Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Cytokine and Growth Factor Reviews 60 (2021) 46–51

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

The conundrum of current anti-SARS-CoV-2 vaccines

Maurizio Federico

National Center for Global Health, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161, Rome, Italy

ARTICLE INFO

Keywords
SARS-CoV-2
Vaccine
Humoral immunity
Adenoviral vector
$CD8^+$ T-cell immunity

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has given rise to the urgent need for vaccines and therapeutic interventions to address the spread of the SARS-CoV-2 virus. SARS-CoV-2 vaccines in development, and those being distributed currently, have been designed to induce neutralizing antibodies using the spike protein of the virus as an immunogen. However, the immunological correlates of protection against the virus remain unknown. This raises questions about the efficacy of current vaccination strategies. In addition, safety profiles of several vaccines seem inadequate or have not yet been evaluated under controlled experimentation. Here, evidence from the literature regarding the efforts already made to identify the immunological correlates of protection against SARS-CoV-2 infection are summarized. Furthermore, key biological features of most of the advanced vaccines and considerations regarding their safety and expected efficacy are highlighted.

1. Introduction

By the end of January 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected more than 100 million people, causing approximately 2.2 million deaths [1]. Given the nature and severity of coronavirus disease (COVID-19), there is a need to fight the viral spread through behavioral changes and social and medical interventions. Among the latter, widespread efforts have been made to produce vaccines for large-scale administration. All current vaccine strategies have been developed to generate anti-spike protein (S) neutralizing antibodies (Abs). This strategy has been pursued through different technologies via the delivery of messenger RNA (mRNA), adenoviral vectors, recombinant proteins, and inactivated viral particles.

The urgency in tackling the pandemic strongly reduced the time allocated to the three phases typically needed to achieve vaccine licensure. However, unproven technologies have been proposed and pursued to produce vaccines that are currently being distributed. Applied on a global scale, these new strategies could achieve important advancements in vaccine technology. However, in some cases, safety concerns need to be revisited.

Furthermore, two additional aspects must be considered in the overall evaluation of vaccines: efficacy and duration of immune response. The immunological correlates of protection against SARS-CoV-2 infection are still unknown. On the other hand, the restricted observation times did not allow a reliable evaluation of the duration of immune response induced by the current anti-SARS-CoV-2 vaccines.

Here, useful data are summarized from the literature to clarify the course of humoral immunity in SARS-CoV-2-related pathogenesis in humans. On this basis, the expected efficacy and the duration of immune response of diverse vaccines are evaluated. In addition, possible issues concerning the safety profiles of the diverse vaccines are analyzed.

1.1. What is the immunological correlate of protection against SARS-CoV-2 infection?

Most commonly, the term “correlate of protection” refers to a laboratory parameter associated with protection from a clinical disease [2]. When this concept is applied to the immune response against SARS-CoV-2, there are several uncertainties. For instance, data from a detailed immunological study on hundreds of infected patients, extended for up to 8 months after symptoms onset, did not provide definitive conclusions about the mechanisms of protective immunity [3]. On this basis, it has been proposed that a coordinated action of $CD4^+$ T cells, $CD8^+$ T cells, and neutralizing Abs is necessary to control SARS-CoV-2 infection [3,4]. Results from a study on rhesus macaques

Abbreviations: Ab, antibody; ACE-2, angiotensin-converting enzyme 2; ADE, antibody-dependent enhancement; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; M, membrane protein; MHC, major histocompatibility complex; mRNA, messenger RNA; N, nucleocapsid protein; PEG, polyethylene glycol; PSO, post symptoms onset; RBD, receptor-binding domain; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

E-mail address: maurizio.federico@iss.it.

https://doi.org/10.1016/j.cytogfr.2021.03.001
Received 12 February 2021; Received in revised form 3 March 2021; Accepted 4 March 2021
Available online 6 March 2021
1359-6101/© 2021 Elsevier Ltd. All rights reserved.

indicated that adequate levels of anti-SARS-CoV-2 immunoglobulin G (IgG) can protect against infection and that cellular immunity contributes to protection in the case of subprotective Ab titers [5].

