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Editorial overview: Preventive and therapeutic vaccines: Vaccination against viral disease — current advances and challenges
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Preventive vaccination was launched by Edward Jenner’s fundamental experiment more than 200 years ago [1]. The inoculation of fluids from cowpox lesions protected an eight year-old boy against the challenge with smallpox. Today vaccination is clearly one of the most important and effective public health measures to reduce the impact of virus-associated infectious diseases. Vaccination allowed for global eradication of smallpox and eliminated poliomyelitis from Europe. We have prophylactic vaccines at hand to provide solid protection against yellow fever, rabies, measles, mumps, rubella, varicella, hepatitis A and B, tick borne and Japanese encephalitis [2]. Indeed, worldwide vaccination prevents millions of cases of measles and influenza each year. Despite these great successes, new and efficacious vaccines are urgently needed against the continuous threat of emerging and re-emerging infections [3]. Moreover, in our efforts to prevent and treat important infectious diseases which the scientific community has known about for years, many of the “old” challenges remain.

For decades, the availability of influenza vaccines has helped to reduce morbidity and mortality related to influenza virus infections. However, influenza virus vaccines still have shortcomings with regard to effectiveness against antigenic drift variants of seasonal influenza viruses. Moreover, these vaccines offer little or no protection against influenza viruses of a novel subtype with pandemic potential. Schotsaert and Garcia-Sastre address these limitations by comparing the mechanisms of immunity induced by inactivated influenza vaccines with those of live attenuated influenza vaccines. Trivalent inactivated vaccines are most commonly used to immunize human populations against seasonal influenza. More recently, quadrivalent inactivated vaccines are used to provide an additional antigenically different influenza B virus ingredient. The live attenuated influenza virus vaccines are a vaccine type intended to mimic natural infection and induce T cell mediated immunity in humans. The judgement of vaccine effectiveness in vaccinated individuals, however, is still exclusively based on the levels of hemagglutinin-specific virus-neutralizing antibodies in sera. The consideration of other correlates of protective immunity and influenza virus antigens additional to hemagglutinin offer the promise of developing more universal influenza vaccines that induce heterosubtypic protective immunity against seasonal and potentially pandemic influenza viruses.

In the more recent past, we are facing an era of emerging epidemics of virus infections unprecedented with regard to scope, scale and world-wide impact. Major disease burden in humans is associated with arthropod-borne flaviviruses including Dengue virus (DENV), West Nile virus (WNV) and Zika virus (ZIKV) which are all transmitted by mosquitoes. Two of the review
papers report on the status quo of vaccines targeting these flaviviruses. Fernandez and Diamond elaborate on the current strategies to make ZIKV specific vaccines readily available. Remarkably, within a short time after the epidemic emergence of ZIKV in 2015, several candidate vaccines have been created and advance towards clinical testing. These vaccines are based on various approaches including viral vectors or nucleic acid delivery. Common target antigens are the viral envelope proteins prM-E for induction of protective humoral immunity to ZIKV. In addition, the authors detail the complexities of developing a ZIKV vaccine in the context of possible cross-reactive immunity to other flaviviruses, along with the potential for occurrence of the Guillain-Barré syndrome being associated with ZIKV infection by epidemiological studies. How the actual clinical development of such new vaccines proceeds is discussed by Scherwitzl et al. The different options of preventive vaccination against DENV, WNV or ZIKV infections are presented with a focus on candidate vaccines already undergoing clinical evaluation in humans. Substantial progress has been made for DENV vaccines, with a first vaccine being licensed in various dengue endemic countries and other vaccine candidates having reached phase III clinical testing.

Okba et al. address the particular vaccine issues associated with the recent emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV), a novel human coronavirus causing a disease with similarities to the severe acute respiratory syndrome (SARS). Domedary camels are the critical animal reservoir responsible for spreading the virus to humans, and vaccines targeting this primary zoonotic infection could be used both in camels and in selected human populations. Healthcare workers and persons in contact with camels or patients are among those at risk for MERS-CoV infections. Initial promising approaches of vaccine development focus on the MERS-CoV spike protein as the key antigen and are readily advancing to clinical testing in humans. Moreover, increasing the knowledge about the mechanisms of protective immunity to MERS-CoV infections in humans and animals should result in identifying more-broadly effective immune responses and developing preventive means against other potentially emerging coronaviruses.

