Chapter 61

Current Trends in Vaccine Technologies: Innovations and Challenges

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ABSTRACT

Although vaccination is highly effective in decreasing or eliminating diseases caused by pathogens, there are still certain diseases and new infections that pose intrinsic challenges in the development of effective vaccines. Moreover, the process of creating vaccinations for persons who have weakened immune systems or pre-existing medical disorders poses substantial challenges. Emerging non-viral vaccine technologies offer fresh ways to get beyond the current barriers in vaccine production, in addition to conventional vaccinations such as live attenuated or deactivated vaccines, subunit vaccines, and viral vector vaccines. These technologies include viral-like particles and nanoparticle vaccines, DNA/RNA vaccines, and rational vaccine design. Our understanding of vaccine immunology has been considerably enhanced as a result of these breakthroughs, which have provided essential insights for the creation of vaccines against a wide range of diseases. These vaccines will be effective against a wide range of diseases, including newly developing infectious diseases such as COVID-19 and diseases that have previously shown resistance to vaccination. This chapter presents a complete overview of newly emerging non-viral technologies for vaccine production, as well as an examination of their potential uses in addressing the most critical problems in vaccine development.

KEYWORDS
Nanoparticle-based vaccinations, Non-viral DNA-RNA vaccinations, Infectious diseases, Vaccine development, Vaccinations for cancer

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INTRODUCTION

Since the late 18th century, when Edward Jenner discovered the smallpox vaccine, vaccination has been essential in preventing disease. In spite of immunizations' noteworthy successes in preventing and treating a wide range of illnesses, vaccine distribution and research still face significant challenges (Mohsen et al., 2017). Widespread and severely impactful diseases like HIV and influenza make it difficult to maintain successful immunization programs. In order to respond swiftly to outbreaks, it is necessary to hasten vaccine testing and licensing processes. The most recent worldwide COVID-19 pandemic, which was caused by the SARS-CoV-2 virus, provided direct evidence of this assertion. This pandemic resulted in a significant loss of life and had profound economic consequences. A multitude of vaccinations were expeditiously formulated and exposed to rigorous clinical studies (Dudek et al., 2006). Messenger RNA (mRNA) vaccines have demonstrated remarkable potential due to their artificial composition and ability to be manufactured with flexibility in terms of sequence (Dagan et al., 2021).

This enables the rapid and adaptable development and production of vaccinations. Given these advantages, Moderna, Inc. created and manufactured an mRNA vaccine (mRNA-1273) for SARS-CoV-2 human trials with remarkable speed and success (Condit et al., 2014). This astounding feat was completed in only 42 days after getting the target antigen's nucleotide sequence. These mRNA vaccines developed by Moderna and Pfizer/BioNTech for SARS-CoV-2 have demonstrated impressive effectiveness, with an efficacy rate of approximately 90% over a monitoring period of up to 6 months. This has been noted in the general population as well as in phase III clinical trials (Chackerian, 2007).

This is in addition to their straightforward design and manufacturing process. Both vaccines obtained extensive authorization for human utilization and started being dispensed in December 2020. Consequently, the widespread delivery

of such formulations to a significant population has significantly helped to the reduction in the incidence of COVID-19 cases and fatalities in countries which have established robust immunization strategies. The rapid and unmistakable success of mRNA vaccines has catapulted them into the spotlight, garnering attention from both the scientific community and the general public (Dhanwani et al., 2017).

Selecting the best suitable vaccination platform(s) for the development of pandemic vaccines can be difficult because each platform has its own advantages and downsides. The advantages and disadvantages of the conventional methods used in the production of vaccines, such as live attenuated and inactivated vaccinations and protein subunit vaccines, have been extensively discussed. On rare occasions, inactive immunizations may demonstrate inadequate capacity to generate an immune response or, in uncommon cases, result in exacerbated sickness symptoms (Clem, 2011). Live attenuated vaccinations pose the risk of regressing to a more virulent strain. Furthermore, it is frequently imperative to carry out clinical studies for pandemic vaccinations while an outbreak is ongoing in order to gather essential data regarding their efficacy and safety. However, this limitation narrows the pool of potential vaccines that are suitable for quick medical interventions (Barry, 2018).

