Use of nanoparticles eliminates the requirement for a booster dose. It also plays a vital role in enhancing the availability of vaccine antigen in the cell.

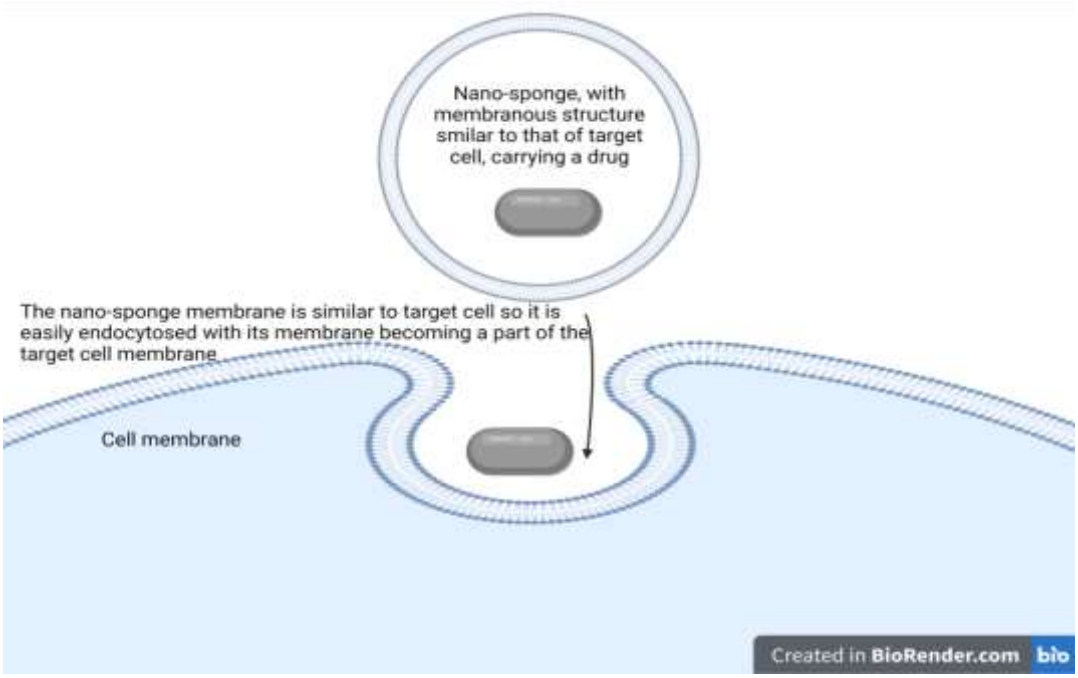

Fig. 4: The mechanism of carrying a drug safely to its target by use of nano-sponges.

Blue Tongue

Bluetongue is a non-enveloped virus with a double capsid protein coating. The capsid of this virus is composed of seven different types of proteins (Zhang et al. 2016). The complex structure of this virus is the reason for making it nearly incurable. Its infection manifests as a serious disease in sheep. It also infects cattle, horses and deer (White and Eaton 1990). The genome of this virus appears to be uniquely made up of 10-double stranded RNA segments. Bluetongue virus has several serotypes but the outermost spike-like VP2 protein has maximum importance. At least 28 different serotypes of the bluetongue virus have been discovered by researchers until now (Wu et al. 2019). The vector responsible for the spread of this virus is the Culicoides species, gnats (biting midges). It is a widely distributed disease in sheep. There are seven structural proteins (VP1-VP7) but VP2 is the most important and causes disease (Zhang et al. 2016). VP2 is the main protein of attachment to the cell for the virus once it gains entry into the body. Experimental data has suggested that VP2 protein interacts with the Sialic acid (SA). The VP2 protein interacts with alpha 2, 3 linked and alpha 2,6 linked SA. To inhibit bluetongue virus infection, lectin inhibitors are used as nanoparticles. As a nanoparticle, lectin inhibitors target SA linkages. The main competitor of lectin inhibitors is alpha 2,3, linked to SA. The main binding sites for SA on VP2 are determined by using mass spectrometry. The higher affinity of VP2 for alpha 2,3 linked SA is revealed by the glycan array (Baker et al. 2019).

Summary

Viruses have been responsible for causing several kinds of diseases in all living beings. Previously viruses have been very hard to fight off because of their rapid mutation along with our inability to develop more and more antiviral drugs. The only option that still stands is vaccination as a prophylactic agent. Vaccination wasn't still a bullet-proof plan as it had some holes like vaccination failure, disease outbreak before the immunity response even showed up, vaccination routes and the slow delivery of antigen to the APCs. Then some recent studies showed that the solution to all of these problems faced by the vaccination schedules lay in nanotechnology. Nanoparticles have several modes to fight off a virus and they can also deliver the vaccine to the right receptors at the APCs. Gold nanoparticles (AuNPs) have been proven helpful to vaccinate animals against foot and mouth disease virus. Silica coated silver nanoparticles (Ag@SiO2) have done the same for Newcastle disease virus in the poultry sector. Likewise, some animals have shown immune response against rabies as well when they were vaccinated with green synthesized silver nanoparticles conjugated with the rabies virus. These research studies have laid a foundation for future achievements in this direction where vaccination and nanotechnology go on fighting all the viral diseases as a prophylactic step.

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