

Preface

Live vaccines were the first vaccines to be used in prevention of infectious diseases, and they are among the most successful vaccines in the more than 200-year history of modern vaccination. To just mention a few of the most prominent examples: live vaccines against smallpox (vaccinia virus, from which the term vaccine is derived), yellow fever (17D strain), polio (Sabin), and tuberculosis (Bacillus Calmette-Guérin – BCG) have literally changed the course of history. These vaccines cause mild or subclinical infections, which closely mimic natural infection by the wild-type pathogens. In many cases, this kind of vaccination elicits long-lasting and comprehensive immune responses without a need for booster immunizations or the inclusion of immune-stimulatory substances (adjuvants). However, live vaccines can often also be burdened by the threat of causing vaccine-induced disease, which may particularly affect immunocompromised individuals or result from spontaneous genetic reversions to a more virulent phenotype. These risks, even if very small, are considered increasingly unacceptable nowadays within a society that expects preventive medicine to be essentially risk-free.

Safety considerations together with an exploding increase of scientific capabilities for recombinant expression and characterization of proteins have shifted the field of vaccine science towards the development of subunit vaccines during the past decades. This development is accompanied by a rapid growth of our understanding of the innate and adaptive immune response and has led to new types of immune-stimulatory substances. These substances could overcome the limitations of subunit vaccines by shaping and enhancing the immune response. The capability to sequence entire genomes has produced the field of reverse vaccinology, which allows identification of new protein subunit vaccine components. The tremendous advances in understanding protein structure have recently created the new area of structural vaccinology, which introduces the concept of rationally designed vaccine antigens.

Do these advances in protein vaccines and adjuvant design mean that the area of replicating vaccines is coming to an end? We do not think so, and this book provides ample evidence to support this conclusion.

Essentially, the same technological advances that are propelling the development of new recombinant and subviral vaccines are also guiding the rational design of a new generation of replicating vaccines, which will combine the intrinsic immunological strengths of this type of vaccine with a flawless safety profile. Molecular biology and immunology provide a deep understanding of pathogenic determinants and pathogen–host interactions as well as the ability to specifically modify these factors. Historically, live vaccines were either derived from apathogenic natural strains or attenuated by methods of serial laboratory passages in various host cells, leading to an undirected process of genetic adaptations. The molecular mechanisms of attenuation were mostly unknown at the time these vaccines were first widely used. In fact, in many cases, the basis for attenuation of currently used live attenuated vaccines still is not fully understood. However, we now witness a quantum leap of technological capacities to specifically modify the genetic make-up of viruses and bacteria. This ability enables the generation of rationally designed live vaccines and, beyond that, the development of completely new types of replicating vaccines, such as vectored vaccines, single-round infectious vaccines, or replicon vaccines. These approaches are linked by the fact that microbial genome amplification and protein expression take place in the vaccine, but the production and spread of infectious progeny as well as the vaccines' interaction with the host defense system are specifically modified to achieve a maximum of vaccine safety and immunogenicity.

This book's intention is to span and illustrate with specific examples a large spectrum of replicating vaccines. We do not attempt to cover the entire field of new approaches. A complete enumeration would be an almost impossible goal, given the enormous wealth of creativity that shapes the development of new replicating vaccines. However, we do intend to provide the reader with a range of typical examples to paint a comprehensive picture of the existing and arising technologies. The topics included range from established or recently introduced live vaccines to novel exploratory approaches, including vectored and replicon based vaccines. In this context, we chose to apply the term “replicating” more broadly than has been done by most authors. Traditionally, “replicating” is considered synonymous with “infectious”, describing a microorganism capable of infecting, multiplying, and spreading in a host. Thus, replicating, infectious, and live vaccines were clearly separated from nonreplicating vaccines such as inactivated whole virus, subunit, or subviral particle vaccines. However, an entire class of new approaches, including self-replicating nucleic acids (replicons), single-round infectious particles, or conditionally replicating agents, does not fully fit either of these two traditional definitions. These novel, rationally designed agents can undergo limited or partial processes of the microbial replication cycle, but they either do not spread to new cells or spread restricted by certain growth conditions or for only a very few replication cycles. However, all of these new approaches share the property of genome replication and protein expression in the host. Growing evidence suggests that the immune response elicited by such vaccines closely mimics that of more typical, classic live vaccines. For these reasons, we extend the meaning of “replicating vaccine” to also include vaccines that undergo partial, limited, or defective

pathogen replication cycles, and we have included such vaccines within the scope of this book, “A new generation of replicating vaccines”. These new types of replicating vaccines promise to carry the successful concept of live vaccines into a new era by combining the immunological strengths of live vaccines with the safety of noninfectious protein vaccines.

The book is structured into four sections, each devoted to another group or aspect of replicating vaccines. Part I provides an overview of existing and recently introduced live vaccines, highlighting their strengths as well as some limitations and concerns. These articles illustrate both the tremendous potential for live vaccine approaches as well as the existing need for improvement with some of these vaccines.

Part II is devoted to the rational design and genetic modifications of microorganisms to generate attenuated vaccine strains. The capability to genetically manipulate bacterial and viral genomes has recently increased by technological leaps in DNA sequencing and synthesis capacities and the establishment of reverse genetics.

Part III summarizes implications of our increased understanding of host–pathogen interactions on the development of live vaccines. This includes the molecular analysis of host tropism and innate immune mechanisms. Insights into how microorganisms interact with cellular components and counteract the host cell defense mechanisms have resulted in a multitude of new approaches for attenuated strain development. These approaches include the directed alteration of host tropism, the generation of increased vulnerability to the host defense system, and the generation of microorganisms that are readily propagated in the laboratory but cause only abortive infections upon inoculation into the vaccine. Part IV highlights some of the above mentioned new types of replicating vaccines that carry the concept of live vaccines a step further. These vaccines include single round infectious particles (pseudo-infectious), vectored vaccines, replicons, and chimeric live vaccine strains.

The next decade will see some members of the new generation of replicating vaccines progress through clinical trials, achieve licensure, and benefit human health. As with all new technologies, there will be many challenges to be addressed, including issues of production, stability, safety, and efficacy. It will be exciting to watch and participate in these new developments, which ultimately will fulfill the promise of creating a safe and friendly life insurance for the twenty-first century.

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