Vector-borne virus platforms and non-viral vaccination methods are examples of recent developments in the field of vaccination. In order to transfer the antigen, viral vector vaccines use a virus that is not related to the specific infection. Researchers have been using a vaccinia viral vector for more than four decades in order to create the hepatitis B surface antigen (HBsAg) in order to protect chimpanzees from contracting hepatitis B (Grgacic and Anderson, 2006). This method has been successful in boosting immunity to the illness. Viral vectors have subsequently been effectively used to immunize various animal species. It is important to note that only one viral vector vaccine—rVSV-ZEBOV—has been officially approved for use in human immunization programs. Specifically, this vaccine is made to combat the Ebola virus (Zimmermann and Curtis, 2019).

Viral vectors originating from paramyxoviruses, herpesviruses, adenoviruses, flaviviruses, and retroviruses have all been used to create vaccines (Plotkin et al., 2014). The advantage of viral vectors is that they can stimulate a strong immune system response without the requirement for additional adjuvants. However, using replication-competent vectors increases the possibility that the compromised viral vector could revert to a hazardous condition (Kushnir et al., 2012). Researchers have looked into the usage of single-cycle as well as replication-deficient viral vectors as viable solutions to address this problem. In some cases, these options can still elicit a significant immune response while offering a higher degree of safety (Condit et al., 2014). There are several obstacles to effective vaccination, one of which is the wide variety of specific viruses (Bettschen et al., 2013; Townsend and Banks, 2020).

Furthermore, the efficacy and safety of vaccinations can be greatly impacted by underlying medical disorders and pre-existing immunity across vaccinated populations (Fahim et al., 2013). Furthermore, vaccinations are an unfeasible treatment due to the complexity of diseases like drug addiction and cancer as well as our poor understanding of the immune responses that offer defence against them. To optimize protection and prevent unfavorable consequences, it is important to determine the optimal balance between the cell-mediated response and antibody response for each particular ailment (Dhanwani et al., 2017). The immune response to vaccination may be influenced by a number of variables, including age, gender, genetic variations, and pre-existing medical disorders (Clem, 2011). Historically, immunizations have been administered using attenuated or inactivated vaccines. But developments in non-viral vaccine technology offer workable alternatives to get around barriers to vaccine production—especially in times of pandemics or outbreaks (Kollmann et al., 2012). This chapter explores novel approaches to creating non-viral vaccines and how they could be used to treat infectious and non-infectious diseases that are both emergent and well-established (Dagan et al., 2021).

Progress in the Development of Non-viral Vaccination Technologies

Virus-like Particle and Nanoparticle Subunit Vaccinations

Subunit vaccines are emerging as a more versatile and appealing alternative to whole-pathogen vaccinations because they can produce large amounts of specific antigens without the full virus (Dudek et al., 2006). However, subunit vaccinations often have a lower potential to induce an immunological response; hence, adjuvants and several administrations are required for maximal effectiveness. Several strategies have been implemented to address this problem, enhancing both the response of the immune system and the long-term effectiveness of subunit vaccines (Coutinho and Chapman, 2011). The production of vaccines involves the utilization of nanoparticles (NPs) and virus-like particles (VLPs). Vaccines containing virus-like particles are produced utilizing techniques that closely mimic the structure of authentic viruses. In both prokaryotic and eukaryotic systems, antigenic proteins can be synthesized and are capable of self-assembly (Mohsen et al., 2017).

By combining protein antigens with carrier molecules, chemical crosslinking is used in nanoparticle (NP) vaccines to increase immunogenicity and prevent antigen degradation (Grgacic and Anderson, 2006). These carriers can be either organic (based on lipids) or inorganic (based on metals or polymers). The capacity of protein oligomer self-assembly to generate nanoparticles for the purpose of acting as carriers and transporters has been demonstrated. Although NPs and VLPs exhibit exceptional stability, NPs' potential to trigger the innate immune response is restricted. However, when it comes to ease of use, economy, consistency, and security, NPs outperform VLPs in a few areas (Becklund et al., 2016). This is so because using NPs does not need using several protein components. In order to compensate for NP vaccines' lower potency in eliciting an immune response in comparison to VLP vaccinations, the carrier can be tailored to the specific

antigen by considering attributes including size, electrical charge, arrangement, and water-repellent qualities (Wertheimer et al., 2014). Furthermore, antigens can be more effectively transferred via antigen-presenting cells (APCs) to other cells by using carriers to precisely transport nanoparticles (NPs) to immune cells (Barry, 2018).