With regard to the virus-induced humoral response in humans, specific Ab responses were found to be elevated in severely ill patients, but remained moderate-to-low or even undetectable in asymptomatic subjects and patients with mild disease [6–11]. This applied to anti-S protein and anti-receptor-binding domain (RBD) Abs, that is, Abs recognizing the S domain binding to the angiotensin-converting enzyme 2 (ACE-2) cell receptor, and to all Ab classes [12–15]. The highest levels of neutralizing Abs, that is, the anti-S Abs identified for their specific ability to block virus entry in in vitro assays, were found in patients with more severe illness [15,16]. Serological time course analysis carried out on hospitalized patients failed to demonstrate a correlation between anti-S Ab levels and patient outcomes [15]. However, many deceased patients developed very high levels of anti-S, anti-RBD, and neutralizing Abs [15,17–19]. In addition, the kinetics of the decay of anti-S, anti-RBD, and neutralizing Abs was strongly correlated [15]. This evidence goes against the hypothesis that the quality, rather than quantity of Ab response, may predict the patient's outcome.

Taken together, these clinical observations raise serious questions about the correlates of protection against a SARS-CoV-2 infection.

1.2. What is the duration of immune response of anti-S Abs?

The duration of the induced immune response is a critical hallmark of any vaccine. The humoral immune response relies on the production of Abs as well as the generation of memory B cells that can undergo reactivation upon antigen recognition. The duration of the anti-SARS-CoV-2 antibody response was evaluated for a reasonable time in infected patients. Conversely, the observation times following vaccine administration were restricted. Dan and colleagues reported that the half-life ($t_{1/2}$) of post symptoms onset (PSO) anti-S Abs was 103 days, as calculated in infected patients tested at least at two time points [3]. The half-life of anti-RBD Abs was 69 days, and that of neutralizing Abs was 27 days. In these cases, the decay curves were recognized as extended plateaus. In contrast, the $t_{1/2}$ of anti-S and anti-RBD IgAs did not exceed 30 days. In this study, the levels of anti-S humoral response appeared variable, with more than 2 logs of difference among infected subjects [3]. In another study, a parallel decay of anti-S, anti-RBD, and neutralizing Abs was reported, starting at one to a few months after symptoms onset, with inpatients developing higher Ab titers than outpatients [15]. This decline was more rapid in asymptomatic and mildly ill patients. In general, data from Ab levels and kinetics of decay appear inconsistent among different investigations [3,12,13,15,20,21].

Ab waning may not necessarily imply unresponsiveness in a subsequent antigen recognition, considering that humoral immunity can be promptly reactivated in the presence of a pool of memory B cells. In the case of SARS-CoV-2 infection, different studies have demonstrated the persistence of circulating virus-specific memory B cells for up to 8 months [3,22–24]. However, the formation of a pool of memory B cells in airway tissues remains uncertain. Lymphocytes residing in the lungs are essentially a self-renewing cell population, and this population is only minimally replenished by circulating cells [25]. Thus, the presence of virus-specific circulating memory B cells would not necessarily mirror adequate levels of immunity in lung tissues, which are the region most involved in SARS-CoV-2 pathogenesis. This may be a critical issue in the case of anti-SARS-CoV-2 vaccines, since the rapid decrease in Ab response in the absence of an effective pool of memory B cells in the lungs may imply the requirement of frequent booster doses.

1.3. Vaccines based on mRNA technology

This is the first time that vaccines based on mRNA technology have been proposed for the human population. These vaccine formulations comprise mRNA molecules where uracil bases are replaced with a pseudouridine analogue [26] and complexed with hydrophobic lipid nanoparticles [27] to allow efficient entry into the cells of the injected host. The lipid nanoparticles are 70–100 nm in diameter and are prepared using an ionizable amino lipid, phospholipids, cholesterol, and a polyethylene glycol (PEG)-ylated lipid [28]. In the case of anti-SARS-CoV-2 vaccines, mRNA codes for a SARS-CoV-2 S protein with two proline mutations that stabilize its prefusion conformation [29] in order to favor the generation of neutralizing Abs. Because of lipid complexing, injected mRNA molecules can access the cytoplasm of host cells, thereby initiating S protein synthesis. The viral protein is assumed to be secreted and recognized by the host immune system as a non-self product that eventually elicits humoral immunity. When the mRNA molecules enter an antigen-presenting cell, peptides derived from the neo-synthesized product may be uploaded to major histocompatibility complex (MHC) class I molecules, thereby initiating the process leading to an antiviral $CD8^+$ T-cell immune response.

