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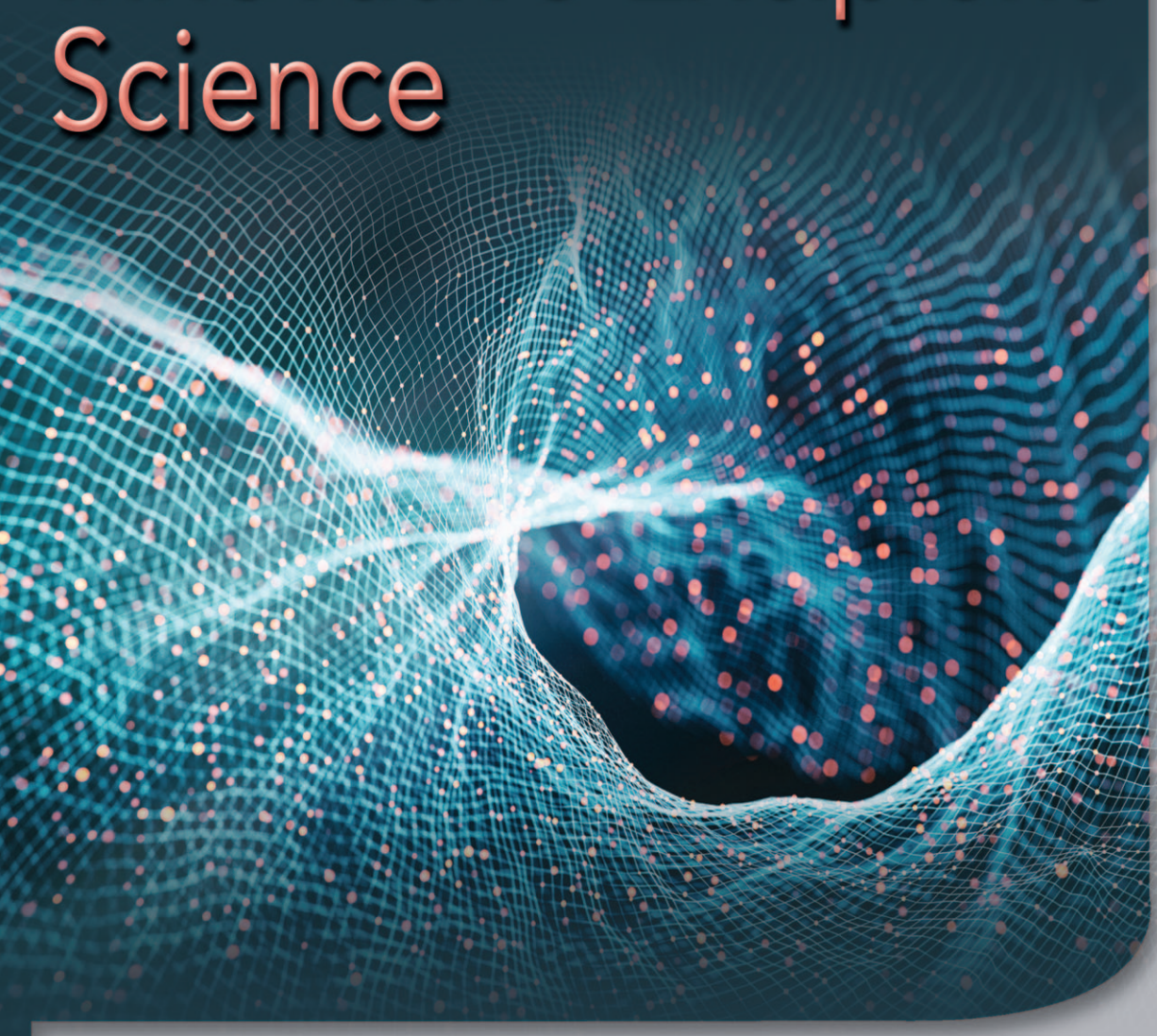

The Science & Business of Pharmaceutical and Biological Drug Development

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VACCINE DEVELOPMENT

Therapeutic Vaccines Development: At the Edge of a New Revolution

By: Mario Davinelli, PhD; Narcisa Mesaros, MD; David Morland, BSc, CBiol; and Judith Neville, PhD

INTRODUCTION

The development of prophylactic vaccines is a fundamental aspect of modern medicine. In recent years, there has been a resurging interest in the creation of new vaccines, driven by a growing recognition of their importance in preventing infectious diseases morbidity and mortality and improving public health.