DNA and RNA Vaccines

Because of their exciting potential, vaccines based on nucleic acids, such DNA and RNA vaccines, have attracted a lot of attention in the field of immunization research. These vaccines have benefits like durability, favorable biosafety characteristics, cost-effectiveness, and efficient production—the latter being especially true of DNA vaccines (Kushnir et al., 2012). The potential of nucleic acid vaccines for rapidly producing immunizations against newly emerging infectious diseases has received a lot of attention. Although there aren't many DNA vaccines approved for use in animals, research in lab settings and on small animal models has demonstrated that DNA vaccines can elicit an immune response and offer protection (Kogut et a*l*., 2012). DNA vaccines have not been able to trigger an immune response to the degree that was first predicted in either human or animal model (Zimmermann and Curtis, 2019). The fact that DNA vaccines given intramuscularly mainly stimulate cell-mediated immune responses offers one explanation for this phenomenon (Bialkowski et al., 2016). Fig 1 depicts the immune response and HPV vaccine design based on vector length polymorphisms.

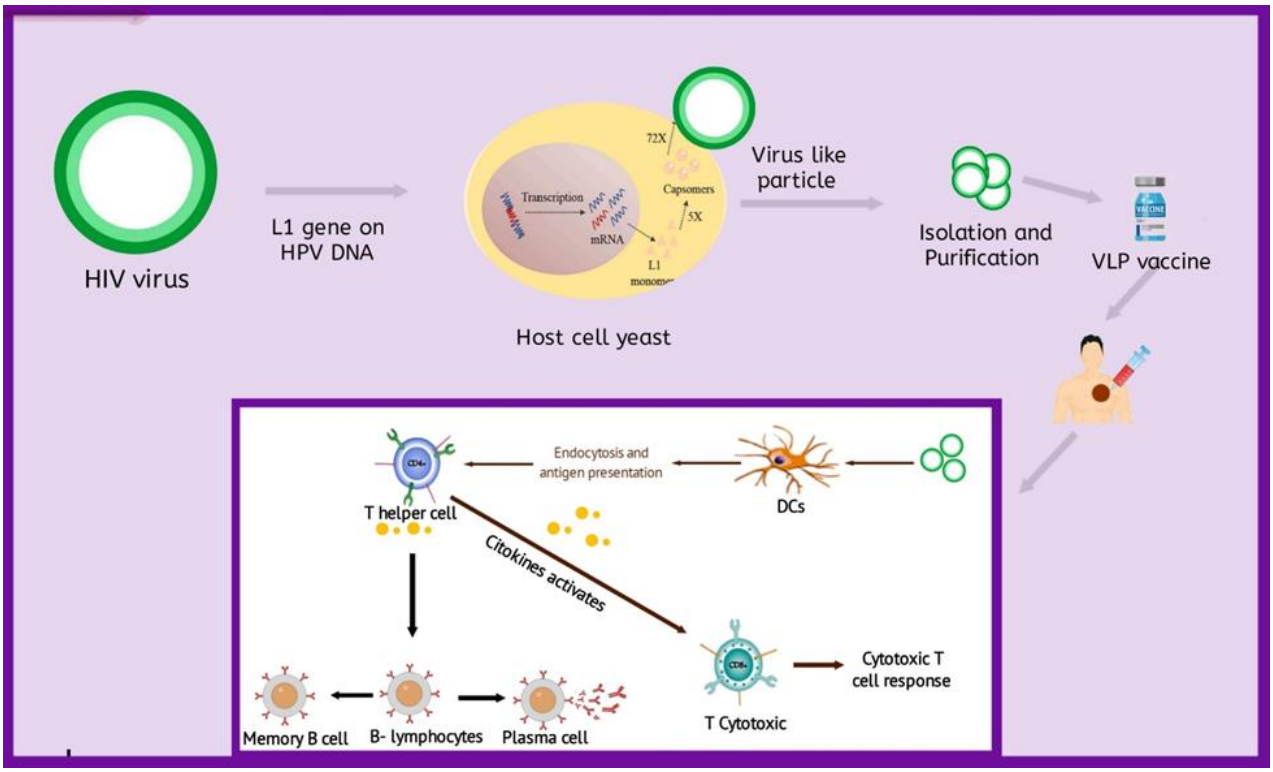

Fig. 1: The immune response and HPV vaccine design based on vector length polymorphisms.