A wealth of data supports the conclusion that this strategy leads to a robust humoral response [30–32] associated with apparent protection from severe symptoms [33–35]. To the best of our knowledge, mRNA-based vaccines do not present major safety concerns, besides short-term adverse reactions of limited severity. However, at present, nothing is known about unpredictable, long-term adverse reactions that could have been monitored only by extended phase III clinical trials. In addition, the limited observation times preclude a reliable evaluation regarding the duration of humoral response and need for Ab response reactivation.

1.4. Vaccines based on human adenoviral vectors

The use of adenoviral vectors is considered the "gold standard" in preclinical vaccine experimentation because of the high levels of humoral and cellular immune response against the antigen of interest that these vectors elicit in animals. This technology has been translated into anti-SARS-CoV-2 human vaccines with vectors derived from both human and non-human primate virus strains.

Adenoviruses are non-enveloped, icosahedral viruses approximately 90 nm diameter, with a linear double-stranded DNA genome of 28–40 kilobases, expressing 22–40 genes depending on the virus type [36]. Human adenoviruses have more than 50 serotypes, divided into seven species (A to G). Serotypes 2 and 5 are the most widely studied. Adenoviruses can infect dividing and non-dividing cells, and have a broad tropism.

Adenoviral vectors are generally produced in mammalian cells by recombination between homologous parts of the genome. In classic laboratory protocols, DNA molecules expressing a replication-defective adenoviral backbone and a shuttle vector carrying the gene of interest are co-transfected in mammalian cells, complementing the backbone defectiveness. Sequences of the gene of interest are transferred to the viral backbone through recombination, guided by homologous sequences present in the two DNA molecules. Adenoviral vectors are commonly produced by co-transfection in HEK-293 cells engineered to complement the defectiveness in the viral backbone, most frequently involving deletions in the E1a, E1b, E3, and E4 genes. In more advanced technologies, the homologous recombination step occurs in bacteria [37]. The most popular adenoviral vectors are based on the genomes of serotypes 5 and 26.

Two aspects should be considered when adenoviral vector-based technology is applied to human vaccines: (i) the engineered adenoviral genome is quite large and expresses, besides the gene of interest, several additional proteins including capsid proteins II (hexon), III (penton base), IIIa, IV (fiber), VI, VIII, and IX; core proteins V, VII, and X; and the terminal protein TP, and (ii) adenoviral genomes are prone to recombination, a feature that can have consequences in the case of non-human adenoviral vector-based vaccines.

The injection of adenoviral vector particles implies that a single vaccine administration can generate a widespread immune response

against the structural adenoviral products. The unavoidable vector-specific immunity could be minimized by the use of last-generation, high-capacity adenoviral vectors [38]; however, these have not yet been approved for clinical use.

Adenovirus infection in immune-competent individuals mostly results in mild, self-limiting pathologies. It is quite common in humans, and virus-specific IgGs persist after infection. For instance, 60–80% of a Chinese population had neutralizing Abs against adenovirus serotype 5, and 20–50% had neutralizing Abs against serotype 26 [39]. The data obtained by analyzing a Brazilian population was consistent with the findings of the Chinese population [40]. In another study on individuals from sub-Saharan Africa, 100 % of persons displayed neutralizing Abs against serotype 5, and 21 % against serotype 26 [41].

