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PREFACE

Preface

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Chronic viral hepatitis is one of the most import infections worldwide causing more than 1 million deaths annually. Among the agents leading to this debilitating, life-shortening disease, hepatitis B virus (HBV) is most prevalent with more than 240 million chronic carriers. According to the latest fact sheet from WHO, about 15–25 % of those carriers develop the difficult to treat late sequelae liver cirrhosis and hepatocellular carcinoma giving rise to more than 780,000 HBV-related deaths annually [1]. In spite of its enormous public health significance, the efforts of pharmaceutical industry and public funding agencies to develop new concepts of HBV therapy are limited. The NIH, e.g., spent in 2011 3.184 million US dollars for research on HIV, 102 million for HCV and 54 million for HBV although the number of affected patients in the USA is in the same order of magnitude for all three viruses [2]. In fact, most of the current drugs against HBV were developed for HIV or other viruses, and some were found to be effective against HBV only accidentally in HIV co-infected patients [3].

One of the reasons that HBV therapy is relatively low in the priority list of research and development is the belief that HBV will be eradicated or at least controlled by vaccination on long term. Effective and safe prophylactic vaccines against HBV infection are available since 1982. In 1992, WHO has recommended global vaccination "as soon as possible after birth, preferably within 24 h" [1]. (Alternatively, pregnant women may be tested for HBV surface antigen (HBsAg) and only newborns from positive mothers are immediately vaccinated while the other infants are given the hepatitis B vaccine later during the normal childhood vaccination scheme [4].) Vaccine coverage has steadily increased since 1992 with currently 183 member states of WHO following this recommendation and an overall rate of 79 % vaccinated children. The protection rate is assumed to be 95 %, and this very high efficacy has contributed to a decrease in the prevalence of HBV carriers from 8–15 to 1 % in young vaccinated adults living in highly endemic countries which have early implemented a rigorous vaccination campaign like Taiwan or Thailand [1].

These great achievements can of course not change the fate of the huge number of patients who were already infected in the pre-vaccination area. But there is another potential reason for the low attention toward HBV infection: The perception that the current status of HBV therapy is already satisfactory. Considerable progress has been made indeed in antiviral therapy of chronic hepatitis B within the last 20 years using inhibitors of the HBV reverse transcriptase [5]. After initial problems with low efficacy and/or resistance development, the most recent drugs tenofovir and entecavir are well tolerated and able to block genome maturation, formation of stable nucleocapsids and release of new infectious virions with very low risk of resistance development. This in turn stops HBV inflammatory disease and may even lead to partial reversal of liver fibrosis. The big disadvantage of this therapeutic concept is that stopping reverse transcription does not remove the preexisting covalently closed circular HBV DNA in the nuclei of infected hepatocytes. In the absence of inflammatory reactions, HBV-infected hepatocytes are extremely long-lived, and they continue expressing the viral genome products like HBsAg, HBeAg, reverse transcriptase,

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immature nucleocapsids and the RNA pregenome in virtually unchanged amounts (for review see [6]). Thus, in most patients, the therapy has to be given forever to prevent recurrence of HBV replication and clinical disease. This, in turn is for many countries with the highest prevalence of chronic hepatitis B an almost prohibitive economic burden.

This is the point where the topic of this special issue of *Medical Microbiology and Immunology* (MMI) on "*Therapeutic vaccination in chronic hepatitis B—approaches, problems, and new perspectives*" comes into play. In contrast to HIV and HCV, HBV infections rarely become chronic if they hit healthy adult persons. Although HBV replication and antigen production may reach very high levels before the onset of acute hepatitis B, HBV-specific T cells are finally activated, proliferate and are able to stop HBV gene expression and to eliminate the great majority of infected hepatocytes. It is known that many resolving acute HBV infections result not only in immunity but at the same time in an occult low-level HBV infection of the liver which may reactivate if the patient's immune system (in particular the B cells) is heavily suppressed. Thus, there seems to be only a gradual difference between those patients who overcome the infection and those who develop only partial immunity leading to chronic inflammation instead of cure. The articles of this special issue are mainly devoted to the question why the immune system has failed in patients with chronic hepatitis B and how the obviously absent or weak immune response can be activated to a degree as in the resolving acute HBV infections.