The advancement of DNA/RNA vaccines poses numerous obstacles. While vaccinations based on microbes are generally associated with more safety issues, it is important to note that these vaccines also have their own distinct safety risks (Plotkin et al., 2014). Early studies indicated that DNA vaccines had the potential to occasionally integrate into chromosomes in a random manner (Angsantikul et al., 2017). However, further examinations demonstrated that this occurrence was much less frequent compared to spontaneous genetic alterations (Chackerian, 2007). However, a later analysis found no proof of chromosomal integration after DNA immunization, indicating that such an event did not occur (Isanaka et al., 2017). The possibility that DNA vaccination may introduce unwanted bacterial DNA components, like genes connected to antibiotic resistance, into the gut microbiota raises theoretical concerns (Kennedy et al., 2006). The World Health Organization (WHO) has categorized messenger RNA (mRNA) vaccines as a distinct therapeutic class due to their unique properties. However, there is currently insufficient empirical evidence to fully support this notion (Hobernik and Bros, 2018). To address vaccine safety issues, regulatory guidelines for clinical trials involving DNA immunization have been devised in both the United States and Europe (Li et al., 2017). The methods involved in synthesizing vaccinations using nanoparticles have been demonstrated in Fig 2.

On the other hand, immunizations based on mRNA offer benefits like the complete absence of chromosomal integration or prolonged expression (Khan, 2013). Adopting cell-free technologies for the production of vaccines has the additional benefit of reducing the likelihood of bacterial contamination throughout the process (Al-Halifa et al., 2019). However, because of the narrow scope of human studies pertaining to mRNA vaccines, there are currently no established

regulatory protocols that are expressly designed for this class of vaccines (Zhang et al., 2017).