Despite these premises, anti-SARS-CoV-2 vaccines based on adenoviral vectors from serotype 5 have been produced and administered [42]. In some instances, the vaccination schedule includes boosting with a vector based on serotype 26 [43], which has the advantage of a lower seroprevalence in humans. In other cases, the vaccination schedule includes two inoculations with a vector from serotype 26 [44]. Vector neutralization, ultimately inhibiting the anti-S immune response, is expected to occur in all subjects already experiencing natural infection with serotypes 5 and/or 26. In case of uninfected subjects, anti-vector immunity takes place after the first immunization, which severely curtails the efficacy of vaccine boosts. Furthermore, the anti-vector immunity is also expected to heavily affect possible re-boosting, which is to be applied after the decay of the immune response induced by the first vaccination cycle.

The $CD8^+$ T-cell response against the diverse adenoviral proteins that natural infection and vaccine administration can elicit, is also a hurdle. In this regard, adenovirus-specific $CD8^+$ T lymphocytes have been proven to be widespread, polyfunctional, and cross-reactive against antigens from different human serotypes, as well as from vectors derived from non-human primates [45].

1.5. Vaccines based on non-human adenoviral vectors

In an effort to elude the neutralization effects of pre-existing immunity, vaccines based on vectors from non-human primate adenoviruses have been produced and are currently being administered [46–49]. The underlying technology is essentially the same as that used to produce vaccines based on vectors from human adenoviruses. After the first inoculation, anti-vector immunity would strongly decrease the immunogenicity of these vaccine preparations. Most importantly, the delivery of non-human adenovirus-based vectors puts vaccine recipients who were previously infected with human adenoviruses at a risk of generating new and unpredictable chimeric virus species. In fact, severely pathogenic virus species may arise as a result of recombination events. Recombination is quite frequent within adenovirus genomes, as largely documented by data obtained by sequencing genomes from people co-infected with different human adenovirus types [50–52]. In vaccinated individuals, a non-human viral vector may enter a single cell that is already infected with a human adenovirus. Considering the very high sequence homology between human and non-human primate adenoviruses (> 95 %), intracellular recombination events are likely to occur. Even if at present only theoretical, the likelihood that a similar, potentially catastrophic event may occur is expected to increase with the increase in the number of vaccinations.

1.6. Vaccines based on inactivated viruses and recombinant proteins

Anti-SARS-CoV-2 vaccines based on the association of recombinant trimeric S protein with adjuvants [53], as well as the whole inactivated virus [54], have also been designed and produced. These approaches resemble “traditional” vaccine strategies already applied to fight other infectious agents, and hence in principle possess high safety profiles. However, issues with Ab efficacy and the duration of immune response are expected to mirror those already described for the humoral responses elicited through less conventional vaccine strategies.

2. Conclusions

The major unresolved issue in current anti-SARS-CoV-2 vaccine strategies is that the immunological correlates of protection against the virus in humans remain unknown. Results from several clinical observations are consistent with the idea that the levels of anti-S Abs do not correlate with patient outcome, and this evidence may have consequences for predicting vaccine efficacy. It is conceivable that quality (e.g., affinity, avidity, and specificity) rather than quantity of Abs produced will be critical for virus blockade. More accurate laboratory analyses are required to validate this hypothesis since, at present, the patient outcome appears to be independent of the relative amounts of anti-RBD and neutralizing Abs produced.

A potential obstacle in the development of a SARS-CoV-2 vaccine is the risk of triggering Ab-dependent enhancement (ADE) of virus infection and/or immunopathology, as has already been documented for SARS-CoV [55–57] and has been recently suggested for SARS-CoV-2 [58–60]. The lack of ADE-related events during the current mass vaccination tentatively excludes the possibility that some vaccines might worsen the disease rather than prevent it, as seen with the Dengvaxia tetravalent yellow fever-dengue Ab-generating vaccine [61].

Vaccine strategies employing adenoviral vectors are controversial in terms of efficacy and safety. Further, when not already present, as in the case of vectors based on non-human adenoviruses, the induction of neutralizing anti-vector immunity seems unavoidable, as also described in recent clinical trial reports although in sparse and hidden ways [42, 44]. An additional inhibitory mechanism is represented by vector-specific $CD8^+$ T-cell immunity. When adenoviral vectors enter professional and semi-professional antigen-presenting cells, peptides from viral proteins can associate with MHC class I molecules, thereby eliciting pools of $CD8^+$ T lymphocytes that recognize, attack, and destroy cells expressing the products of adenoviral vectors. These events would strongly limit the effectiveness of vaccine boosts.

