

Novel Vaccination Strategies

Edited by
Stefan H. E. Kaufmann



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Novel Vaccination Strategies

*"We are not only responsible for what we do –
but also for what we do not do."*

Voltaire

Preface

Of last year's 56 million instances of premature death, almost 17 million were due to infectious diseases. This translates into one dead individual every two seconds. Annual instances of death caused by each of the two leading infections, AIDS and tuberculosis, exceed the mortalities caused by injuries, diabetes, Alzheimer's disease, Parkinson's disease, multiple sclerosis, breast cancer, and rheumatic diseases together. Similarly, almost 40% of all life-years lost by disability are due to infectious diseases; this is more than all losses due to injuries, neuropsychiatric disorders, cardiovascular diseases, and cancer that follow in these dreadful statistics. Yet, there is another side to the picture, and that is that we have an extraordinarily effective measure for prevention of infectious diseases at hand. These are vaccines, which annually save more than 8 million lives, which translates into one person saved every 5 seconds. Vaccination is not only effective but it is also the most cost-efficient measure in medicine. Unfortunately, 2 to 3 million additional lives are currently being lost due to the fact that already-existing vaccines are not being made available to everybody.

Wherever broadscale vaccination programs have been implemented, their success rates are remarkable. Incidences of measles, polio, rubella, mumps, pertussis, and diphtheria have all been dramatically reduced in countries where broadscale vaccination programs exist. The vaccines against these diseases were developed mostly by trial and error, and therefore could only be successful for pathogens that cause disease in a direct way. Pathogens that use more tricky strategies and subvert, impair, or misdirect the host immune response cannot be prevented by such a strategy. The next generation of vaccines has to be designed in a rational way, on the basis of our increasing knowledge of immunology and molecular genetics at the interface between pathogen and host. Fortunately, basic sciences have advanced dramatically during the past decade, and we now have available the genomic blueprints of all major pathogens as well as of the human host and the most-favored experimental animal model, the mouse.

It is the goal of this book, “Novel Vaccination Strategies”, to benefit from recent achievements in basic research for the rational design of novel vaccination strategies against diseases that have thus far evaded successful control. In addition, it includes a kind of retrospective review of vaccine examples that have already demonstrated their great efficacy, so that we can learn from these experiences.

The immune system is the target of all vaccination strategies and, hence, a great part of this book tries to decipher the immune mechanisms underlying control of the plethora of infectious agents. It is generally accepted that the acquired immune response, which accounts for specificity and memory, is the ultimate target of vaccination. Yet, the acquired immune response often fails to directly attack pathogens, and rather does so by activating innate immune mechanisms. Hence, the innate immune response is under the stringent control of the acquired immune response. More recently, we have also learnt that the acquired immune response is not activated by pathogens directly, but rather through mediation of the innate immune system. The innate immune response senses invading pathogens or vaccines and then instructs the acquired immune system to develop the most appropriate response against the homologous pathogen. Unfortunately, many pathogens have developed tricks to deviate host responses from the default direction. Here lies a major Achilles’ heel of the immune system and also a chance for rational vaccine design. For many infections that cannot be controlled by vaccines thus far, it will be important to induce an immune response that is better than the one stimulated by natural infection.

Much can be expected from novel adjuvants capable of stimulating the most adequate immune response for a given pathogen. Adjuvants will be required particularly for subunit vaccines, whether they be based on naked DNA, on protein, or on carbohydrate antigens. The right formulation comprising both the protective antigen and the appropriate adjuvant will define the success of a future subunit vaccine. Yet, it is likely that for certain diseases, subunit vaccines comprising only a few specific antigens will be insufficient. In these cases viable vaccines will be required, and the choice of the most appropriate recombinant vaccine carrier will be equally difficult.

The list of nature’s scourges is headed by the ‘big three’, that is, AIDS, tuberculosis, and malaria, which represent major challenges for rational vaccine design. Therefore, specific chapters are devoted to vaccine development against these diseases, as well as to vaccination strategies against *Helicobacter pylori*, which is responsible not only for gastric ulcers but also for certain forms of stomach cancer. Moreover, a chapter on vaccines against bioterror agents has been included, since we have become aware of the dreadful possibilities infectious agents offer to those who want to pervert our increasing knowledge about infectious diseases.

We have to be aware that we live in a world that has been populated by microorganisms for more than 3 billion years, while the beginning of mankind dates back only 5 million years. Hence, it would be unreasonable to think that we can conquer all microbes successfully. Rather, we have to accept that the survival strategies of most microbes, which are based on a combination of rapid replication and rapid change, are highly successful and that our current knowledge may not be sufficient for designing vaccines against the most devious pathogens. Moreover, the undesired

possibility needs to be considered that novel, more hazardous strains may evolve under the pressure of imperfect vaccines.

By design, this book focuses on the scientific basis of rational vaccine design. This is not, however, meant to underestimate the importance of subsequent development, safety assessment, and clinical trials. Two chapters have been included that deal with two important aspects downstream of vaccine research: safety assessment and cost-efficiency aspects of vaccination. It has become clear that the complete process of vaccine development is most successful as a close interaction between basic research, mostly done at public academic institutions, and development, best done by private industry. Unfortunately, vaccine development is not always high on the list of interests of industry. After all, the major goal of a successful vaccine is eradication of the targeted disease. Consequently, the most successful vaccine will concomitantly eradicate its own market. Moreover, many vaccines are needed for diseases that are most prevalent in countries that have the least financial resources. As a consequence, the return on investment for some vaccines may be too low to attract industry partners. On the other hand, public health systems would receive a profound return on investment. This has been proven impressively by the vaccines currently available. For every dollar that is spent on vaccination against measles, mumps, rubella, diphtheria, pertussis, or tetanus the public hand saves \$10 to \$20. Vaccination against childhood tuberculosis, tetanus, polio, measles, and hepatitis B prolongs healthy life by one year for a cost of \$10 to \$40. It is obvious that, not only the protected individual, but also the general public benefits enormously from vaccination.

Currently available vaccines have proven their great cost-efficiency and success in an impressive way. Their availability has been made possible by efforts dating back several decades. Recent achievements in basic research have now laid a new foundation for rational design of novel vaccines, and the general public will benefit from such vaccines in future decades, provided appropriate efforts are undertaken now.

Stefan H. E. Kaufmann

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