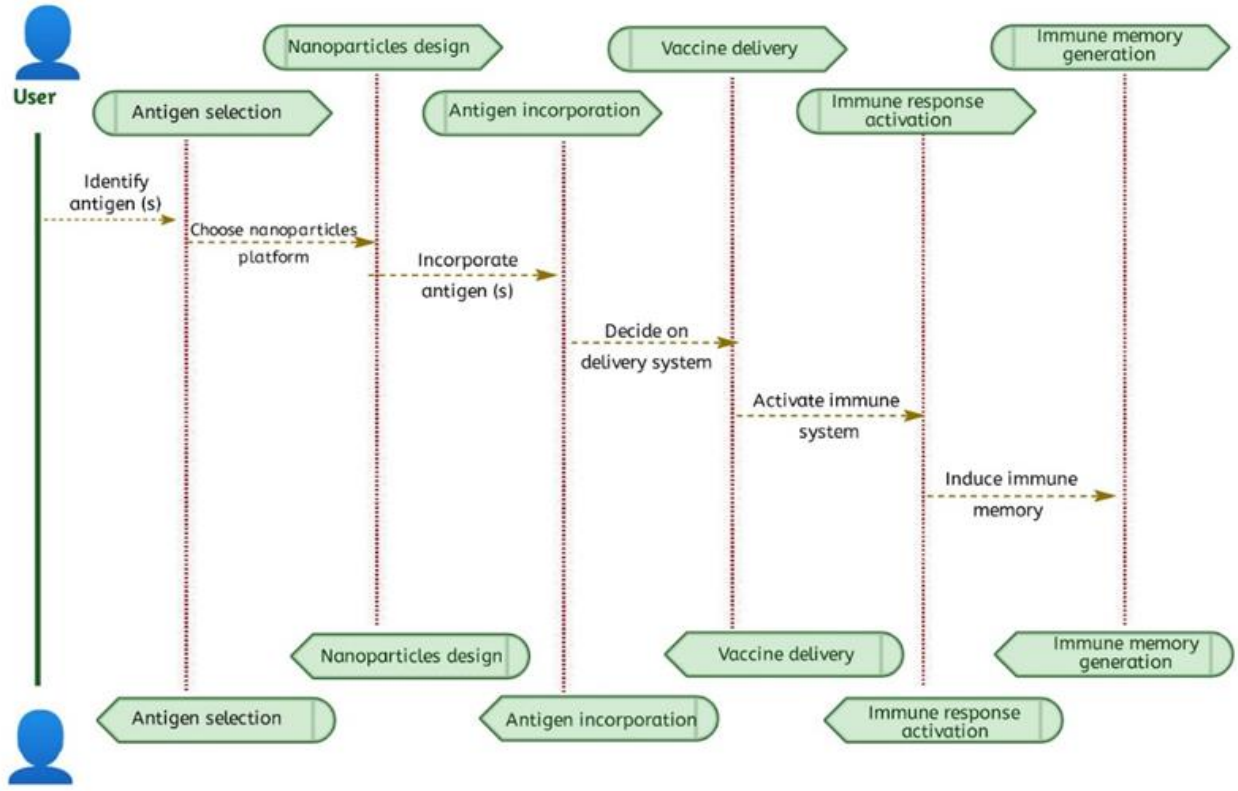

Fig. 2: The methods involved in synthesizing vaccinations using nanoparticles

Rationally Designed Vaccines

A critical first step in creating non-viral vaccines is figuring out which antigens will effectively elicit a protective immune response (Kitchin, 2011). Recent progress has brought forth novel techniques for the identification and development of antigens (Liljeroos et al., 2015). Conventional vaccinations are usually produced by attenuating or inactivating infections and using a small number of chosen antigens as vaccine constituents (Li et al., 2017). Reverse vaccinology is a method that involves sequencing the complete genome of a virus to recognize all of its antigens and assess their ability to stimulate protective antibody responses shown in Fig 3Scientists can successfully produce vaccine candidates that stimulate an immune response by combining reverse vaccinology with standard immunization procedures (Chackerian, 2007).

Progress in Non-viral Vaccine Systems

Vaccines for Immunosuppressed Individuals

Vaccination has a lower success rate among infants, the elderly, and persons with preexisting immunodeficiencies because their immune systems do not react well (Neek et al., 2019). Considering the unique immunosuppressive processes associated with each of these groups is essential for formulating the best immunization strategy (Sahin and Türeci, 2018). It is commonly assumed that young children, especially newborns and neonates, have weakened immune systems since their immune systems are still developing and becoming specialized (Rueckert and Guzmán, 2012). They are therefore more vulnerable to infections. This group has immunosuppression due to a multitude of factors. Decreased cytokine production that triggers Th17 cell responses through Toll-like receptors (TLRs) is one frequent outcome. In addition, neonates have elevated levels of anti-inflammatory cytokines, especially in preterm infants (Aurisicchio et al., 2018)

Conversely, Immunosenescence is a term used to describe the weakening of the immune system in older people. This state is distinguished by an intricate combination of alterations that results in a decline in both adaptive and innate immune responses, loss of lymphoid tissue structure, and an increase in proinflammatory cytokines and chemokines (Tagliamonte et al., 2014). Several changes have been documented, including a reduction in antigen absorption by dendritic cells, a decrease in macrophages' ability to engulf apoptotic cells, a loss in the population of naive T cells, and a decreased diversity of B cells. When it comes to diseases or drugs that lower immunity, the difficulties of immunization are different from those caused by natural ageing of the immune system (Maeng and Berzofsky, 2019). It is well-known that the medicine known as steroids promotes immunosuppression, and this fact has been the subject of much research. For example, dendritic cells can undergo a transition into tolerogenic dendritic cells when exposed to steroids. The development of regulatory T cells is greatly aided by these specific dendritic cells (Kramps and Elbers, 2017).