The most alarming perspective pertains to the use of non-human adenoviral vectors. It is widely accepted that new and aggressive epidemics arose from the passage and adaption of viruses from animals to humans. This was hypothesized, among others, for HIV, avian and swine influenza viruses, and, lastly, SARS-CoV-2. In the case of vaccinations with non-human adenoviral vectors, natural barriers can be overcome by delivering a non-human viral genome directly into cells. DNA recombination between different adenovirus species may occur when the target cells are already infected with a human adenovirus. Since DNA recombination events are based on the recognition of stretches of identical sequences, and there is high sequence homology between human and non-human primate adenoviruses (> 95 %), the emergence of recombinant adenoviruses from vaccinated individuals is, although rare, a possible event. The positive selection of even a single new pathogenic adenovirus species would have unpredictable and ungovernable consequences globally.

It is conceivable that protection against SARS-CoV-2 infection would be the result of the coordinated action of humoral and cellular immunity. Consequently, besides the induction of neutralizing Abs, additional antiviral preventive strategies should be pursued. Several experimental and clinical studies prove the beneficial effect of virus-specific $CD8^+$ T-cell immunity. T cells provide therapeutic benefits by directly inducing lysis of virus-infected cells and shaping the immune response through the release of cytokines critical for suppressing viral infections. $CD8^+$ T-cell responses against respiratory viral infections have been shown to be as important as humoral responses [62–64]. Robust T-cell responses against S, membrane (M), nucleocapsid (N), and ORF1ab proteins have been described in COVID-19 convalescent patients [65,66]. The T-cell response present in asymptomatic and mildly ill infected patients is absent in severely ill patients [67–69]. Notably, $CD8^+$ T-cell responses

against S and N protein have been detected in the peripheral blood of recovered SARS-CoV patients up to 17 years post-infection, in contrast to the early decay of Ab levels [70].

Novel virus variants harboring mutations in S protein and particularly in the RBD, the target of most neutralizing Abs, are emerging worldwide. Current vaccines were based on the S protein sequence from the virus isolated early in the epidemic in Wuhan. Many groups have published data on vaccine cross-neutralization. Results from two recent studies based on different in vitro neutralization assays concluded that current mRNA-based vaccines cross-neutralize both P.1 (Brazil variant) and B.1.351 (South African variant) poorly [71,72]. Due to the widespread diffusion of the virus, the rapid emergence of mutations is not surprising. Redesigning vaccines based on new sequences may result in an element of selective pressure in the case of large-scale vaccinations. Conversely, a strategy for a universal vaccine including a component that induces effective $CD8^+$ T-cell immunity could break such a potential vicious circle.

Although a strong $CD8^+$ T-cell response should be a component of any vaccine regimen for SARS-CoV-2, no reliable vaccine technology for the induction of cell immunity has been validated for humans to date. In this regard, adenoviral vectors produced reproducible positive results in preclinical settings in terms of induction of $CD8^+$ T-cell immunity in a wide range of applications. However, results from trials with anti-SARS-CoV-2 human vaccines appeared modest [39] and, in some cases, elusive [35].

In conclusion, the extraordinary rapidity of producing diverse anti-SARS-CoV-2 vaccine options has caused several questions about their efficacy, duration of immune response, and safety. Intensive basic and preclinical research is needed to define pathogenesis, immunopathogenesis, and correlates of protection against SARS-CoV-2 infection. This is the only way to achieve safe and effective preventive and therapeutic interventions.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

No specific grants from funding agencies in the public, commercial, or not-for-profit sectors pertain to the present manuscript