In **part A on immunopathogenesis**, *Katrin Busch* and *Robert Thimme* recapitulate the natural history of chronic hepatitis B and introduce the reader to recent findings on the life cycle of HBV including the long-sought-for viral entry receptor NTCP which binds to the preS1 domain in the viral envelope. Since the early 1970s, it is believed that the pathogenesis of HBV is caused mainly by HBV-specific cytotoxic T cells, whereas the innate immune response is seemingly absent. The pioneer of HBV immunity research, Frank Chisari, even coined the term "stealth virus" for HBV because it is not recognized by the innate defense mechanisms [7]. Although HBV may be a weak inductor of innate immunity *Ejuan Zhang* and *Mengji Lu* point out very clearly that activation of Toll-like receptors may induce an HBV-suppressing activity in the infected hepatocytes and suggest them as therapeutic targets together with other antiviral factors, may they be immunological or biochemical, to overcome chronic hepatitis B. The difficulty to induce immune responses against all kinds of hepatitis viruses is partially explained by the tolerogenic properties of liver-associated antigens. *Percy Knolle, Jan Böttcher* and *Li-Rung Huang* et al. study since long the pathways of immunity against hepatic viruses. They show the essential role of liver sinusoidal endothelial cells (LSECs) for local antigen presentation and describe novel "intrahepatic myeloid cell aggregates associated with T-cell expansion (iMATE)" as centers of an effective antiviral response. The two major viruses of chronic hepatitis, HBV and HCV, are very different concerning their structure and replication, but they have in common that their pathogenicity is mainly caused by an inefficient T-cell response. The spectrum of the recognized T-cell epitopes is not only defined by the viral protein sequences and the T-cell receptor repertoire but also by the HLA class I molecules of the host which present the processed antigens to the T cells. *Jörg Timm* and *Christopher Walker* have extensively studied the interdependence of these three components and have shown that the class I epitopes undergo an HLA-dependent immune escape in HCV and lead to hyporeactivity of CD8+ T cells. Whether these findings can be extended to HBV is open, but at least for HBeAg-negative HBV chronic infections with their high sequence variability similarities are likely.

As the title of the special issue suggests, vaccination with HBV antigens is a major topic. **Part B on hepatitis B vaccines** starts with a review on the history and current practice of *prophylactic* vaccination against HBV infections. *Wolfram Gerlich* describes the discovery of HBsAg as a vaccine, the development of the second- and third-generation vaccines, and acknowledges the great successes of perinatal vaccination, but he also mentions the incomplete long-term protection, asymptomatic breakthroughs and the too narrow antigen spectrum of the currently used second-generation vaccines which lack the most prevalent HBsAg subtype determinants *y* or *r* and the neutralizing preS1 epitopes. One of the more advanced third-generation vaccines is Sci B Vac™ which contains the three antigenic domains preS1, preS2 and S-HBsAg of the HBV surface proteins. Furthermore, its antigens are more similar to the natural HBV antigens because they are expressed in mammalian cells, whereas the standard second-generation vaccines are produced in yeast cultures and have an altered glycosylation and conformation. *Daniel Shouval, Hedwig Roggendorf* and *Michael Roggendorf* describe the superior immunogenicity of this vaccine which requires e.g., only two doses instead of three and induces a more rapid appearance of anti-HBs antibodies in vaccinated newborns or in health care workers at the beginning of their employment. Most importantly, they report preliminary results of therapeutic vaccination with Sci B Vac given together with the antiviral drug lamivudine to chronic hepatitis B patients in Vietnam. An indispensable component of non-replicating vaccines is adjuvants. While the classical aluminum compounds are sufficient for the regular hepatitis B vaccination, difficult to immunize recipients need stronger adjuvants. As is described by *Geert Leroux-Roels,* new adjuvants have been used safely in millions of recipients and are able to considerably enhance the immune response against HBV, possibly even to a point where therapeutic vaccination comes into reach.

Therapeutic vaccination (**discussed in part C**) has a long tradition since Robert Koch attempted to cure tuberculosis by tuberculin. However, in opposite to preventive, all approaches to therapeutic vaccination against infectious (and tumor) diseases resembled a Sisyphean challenge and revealed to be not very promising [8]. It is the long and intensive research on hepatitis B and C chronicity which now opens a new outlook and makes us see light at the end of the tunnel. The principle idea of therapeutic vaccination is no longer controversial, but the concepts for its realization are still much debated. *Eleanor Barnes* starts with a discussion of the potential ways to achieve therapeutic immunization in chronic hepatitis B and mentions her own studies on immunization of HCV patients using adenovirus or vaccinia virus vectors for HCV antigen expression. These novel approaches may be applicable or even more suitable for HBV patients. *Sarene Koh* and *Antonio Bertoletti* dissect the patterns of T-cell dysfunction during chronic hepatitis B and suggest that activating antigen-presenting cells or blocking inhibitory receptors of T-cell-like PD1 may be interesting concepts. One step further in the future, they mention the possibility to artificially transfer engineered HBV-specific T-cell receptors to the patients' T cells. Before such concepts can become reality animal experiments are necessary. The most relevant host animal would be the chimpanzee, but ethical and economic reasons normally prohibit the use of this animal species. *Claudia Dembek* and *Ulrike Protzer* describe the various tricks how the HBV-nonsusceptible animal species mouse can be manipulated to allow in vivo studies of acute and chronic HBV infection including the full spectrum of possible immune reactions. Closer related to the natural course of human HBV infections is the woodchuck hepatitis virus (WHV) infection in its natural host, the American marmot species woodchuck which lives in the forests of the East coast. *Anna Kosinska, Jia Liu* and *Mengji Lu* in the group of *Michael Roggendorf* report about their numerous, steadily improving attempts to mitigate or even cure the chronic WHV infection. The group reported recently for the first time that breaking WHV immune tolerance and suppressing WHV replication is possible by using a combination of antiviral therapy, vaccination and most modern techniques to rejuvenate T-cell function [9, 10].