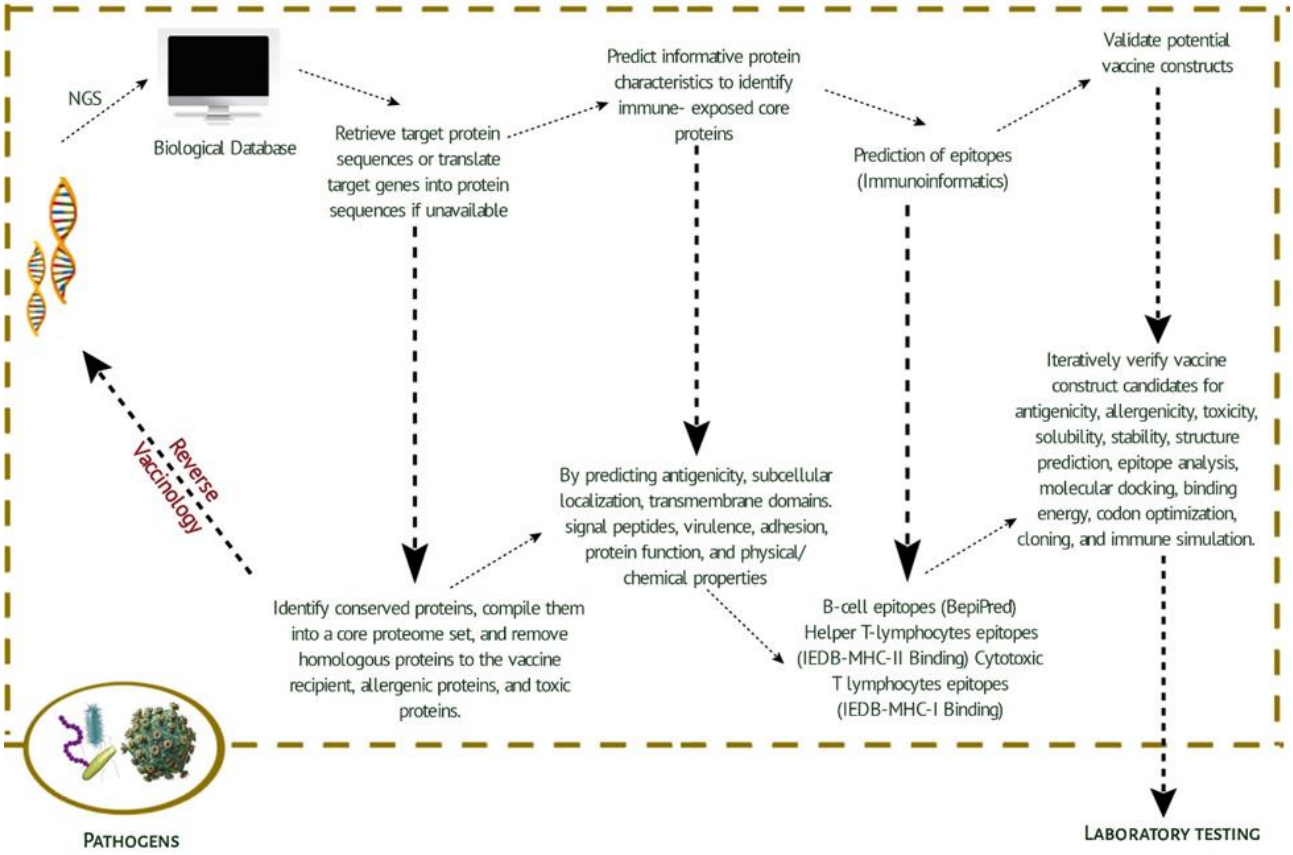

Fig. 3: The Reverse Vaccinology approach utilizes immunoinformatic, genome mining, and computer analysis to uncover and choose promising vaccine candidates

Vaccines with Non-traditional Antigens

When it comes to nonprotein antigens in particular, vaccinations made of nanoparticles (NP) or virus-like particles (VLP) provide a safer and more adaptable option. A diverse array of chemicals can be delivered as antigens by these vaccinations (Bahl et al., 2017). Vaccines utilizing NPs provide for greater design freedom by leveraging the bond between a therapeutic component and a chemical hapten carrier. Vaccines against drugs of abuse aim to trigger an immune response through antibodies that can block the effects of the drug before they enter the brain, so averting any potentially mind-altering effects. The purpose of hapten carriers, which are powerful B cell antigens, is to stimulate the immune system to react against particular drugs (Wu and Wong, 2007). Maintaining the vaccine's structural integrity and boosting B cell responses require the hapten and linker to be designed as optimally as possible (Myhr, 2017). It is also possible to augment T cell responses, especially CD4 T cell responses, which can improve B cell activity, by pairing the immunization with a protein carrier. Nevertheless, it remains uncertain whether an elevated CD4 Th2:Th1 ratio is directly associated with the efficacy of vaccinations that specifically target drugs of abuse. *(*El-Attar et al., 2009; (Boigard et al., 2017).

When designing immunizations against addictive drugs, it is crucial to determine whether the main emphasis should be on the drug itself or on its potentially more potent metabolites with psychoactive effects. This is because the latter compounds may offer a higher level of protection. Heroin immunizations are a perfect example of why this decision is extremely important. The most effective vaccinations are those that have a molecular structure similar to 6-acetylmorphine (6AM), the euphoric heroin metabolite (Pati et al., 2018). Published clinical trial results are available for vaccinations specifically designed to target nicotine and cocaine addictions (Pillay et al., 2010). Nevertheless, these vaccinations have demonstrated efficacy solely in a particular subgroup of patients who were capable of producing substantial quantities of neutralizing antibodies (Kübler et al., 2015; Lizotte et al., 2016). Additional in-depth analyses of the latest developments in immunization tactics for minimizing medication utilization can be located in alternative references (Franco et al., 2011).

