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The Old and the New: successful vaccines of the 20th century and approaches to making vaccines for the important diseases of the 21st century:

Editorial overview

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Introduction

The 20th century saw great successes at developing vaccines for many acute infectious diseases such that we now have an arsenal of 31 vaccines that are licensed in the United States to prevent infectious diseases [1,2]. The 21st century is seeing vaccine development take on the challenge of developing vaccines for chronic infectious and noninfectious diseases as morbidity and mortality owing to these conditions is becoming an ever-increasing public health problem and economic cost. This is a tough challenge due to the complexity of these chronic diseases.

In this volume, we describe the current status of two well-established vaccines, yellow fever and smallpox, as examples of hugely successful vaccines at controlling two major infectious diseases. Surprisingly, even though these vaccines are very successful our knowledge regarding how these vaccines work is relatively rudimentary and both still have problems with rare, but important, side effects. We also include malaria and tuberculosis as examples of two chronic infectious diseases where vaccine development has proved to be very complex yet is crucial for public health in the 21st century. An important approach in the 21st century will be enhancing the immune response of candidate vaccines and this volume also describes research on three approaches: adjuvants, prime-boost strategies, and mucosal immunity. Finally, chronic noninfectious diseases continue to become an ever-increasing cause of morbidity and therapeutic vaccines offer a potentially attractive route to controlling these conditions. We use Alzheimer's disease as a prime example of the problems and hopes for a vaccine to control such conditions. A brief summary of the articles in this volume is provided below.

Yellow fever

The yellow fever 17D vaccine was developed in the 1930s and played a major role in controlling the mosquito-borne disease yellow fever. Barrett and Teuwen review the progress that has been made recently in understanding the mechanism of immunity by the 17D vaccine but there are still major gaps in our knowledge. Although a very successful and efficacious vaccine, there are still rare cases of severe adverse events (SAEs) following immunization. The mechanism of these SAEs is not understood at present but advances in understanding the mechanism of immunity hold promise to help reveal why such events occur.

Smallpox

The smallpox vaccine is one of the oldest vaccines and has been very successful, resulting in eradication of smallpox in the 1980s. Even though we have other vaccines that target diseases only found in humans and do not have animal reservoirs (e.g. measles), smallpox is the only disease where the various arms of public health have successfully worked together to eradicate a disease and the agent that causes it. Kennedy and colleagues review our knowledge and gaps regarding the mechanism of action of this vaccine. In particular, they describe the role of host genetics in the induction of the host immune response. Such genetic profiling may help in elucidating why smallpox vaccine causes rare SAEs, and in informing new vaccine development.

Malaria

Malaria is the prototypical parasitic disease where vaccines are crucial to controlling this chronic disease. Great strides in our knowledge of malaria has been made in recent years yet the complexity of the plasmodium life cycle has made vaccine development challenging. Casares and Richie review the challenges and novel approaches needed to successfully develop a malaria vaccine. The sophistication of plasmodium, including its ability to escape the innate and adaptive immune response, is a lesson to all vaccine researchers. Although there are some promising candidate vaccines, the ability of the parasite to evade the immune response is a major concern and novel approaches to immunogenicity will be needed.

Tuberculosis

Tuberculosis is an age-old scourge that continues to ravage developing countries and persons in the developed world with immunocompromising conditions. Barker and colleagues provide an overview of current TB vaccine developments and in particular focus on new immunologic insights that will enhance the development of a TB vaccine. Novel vaccine approaches, and new tools to identify immunogenic TB proteins and cell-mediated immune responses will facilitate TB vaccine development.

Approaches to improving immunogenicity: adjuvants

Crucial to advancing vaccine development in the 21st century will be the development of novel adjuvants designed to enhance the immunogenicity of novel antigens. Both TLR-dependent and TLR-independent pathways appear to be important. De Gregorio and colleagues provide a succinct summary of the immunology of TLR-independent vaccine adjuvants, particularly those that activate dendritic cells, which play a crucial role in the development of an effective immune response.

Approaches to improving immunogenicity: prime-boost regimens

The last two decades of the 20th century saw the utilization of prime-boost regimens to improve immunogenicity of vaccines. Shan Lu reviews various prime-boost regimens that have been used for traditional vaccines in the 20th century, including homologous and heterologous approaches. He also discusses current approaches of heterologous prime-boost regimens that are being investigated in the 21st century to improve immunogenicity of current candidate vaccines. This approach has broad application to the development of both chronic infectious disease and chronic noninfectious disease vaccines.

Approaches to improving immunogenicity: mucosal immunity

The last 25 years have revealed the major role and importance of the mucosal immune response. Takahashi and colleagues review the various components of mucosal immunity focusing on the gastrointestinal tract and oral delivery of vaccines. They use cholera vaccine as an example, describe the limitations of cholera vaccines, and show how novel delivery systems, such as plant-based immunogens, can be used to enhance the immune response.

Alzheimer's disease

In the 21st century chronic noninfectious diseases are becoming a major problem for society and this is exemplified by Alzheimer's disease, the most common neurodegenerative disorder. To date the major vaccine approach has been to develop therapeutic vaccines based on amyloid beta (A β) peptide, a component of senile plaques. Despite immense efforts involving multiple 'immunizations,' success has been limited for either passive or active vaccination regimens. The review by Kaye and Jackson describes the complexities of Alzheimer's disease and recent approaches to the development of an Alzheimer's vaccine; in particular those that are focusing on the microtubule binding protein tau, a component of the neurofibrillary tangles. Tau plays an important role in the normal function of regulating axonal transport in neurons but a pathological hallmark of Alzheimer's disease is deposition of tau. Furthermore, tau is associated with a number of neurodegenerative conditions, which suggests that targeting tau for vaccine development may have many applications. Kaye and Jackson provide a description of the complexities of vaccine development for a disease characterized by pathogenesis associated with protein misfolding and aggregation.

Summary

Overall, the success of developing vaccines against acute diseases in the 20th century has laid the groundwork for vaccine development for chronic diseases in the 21st century. It is clear that we are still identifying the appropriate immunogens for inclusion in vaccines for chronic diseases and once identified our progress in enhancing the immune response is crucial for controlling these conditions either as prophylactic or therapeutic vaccines. We now enter a second 'golden age' of vaccinology in the enhanced understanding of common diseases, vaccine development against chronic noninfectious diseases, and in better integrating advances in biology, genomics, immunology, molecular biology, and virology.

Acknowledgments

We are very grateful to our colleagues who participated in writing the various reviews for this volume and identifying exciting areas for vaccine development in the 21st century. We trust our readers will find this information useful in the cause of decreasing human suffering due to preventable diseases.

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Biographies

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