The state of therapeutic possibilities is summarized in **part D on clinical studies**. The country with the highest burden of chronic hepatitis B is China. *Xin Zheng, Junzhong Wang* and *Dongliang Yang* describe the current situation with estimated 93 million HBsAg carriers and 20 million symptomatic patients needing antiviral therapy. Due to market restrictions, only the suboptimal HBV drugs lamivudine, telbivudine and adefovir are available in China at affordable costs. Chinese researchers have optimized combination therapy with these drugs, but an immune therapy which would control HBV instead of only suppressing it would be most important for this huge population. *Marie-Louise Michel* and her group are the pioneers of therapeutic vaccination against chronic hepatitis B over the last 20 years. She summarizes her own and the other clinical trials attempting to induce immunological control of HBV in the patients. After a promising start, the results were overall disappointing which explains the ambiguous title of her paper: "*Therapeutic vaccines in treating chronic hepatitis B: the end of the beginning or the beginning of the end?"* In view of the new, in this issue reviewed findings on the immune regulation in chronic infections, she comes to the conclusion that a new era will come instead of the end. One of those approaches which raised many unmet expectations is DNA vaccination. However, *Matti Sällberg* et al. explain that the shortcomings of this technique of indirect antigen delivery are mainly caused by the inefficient entry of the DNA into a too small number of target cells. Electroporation is a well-known technique for transfection of cell cultures or for destruction of tumor tissue in patients, but recently Matti Sällberg's group has applied it also for the delivery of genes encoding viral antigens to human volunteers for "genetic immunization" with good results.

This excellent collection of review articles is the printed outcome of a conference with the same title as this special issue of MMI: "*Therapeutic Vaccination in Chronic Hepatitis B*". It was held in 2013 at the University Hospital of Essen and organized by the Chinese-German research Group Transregio 60 (TRR60), which pursues a joint research program supported by the Deutsche Forschungsgemeinschaft (German Research Foundation) and the National Natural Sciences foundation of China. The TRR60 group was founded in July 2009 under the leadership of their first spokesman Michael Roggendorf who also shaped the research program of the TRR: "Mutual interaction of chronic viruses with cells of the immune system: from fundamental research to immunotherapy and vaccination". In 2013, the annual meeting of the TRR60 was devoted to the topic "Therapeutic vaccination in chronic hepatitis B" which is a major working field of Michael Roggendorf. He arranged a highly attractive scientific program with internationally leading experts. He also asked the speakers to write reviews on the work presented and most of them agreed.

The TRR60 is currently in its second funding period, but Michel Roggendorf has now stepped down as spokesman because he has retired for reasons of age from his position as Professor and Director of the Institute for Virology in Essen. The conference was in fact his scientific farewell party with his colleagues and peers after more than 40 years of medical and scientific work in virology. Michael Roggendorf was and is one of the international leaders in research on viral hepatitis including HBV, HCV and HDV. This appreciation is exemplified by his contribution to this special issue. He and his group were the first who have fully exploited the potential of the woodchuck

model to study immunotherapy of HBV-like infections and were the first to succeed at least partially in overcoming chronicity in this model and paving the way for similar approaches in human patients. In addition, his competence covers several fields in medical virology, both in terms of basic and translational research including practical diagnosis of viral infections. It is not surprising that he was for decades speaker of the diagnostic committee of the two German societies for Virology (GfV and DVV) and has essentially contributed to the high level of clinical virology in Germany and elsewhere. As mentioned above, one of his other big achievements is the establishment of a long-lasting and very productive collaboration between China and Germany in the field of medical virology. The scientific community is indebted to Michael Roggendorf for his eminent contributions and grateful that he will continue his work as professor emeritus at the Technical University Munich. We as co-editors thank him for assembling such a great list of contributions for this special issue of MMI.

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