Furthermore, toxoid vaccines use vaccine formulations containing VLP and NP to rapidly neutralize cytotoxic substances, like bacterial toxins, that are incapable of being produced in their whole and functional form. The DTaP inactivated subunit vaccine, which guards against pertussis, tetanus, and diphtheria, is a commonly known immunization. Preclinical research is currently being conducted to evaluate this approach, which has the potential to create effective immunizations against MRSA (Frietze et al., 2016).

Therapeutic Non-communicable Disease Vaccines

There has been a recent change in the utilization of immunizations for both the treatment of illnesses and the prevention of diseases. Improvements in vaccine research and manufacturing capabilities have accelerated the process. The development of effective immunization tactics depends on the discovery of unique protein markers connected to a particular disease phenotype. However, antigen-presenting cells (APCs) can miss these signals, which would hinder the start of an immune reaction. As a result of the difficulty in creating successful cancer treatments and the requirement for individualized treatment, cancer vaccines have garnered a significant amount of attention in the discipline of therapeutic vaccinations *(*Song et al., 2011).

The objective of these cancer vaccines is to stimulate the production of antibodies specifically targeting antigens found only on cancer cells. The development of cancer vaccines has proven to be difficult, especially when using viral vectors, due of the immunosuppressive effects of cancer. However, non-viral immunizations offer improved safety features, which bode well for the development of cancer vaccines (Dhanasooraj et al., 2016). To enhance the effectiveness of cancer vaccines, it is crucial to include an antigen that is specific to the genetic changes found in each type of cancer. This approach is particularly beneficial when used in conjunction with other treatments, as it helps overcome the body's natural resistance to immune responses (Zhou et al., 2011). Furthermore, non-viral vaccinations offer a more efficient way to encode antigens for nucleic acid vaccines or purify proteins for subunit vaccines, giving them an advantage over viral vaccinations in the creation of cancer vaccines (Garçon et al., 2007).

Vaccines against Rapidly Emerging Viral Diseases

The public health system has encountered substantial obstacles as a result of the advent of new and recurring diseases, such as the pandemic influenza virus, Ebola virus, Zika virus, dengue virus, and the ongoing global pandemic caused by SARS-CoV-2. Accelerated vaccine development and distribution are essential for effectively combating these diseases, including future outbreaks that the World Health Organization (WHO) has designated as "disease X". An ideal vaccination platform should be affordable, able to be developed quickly, and easily extensible for large-scale manufacture in order to meet global demand during a pandemic.

Furthermore, given the difficulties of preserving cold chain storage in less developed areas, the sensitivity to temperature becomes a crucial factor in the creation of vaccines. The development of heat stable vaccines is crucial in regions with poor transportation and refrigeration systems to offer efficient safeguarding against severe infections (Desai et al., 2010). This vaccine is an example of this. In view of the continual growth in the number of pandemics that are occurring all over the world, there is an imperative need to develop vaccinations that are not only cost-effective but also flexible and resistant to heat in order to combat these problems (Han et al., 2018). The present vaccine development process faces many obstacles related to resource availability and regulatory requirements. It is projected that the time and expense to produce a vaccine will range from 5 to 18 years, and it will cost between $250 million and $500 million.

Conclusion

According to modern medical research, vaccinations are the most cost-effective way to protect against infectious diseases. Thanks to immunizations, several diseases that formerly afflicted and killed tens of thousands of children and adults have been significantly reduced, and in some cases totally eradicated. In order to reduce the probability of a pandemic outbreak, vaccinations are the most efficient defense strategy. They will also be essential in combating any potential pandemic in the future. The capacity and effectiveness of traditional vaccination techniques have been significantly improved by recent developments in non-viral vaccination technology. Long-standing problems in the field of vaccination may be resolved with these innovative strategies by customizing safety, immunogenicity, protection breadth, scalability, and ease of production. Furthermore, new avenues for vaccination have been opened up by the advancement of non-viral vaccine technologies, including the use of immunizations to treat drug addiction and cancer. Additional research and vaccine development are required to address the difficulties highlighted by newly developing infectious diseases and noncommunicable illnesses. Multidisciplinary collaboration and ongoing evaluation of immunization schedules are required for this. Maintaining a leading position in scientific research will be essential to the development of vaccines for the foreseeable future.

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