
Preface

Vaccination is the single most important medical intervention having saved more lives than any other. As such it is an outstanding and amazing achievement of the human mind, and yet admittedly vaccinology for the longest time has been driven purely empirically. In the last 3 decades, the advent of novel scientific disciplines including molecular microbiology, molecular genetics, and molecular immunology but also novel manufacturing technologies has changed the approach to vaccine development entirely. For the first time, we can decipher the detailed structures and even the attack programs of our foes, and insights into the mechanisms of protective immunity on the cellular and molecular level allow rational design of vaccine candidates. But the impact of this recent scientific and technology progress extends even further into the development and manufacturing of vaccines allowing for higher purity, more detailed characterization, and, as the ultimate consequence, improved safety. Finally, also clinical evaluation has been elevated from mere efficacy testing to a complex reading of immune response applying an ever-increasing battery of surrogate parameters and correlates of protection.

This book aims to give overview and insight into the by now increasingly rational approach to vaccine discovery, design, and development. As such it provides state-of-the-art contributions by some of the leading experts within academia, biotech, pharma industry, and regulatory agencies. Our overruling motivation has been to collect and integrate chapters into the book with the aim to instruct readers who are not yet highly specialized experts, but eager to enter the arena of vaccine development from a practical, pragmatic, and translational perspective. Thus, we have asked the authors to rather transmit their knowledge at hand of concrete examples and not to write a highly specialized contribution, driven to communicate latest state of the art R&D results to their peers. For the same reason, we have also tried to recruit for most chapters authors from different organizations to join their competence and, thus, to avoid a too narrow scope of the respective contributions.

The first part gives us the scientific basis: Alkan describes the fundamentals of immunology, the complex interplay between the quick, hard-wired innate immune responses and the more refined adaptive responses leading ideally to eradication of infection and long-lasting immunity, which is the ultimate aim of vaccines of course. The following two chapters provide the key ingredients of modern vaccines, antigens, and adjuvants. Nagy and Grandi summarize well the major genomic

approaches to microbial antigen discovery that allow for an unbiased genome wide search for protective antigens. Fox and O'Hagan give an overview of modern adjuvants. These are critically important for molecularly defined vaccines devoid of toxic microbial contaminants setting the immune system on alarm. In particular, discoveries like the Toll-like-receptor system or the inflammasome have allowed designing tailor-made new adjuvants and understanding the mode of action of some traditional adjuvants in retrospect. Efficacy and immunicity of vaccines may also be facilitated by delivering vaccines to tissues, such as the epidermis, where the density of dendritic cells, critical for a potent immune response, is more optimal, than e.g. in the muscle tissue targeted by most registered vaccines. Addressing this important issue, Flyer and Ellingsworth share their experiences in trans-dermal immunization techniques that could in future avoid parenteral needle-based applications with all their inherent issues of cross-contamination and inadvertent spread of disease. Furthermore, Weiss and Löbner summarize the impressive potential of applying live microbes for vaccine delivery. This approach brings us full circle back from molecularly defined vaccines to live organisms with their undisputed abilities to induce powerful immune responses.

The second part deals with the all important aspects of production, purification, and formulation of vaccines. Wacker and Casimiro show us the power of using recombinant microbes for synthesizing vaccines and/or vaccine components in fermentation processes that go beyond the classical paradigms, namely the synthesis of glycosidic structures, as needed for conjugated vaccines. In their comprehensive double feature, Schlegl and Hahn describe in great detail yet in an easy-to-grasp way the fascinating aspects of purification and formulation, both of which are decisive processes for the potency and hence effectiveness of vaccines, but also for the extreme degree of reducibility required for complex biologics, such as vaccines, in order to meet the regulatory standards.

The final part of this book is devoted to the discussion of concrete vaccine candidates against important diseases and two examples of recently licensed vaccines. The start is provided by two fascinating chapters laying down the concepts for potentially universal influenza vaccines, underscoring the well-recognized importance of this disease exemplified not only by the Spanish Flu from 1918, but also by more recent epidemics of Bird Flu and Swine Flu. We included two such chapters addressing this important challenge of the vaccine arena also for the reason that the current influenza vaccines are relying on the painful process to redesign for nearly each season a novel combination of antigens that aim to protect against the expected incoming influenza strains. In spite of all the challenges impeding vaccine development and the launch of novel vaccines, we are delighted that we also were able to include a chapter on vaccines which recently came to the customers. Dubischar-Kastner et al. provide another double feature on two recently licensed vaccines: the first is a novel vaccine against Japanese Encephalitis, an important disease endemic in a vast and heavily populated area stretching from India to Japan and from China down to the Torres Strait of Australia. The second is Merck's vaccine against Human Papilloma Virus which has opened the door to prevent in the long term cervical and genital HPV-induced

cancers in the later life stage of females, but á la long may be even of men, by alerting in time the immune system in young women to become protective against the virus which normally dives under the radar of the immune system, in spite of its colonization in the target organs.

Finally, as an epilogue Michael Pfeleiderer from the EMA and Paul Ehrlich Institute reminds us on the ever-increasing demands on the risk-benefit profiles of vaccines put by regulatory agencies but also public awareness on vaccine developers and manufacturers. Increasing scientific and technical abilities, increasing development costs, and still very long development timelines, often well above a decade, result in ever better products for the market.

The scientific, technological, and entrepreneurial dynamic forces at work that drive novel and desperately needed vaccines to the customers are facing gigantic challenges going beyond the standard obstacles known to impede pharmaceutical development. The utterly complex and biological nature of the products requires extremely high manufacturing skills, high-quality measures, and high assurance of reproducibility from batch to batch. The prophylactic nature of the products accepts only side-effects that are nonexistent or can be neglected. The registration pathway of vaccines is very difficult from the point of view of demonstrating disease prevention in healthy individuals, as opposed to disease reduction in patients, as seen for therapeutic pharmaceutical products. The customers are difficult to motivate due to the reluctance to accept medical intrusion as healthy individuals and their inability to recognize the danger of diseases that are often already controlled by vaccines.

In spite of all those challenges underpinning vaccine development, we are confident that the present book will become an accepted guide and tool for colleagues and students but also interested laymen to become curious about the practical path leading to novel vaccines and even motivated to learn more about or to join the international network that is devoted and joined to bring the utterly useful and most successful medical intervention to people.

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