References

[1] COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) https://coronavirus.jhu.edu/map.html.
[2] S.A. Plotkin, Vaccines: correlates of vaccine-induced immunity, Clin. Infect. Dis. 47 (2008) 401–409, https://doi.org/10.1086/589862.
[3] J.M. Dan, J. Mateus, Y. Kato, K.M. Hastie, E.D. Yu, C.E. Faliti, A. Grifoni, S. I. Ramirez, S. Haupt, A. Frazier, C. Nakao, V. Rayaprolu, S.A. Rawlings, B. Peters, F. Krammer, V. Simon, E.O. Saphire, D.M. Smith, D. Weiskopf, A. Sette, S. Crotty, Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection, Science (2021), https://doi.org/10.1126/science.abf4063.
[4] A. Sette, S. Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), https://doi.org/10.1016/j.cell.2021.01.007.
[5] K. McMahan, J. Yu, N.B. Mercado, C. Loos, L.H. Tostanoski, A. Chandrashekar, J. Liu, L. Peter, C. Atyeo, A. Zhu, E.A. Bondzie, G. Dagotto, M.S. Gebre, C. Jacob-Dolan, Z. Li, F. Nampanya, S. Patel, L. Pessaint, A. Van Ry, K. Blade, J. Yalley-Ogunro, M. Cabus, R. Brown, A. Cook, E. Teow, H. Andersen, M.G. Lewis, D. A. Lauffenburger, G. Alter, D.H. Barouch, Correlates of protection against SARS-CoV-2 in rhesus macaques, Nature (2020), https://doi.org/10.1038/s41586-020-03041-6.
[6] I.F.-N. Hung, V.C.-C. Cheng, X. Li, A.R. Tam, D.L.-L. Hung, K.H.-Y. Chiu, C.C.-Y. Yip, J.-P. Cai, D.T.-Y. Ho, S.-C. Wong, S.S.-M. Leung, M.-Y. Chu, M.O.-Y. Tang, J. H.-K. Chen, R.W.-S. Poon, A.Y.-F. Fung, R.R. Zhang, E.Y.-W. Yan, L.-L. Chen, C.Y.-K. Choi, K.-H. Leung, T.W.-H. Chung, S.H.-Y. Lam, T.P.-W. Lam, J.F.-W. Chan, K.-H. Chan, T.-C. Wu, P.-L. Ho, J.W.-M. Chan, C.-S. Lau, K.K.-W. To, K.-Y. Yuen, SARS-CoV-2 shedding and seroconversion among passengers quarantined after disembarking a cruise ship: a case series, Lancet Infect. Dis. 20 (2020) 1051–1060, https://doi.org/10.1016/S1473-3099(20)30364-9.
[7] Q.-X. Long, X.-J. Tang, Q.-L. Shi, Q. Li, H.-J. Deng, J. Yuan, J.-L. Hu, W. Xu, Y. Zhang, F.-J. Lv, K. Su, F. Zhang, J. Gong, B. Wu, X.-M. Liu, J.-J. Li, J.-F. Qiu, J. Chen, A.-L. Huang, Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections, Nat. Med. 26 (2020) 1200–1204, https://doi.org/10.1038/s41591-020-0965-6.
[8] T.J. Ripperger, J.L. Uhrlaub, M. Watanabe, R. Wong, Y. Castaneda, H.A. Pizzato, M. R. Thompson, C. Bradshaw, C.C. Weinkauf, C. Bime, H.L. Erickson, K. Knox, B. Bixby, S. Parthasarathy, S. Chaudhary, B. Natt, E. Cristan, T. El Aini, F. Rischard, J. Campion, M. Chopra, M. Insel, A. Sam, J.L. Knepler, A.P. Capaldi, C.M. Spier, M. D. Dake, T. Edwards, M.E. Kaplan, S.J. Scott, C. Hypes, J. Mosier, D.T. Harris, B. J. LaFleur, R. Sprissler, J. Nikolich-Žugich, D. Bhattacharya, Orthogonal SARS-CoV-2 serological assays enable surveillance of low-prevalence communities and reveal durable humoral immunity, Immunity 53 (2020) 925–933, https://doi.org/10.1016/j.immuni.2020.10.004, e4.