Recent advancements in vaccine development have opened new possibilities for the prevention of infectious diseases. These include the following:

- Adjuvants, which are molecules added to antigens with the aim to enhance the vaccine immune response.
- mRNA vaccines, a novel type of vaccine that use genetic instructions that direct the cells to make a protein antigen to induce a targeted immune response. This new vaccine platform proved its effectiveness in respiratory diseases prevention (e.g., SARS-CoV-2 and RSV).[1]
- Vector-based vaccines, which use a modified virus or bacterium to deliver antigens to the immune system, stimulating an immune response against the target pathogen. This vaccine platform proved its efficacy in preventing diseases like Ebola and COVID-19.

There has been a resurging interest in the development of new vaccines, driven by a growing recognition of their importance in preventing infectious diseases morbidity and mortality and improving public health.

THERAPEUTIC VACCINES

Therapeutic vaccines, known also as treatment vaccines, are a type of vaccine designed to treat or manage a disease rather than prevent it.

They work by stimulating the immune system[2] to recognize and attack specific cancer cells, infectious agents, or other antigens, and are used as a treatment strategy to cure or change the course of the disease.

Also, therapeutic vaccines differ from other types of immunotherapies, such as monoclonal antibodies, because they provide active immunization by therapeutically stimulating an immune response.

Immunotherapies based on passive immunization, on the other hand, transfer pre-synthesized elements of the immune system to the patient, so that the body does not need to produce those elements itself, providing short-term protection against infections or clinical conditions. Often, passive immunization is used when no vaccines are available and offers short-term protection, when the patient is immunocompromised or requires initial immune support.

Therapeutic vaccines can be used to treat cancer by targeting specific proteins or antigens that are present on cancer cells membranes. These vaccines can be designed to target a variety of cancers, including melanoma, breast cancer, and prostate cancer. The vaccines can be made from a patient's own tumor cells or from synthetic peptides that mimic the tumor's antigens.

Therapeutic vaccines for infectious diseases work similarly by stimulating the immune system to recognize and attack the infectious agent. These vaccines can treat chronic viral infections like HIV, hepatitis B, and hepatitis C.

Therapeutic vaccines for cancer offer a promising avenue for improving patient outcomes.

Therapeutic vaccines can be developed for autoimmune diseases as well, as they can be targeted against self-antigens involved in those chronic conditions.

One of the advantages of therapeutic vaccines is that they can be tailored to the individual patient's immune system. This personalized approach can improve their effectiveness and reduce the risk of side effects.

THERAPEUTIC VACCINES FOR CANCER

Therapeutic vaccines for cancer offer a promising avenue for improving patient outcomes.[3] They are designed to stimulate the immune system to recognize and attack cancer cells.

Therapeutic cancer vaccines employ various mechanisms to elicit an immune response against cancer cells.[4] Some common mechanisms include the following:

- **Antigen presentation:** Cancer cells often express unique antigens that distinguish them from the healthy cells. Therapeutic vaccines utilize these antigens to train the immune system to specifically recognize and target cancer cells.
- **Activation of immune cells:** Vaccines can stimulate the activation and proliferation of immune cells, essential for eliminating cancer cells (e.g., NKs).
- **Memory response:** Therapeutic vaccines aim to create an immune memory response: the immune system retains the ability to recognize and attack cancer cells, providing long-term protection against disease recurrence.

Therapeutic vaccines for cancer hold several potential benefits, including the following:

- **Targeted treatment:** Unlike traditional cancer treatments, they specifically target cancer cells, sparing healthy cells and tissues, therefore reducing the potential side effects.
- **Personalized approach:** Personalization to each patient's unique cancer antigens allows for a personalized treatment approach that may enhance effectiveness.

Therapeutic vaccines for infectious diseases have shown encouraging results in the treatment of chronic viral infections.

- **Combination therapy:** Used in combination with other cancer treatments, such as chemotherapy or immunotherapy, to enhance their efficacy.

- **Adjuvant treatment options:** In many cases subjects may have achieved a best response or reached a disease stabilization point and therefore therapeutic vaccination presents an opportunity to further improve or ameliorate disease or to prevent recurrence of active disease. In HPV5 there are several approved and effective prophylactic vaccination options, but for those infected with HPV and HPV-mediated malignancies the use of a therapeutic vaccine, together with immune checkpoint inhibition and adjuvants, offers significant potential benefit.

Some problems still exist in the development and implementation of therapeutic cancer vaccines:

- **Tumor heterogeneity:** Cancer tissue is highly heterogeneous within a given patient tumor. This heterogeneity can vary greatly between patients. Developing vaccines that target a wide range of tumor antigens is challenging.

- **Immune suppression:** Cancer cells can manipulate the immune system and create an immunosuppressive environment, hindering the effectiveness of therapeutic vaccines. Overcoming this immune suppression is critical for vaccine efficacy.