With over 200 million people chronically infected, HBV continues to be a major public health problem despite the fact that the infection can be prevented with a recombinant vaccine delivering the yeast-produced envelope protein HBsAg. In their review Kosinska et al. discuss the processes underlying the critical immune tolerance associated with chronic HBV infection. HBV infects the distinct immune environment of the liver and simultaneously produces massive amounts of secreted virus antigen, filamentous and spherical particles, in addition to its infectious progeny. In consequence, mechanisms of functional and deletional tolerance in the virus-specific T cell response are suggested to cooperate in the inhibition of HBV clearance. To overcome immune tolerance in chronic hepatitis B, a
therapeutic vaccine would be highly desired and various approaches are being followed-up to develop appropriate candidate vaccines. Major hurdles, however, include the need to amplify virus-specific effector T cells in the immune privileged environment of the liver. New candidate vaccines and vaccination strategies directing T cells to additional HBV antigens are discussed as well as the combination of therapeutic vaccination with checkpoint inhibition or antiviral drug therapy. Overall these new developments hold great promise to reduce the substantial disease burden related to chronic HBV infection.

In the case of HCV, Chris Walker tackles the question of whether there is still a role for an HCV vaccine, given the very successful antiviral HCV therapy available today. His conclusion is that it is not yet clear whether the therapy is going to be able to reduce the global burden of disease and therefore vaccine development should be pursued with the scope to prevent primary infection, and prevent re-infection of cured individuals. He reports that there are two preventive vaccines in development, one based on eliciting T cell immunity and the other based on neutralizing antibodies. The first one is being tested now in people at risk for HCV infection, while the second one is still in preclinical studies. The observation that following primary infections only 70% of people progress to chronic infection while the others spontaneously resolve the infection, suggests that in 30% of cases the immune system is effective in clearing the infection and therefore the goal of vaccines should not necessarily be to induce sterilizing immunity, but rather to prevent the establishment of chronic infection. Finally, Chris Walker asks the question of whether vaccines can also be developed for those people that have cleared the infection by therapy. The question is, once the infection is cleared, if the immune system will regain the ability to respond to vaccination or if it will remain unable to respond to vaccination as is the case during chronic infection.

The other two papers describe vaccines against Cytomegalovirus (CMV) and respiratory syncytial virus (RSV), both of which were nearly impossible to produce up to a decade ago. These vaccines now seem to be easy to make, thanks to the understanding and engineering of the antigens using structure-based antigen design. In the case of RSV, the crystal structure of the F protein in the post-fusion conformation first, and in the pre-fusion conformation later, showed the remarkable difference between the two structures and allowed engineering of antigens stabilized in the pre-fusion conformation. When used for immunization in animal models, the pre-fusion antigens were shown to induce a ten-fold increase in the titer of neutralizing antibodies, suggesting that this should be the antigen of choice for RSV vaccines.

In the case of CMV, clinical trials performed with the antigen gB and the adjuvant MF59 had shown that although with this vaccine we can induce a 50% protection from infection, this was not good enough for a vaccine. The surprise came when it was found that potent neutralizing antibodies against CMV were not recognizing gB, but a more complex structure composed of 5 proteins, today known as pentamer. This finding gave insight into the mechanism of CMV entry in mammalian cells and aided development of new, very potent antigens to develop vaccines. The pentameric gH/gL/UL128/UL130/UL131 was shown to be used by the virus to enter epithelial cells, while the complex gH/gL/GO is used to enter fibroblasts. Today the pentamer has been expressed in mammalian cells and shown to induce potent neutralizing antibodies and seems to be the antigen of choice for CMV vaccines.

Conclusions
Vaccines are probably the most efficacious public health tools of the 20th Century having greatly reduced both morbidity and mortality from viral diseases across the globe. Today, vaccination against viral disease moves to confront the challenges of emerging infections that are caused by pathogens with little known biology and associated with unpredictable impact on our societies. Moreover, the field still needs to address the massive disease burden from chronic infections caused by viruses that already know the tricks to efficiently evade the human immune system. New insights into the immune correlates of protection from viral diseases and into the vaccine prerequisites for the rational induction of safe and broadly protective immune responses offer promising chances for highly innovative vaccine development. Important aims include the availability of vaccines that can be rapidly produced and delivered to provide protection against emerging or re-emerging viruses. The induction of potent but balanced innate responses upon vaccination holds great promise to overcome the malfunctioning immune defense in chronic infections. The recent advances in vaccine research demonstrate the feasibility to test a wide range of candidate vaccines — including genetically engineered live viruses — in preclinical proof-of-principle studies and in clinical trials in humans.

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