- **Clinical trial design:** Conducting rigorous clinical trials to evaluate therapeutic vaccines' safety and efficacy is essential for their success. Designing and conducting these trials is complex, requires a specific expertise (medical, scientific, and operational) and can be time-consuming.

In summary, therapeutic cancer vaccines provide a targeted and potentially less toxic alternative to traditional cancer treatments. Ongoing research and clinical trials have the potential to unlock the full therapeutic potential of vaccines in the fight against cancer.

Therapeutic cancer vaccines may become a fundamental part of comprehensive cancer treatment strategies, improving patient survival rates and quality of life.

THERAPEUTIC VACCINES FOR INFECTIOUS DISEASES

Therapeutic vaccines for infectious diseases are developed to stimulate the immune system to recognize and neutralize specific infectious agents, such as viruses or bacteria already present in the body.

The development of therapeutic vaccines for infectious diseases involves identifying specific antigens or proteins that are unique to the pathogen. These antigens are then used to stimulate an immune response targeted against that very pathogen.

Therapeutic vaccines for infectious diseases have shown encouraging results in the treatment of chronic viral infections, such as HIV, hepatitis B, and hepatitis C. These products aim to target viral latency, harness the immune system to control the viral load, reduce disease progression, and improve the patient's overall health.

Furthermore, vaccine treatment approaches in infectious diseases have the potential to make significant global health impacts. In Tuberculosis (TB),[6] there is a significant opportunity to investigate a therapeutic vaccine as an adjunctive treatment or to prevent relapses. Given that TB patients long-term sequelae of disease due to immunopathology is present in a substantial portion of patients, investigating the potential to modify post cure pathology may offer a new path for the more effective treatment.

One challenge in the development of therapeutic vaccines for infectious diseases is the ability to elicit a strong, specific, and sustained immune response. The immune system already may be compromised by the infection, making it more difficult to mount an effective response.

Additionally, the high mutation rate of some infectious agents, such as HIV, poses a problem in developing vaccines that can effectively target evolving strains of the virus.

Despite these issues, therapeutic vaccines for infectious diseases continue to be an area of active research. Clinical trials are being conducted to evaluate their safety and efficacy, and ongoing advancements in the technology have the potential to further enhance their effectiveness.

Ongoing research and development in the infectious disease therapeutic vaccines field – as single or combination therapy – hold the promise of improving patient outcomes and reducing the burden of diseases.

THERAPEUTIC VACCINES FOR AUTOIMMUNE DISEASES

Autoimmune diseases occur when the immune system mistakenly attacks healthy cells and tissues. These conditions can lead to chronic inflammation and damage to various organs. While current treatments for autoimmune diseases focus on managing symptoms and suppressing the immune response, therapeutic vaccines offer a novel approach by specifically targeting the underlying cause of these conditions.

The potential benefit of therapeutic vaccines in treating autoimmune diseases is the restoration of immune tolerance and the rebalance of the immune system. Unlike traditional products, they are designed to target specific self-antigens that are involved in the autoimmune response. By inducing a targeted immune response against these self-antigens, therapeutic vaccines modulate the immune system and restore its normal function.

Ongoing research and clinical trials have the potential to unlock the full therapeutic potential of vaccines in the fight against cancer.

Therapeutic vaccines for autoimmune diseases utilize various mechanisms to achieve their desired effects. These include the following:

- Help induce immune tolerance by promoting the generation of regulatory T-cells (Tregs)[7]: Therapeutic vaccines can dampen the autoimmune response by promoting Treg expansion and activation, which are crucial in suppressing immune responses and maintaining immune balance.
- Antigen-specific[7] immune modulation: Through antigen-specific immune modulation, therapeutic vaccines aim to redirect the immune system's attack away from healthy cells/tissues.
- Immune system reset: This approach involves the use of immune-modulating agents[8,9] or to alter the immune response and restore immune tolerance (i.e., recognize self-antigens as harmless).

Therapeutic vaccines for autoimmune diseases potentially provide targeted and personalized treatment options. Some potential benefits include the following:

- **Disease modification:** By targeting the underlying cause of autoimmune diseases, therapeutic vaccines have the potential to modify the disease course.
- **Personalized approach:** Therapeutic vaccines can be tailored to individual patients, considering their specific immune profiles and disease characteristics. This personalized approach may enhance treatment effectiveness and reduce the risk of adverse effects.
- **Long-lasting effects:** Unlike some conventional treatments requiring continuous administration, therapeutic vaccines may induce long-lasting immune tolerance, resulting in sustained disease control.

However, there are challenges associated with the development and implementation of therapeutic vaccines for autoimmune diseases, such as identifying suitable self-antigens, ensuring vaccine safety and efficacy, and optimizing vaccine delivery strategies.

Therapeutic vaccines may represent a viable option for the treatment of autoimmune diseases by specifically targeting the underlying cause of these conditions.

These vaccines have the potential to provide long-lasting disease control and reduce the reliance on immunosuppressive medications.

CLINICAL TRIALS ON THERAPEUTIC VACCINES: UNIQUE FEATURES

Clinical trials on therapeutic vaccines have some unique features compared to clinical trials for preventive vaccines and "traditional" oncology or infectious disease trials. The following are some key aspects:

- **Patient population:** Clinical trials for therapeutic vaccines typically involve patients who have already been diagnosed with a specific disease, such as cancer or chronic infections. The patient population is often more diverse and may include individuals with varying disease stages, treatment histories, comorbidities, and immune profiles.
- **Study design:** The study design for therapeutic vaccine trials differ from preventive vaccine trials. In therapeutic vaccine trials all participants receive standard of care treatment and vaccine's efficacy is evaluated in combination with existing therapies. This significantly increases the complexity of study design and requires additional management of potential treatments interferences.
- **Trial regulations:** Particular attention must be paid, when designing the study, to the ethics of randomized placebo-controlled trials or add on to standard of care.
- **Endpoints:** The primary endpoints in therapeutic vaccine trials often are focused on clinical outcomes, such as tumor response rates, progression-free survival, or viral load reduction, depending on the disease being targeted. Immunological endpoints, such as immune response measurements, also may be assessed to evaluate the vaccine's mechanism of action.
- **Personalized approach:** Therapeutic vaccines can be tailored to each patient's specific disease characteristics, immune status, and genetic profile. This personalized approach requires careful patient selection, vaccine design and monitoring to ensure optimal treatment outcomes.
- **Long-term follow-up:** Therapeutic vaccine trials often require long-term follow-up to assess the durability of the immune response and evaluate the vaccine's impact on disease progression and recurrence. This extended follow-up period increases clinical development complexity of these products, which might require periodic dosing to boost the immune system.
- **Combination therapies:** Many therapeutic vaccine trials explore the use of vaccines in combination with other treatments, such as chemotherapy, radiation therapy or immunotherapy. Evaluating the safety and efficacy of these combination therapies is an important aspect of clinical trials on therapeutic vaccines.
- **Safety monitoring:** Safety monitoring in therapeutic vaccine trials is crucial, particularly when combining vaccines with other treatments. Adverse events related to the vaccine, as well as potential interactions with other therapies, must be carefully monitored and reported.
- **Laboratory and logistics of study materials:** Vaccines are more sensitive to environmental conditions than small molecules and require extra precautions when transported. Laboratory sample management is more complex and specific assays are required to assess the immunogenicity of the vaccine under investigation.

These unique features reflect the complex nature of therapeutic vaccine development and the need to assess their clinical safety, efficacy and potential benefits in a patient population that already has been diagnosed with a specific disease.

SUMMARY

For the most part, therapeutic vaccines are still in the preliminary stages of development. More research is needed to determine their short- and long-term effectiveness. However, clinical trials have shown encouraging results in treating cancer, infectious diseases, and autoimmune conditions.

Therapeutic vaccines are an exciting area of research that has the potential to revolutionize the way we treat diseases. By harnessing the immune system to recognize and attack specific cancer cells, infectious agents, or self-antigens, these vaccines offer a personalized approach to treatment that can drastically prolong patient's life and improve its quality. ◆

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BIOGRAPHIES

Dr. Mario Davinelli serves as Executive Director of Project Delivery within the PPD clinical research business of Thermo Fisher Scientific. He is a member of the vaccines therapeutic unit leadership team, leading the oncology therapeutic vaccines segment. He has been with the business since 2010, serving in various roles of increasing responsibility in project delivery.

Dr. Narcisa Mesaros serves as Vice President of Medical Science and Strategy for Vaccines within the PPD clinical research business of Thermo Fisher Scientific. She joined the business from Janssen where she had been the clinical franchise leader for vaccines. Prior to that she spent 15 years at GSK.

David Morland serves as Vice President of Project Management and Business Segment Lead for Therapeutic Vaccines within the PPD clinical research business of Thermo Fisher Scientific. He has more than 25 years of industry experience leading preclinical toxicology, clinical, data management and project management teams.

Dr. Judith Neville serves as an oversight director for therapeutic vaccines within the PPD clinical research business of Thermo Fisher Scientific. She has 25 years of experience in operational management of clinical trials and product development, with a focus on immunology and infectious diseases.