[9] Y. Wang, L. Zhang, L. Sang, F. Ye, S. Ruan, B. Zhong, T. Song, A.N. Alshukairi, R. Chen, Z. Zhang, M. Gan, A. Zhu, Y. Huang, L. Luo, C.K.P. Mok, M.M. Al Gethamy, H. Tan, Z. Li, X. Huang, F. Li, J. Sun, Y. Zhang, L. Wen, Y. Li, Z. Chen, Z. Zhuang, J. Zhuo, C. Chen, L. Kuang, J. Wang, H. Lv, Y. Jiang, M. Li, Y. Lin, Y. Deng, L. Tang, J. Liang, J. Huang, S. Perlman, N. Zhong, J. Zhao, J.S. Malik Peiris, Y. Li, J. Zhao, Kinetics of viral load and antibody response in relation to COVID-19 severity, J. Clin. Invest. 130 (2020) 5235–5244, https://doi.org/10.1172/JCI138759.
[10] M.C. Woodruff, R.P. Ramonell, D.C. Nguyen, K.S. Cashman, A.S. Saini, N. S. Haddad, A.M. Ley, S. Kyu, J.C. Howell, T. Ozturk, S. Lee, N. Suryadevara, J. B. Case, R. Bugrovsky, W. Chen, J. Estrada, A. Morrison-Porter, A. Derrico, F. A. Anam, M. Sharma, H.M. Wu, S.N. Le, S.A. Jenks, C.M. Tipton, B. Staitieh, J. L. Daiss, E. Ghosn, M.S. Diamond, R.H. Carnahan, J.E. Crowe, W.T. Hu, F.E.-H. Lee, I. Sanz, Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19, Nat. Immunol. 21 (2020) 1506–1516, https://doi.org/10.1038/s41590-020-00814-z.
[11] A.T. Tan, M. Linster, C.W. Tan, N. Le Bert, W.N. Chia, K. Kunasegaran, Y. Zhuang, C.Y.L. Tham, A. Chia, G.J.D. Smith, B. Young, S. Kalimuddin, J.G.H. Low, D. Lye, L.-F. Wang, A. Bertoletti, Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients, Cell Rep. (2021) 108728, https://doi.org/10.1016/j.celrep.2021.108728.
[12] L. Piccoli, Y.-J. Park, M.A. Tortorici, N. Czudnochowski, A.C. Walls, M. Beltramello, C. Silacci-Fregni, D. Pinto, L.E. Rosen, J.E. Bowen, O.J. Acton, S. Jaconi, B. Guarino, A. Minola, F. Zatta, N. Sprugasci, J. Bassi, A. Peter, A. De Marco, J.C. Nix, F. Mele, S. Jovic, B.F. Rodriguez, S.V. Gupta, F. Jin, G. Piumatti, G. Lo Presti, A.F. Pellanda, M. Biggiogero, M. Tarkowski, M.S. Pizzuto, E. Cameroni, C. Havenar-Daughton, M. Smithey, D. Hong, V. Lepori, E. Albanese, A. Ceschi, E. Bernasconi, L. Elzi, P. Ferrari, C. Garzoni, A. Riva, G. Snell, F. Sallusto, K. Fink, H.W. Virgin, A. Lanzavecchia, D. Corti, D. Veesler, Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology, Cell 183 (2020) 1024–1042, https://doi.org/10.1016/j.cell.2020.09.037, e21.
[13] D.F. Robbiani, C. Gaebler, F. Muecksch, J.C.C. Lorenzi, Z. Wang, A. Cho, M. Agudelo, C.O. Barnes, A. Gazumyan, S. Finkin, T. Hägglöf, T.Y. Oliveira, C. Viant, A. Hurley, H.-H. Hoffmann, K.G. Millard, R.G. Kost, M. Cipolla, K. Gordon, F. Bianchini, S.T. Chen, V. Ramos, R. Patel, J. Dizon, I. Shimeliovich, P. Mendoza, H. Hartweger, L. Nogueira, M. Pack, J. Horowitz, F. Schmidt, Y. Weisblum, E. Michailidis, A.W. Ashbrook, E. Waltari, J.E. Pak, K.E. Huey-Tubman, N. Koranda, P.R. Hoffman, A.P. West, C.M. Rice, T. Hatziioannou, P. J. Bjorkman, P.D. Bieniasz, M. Caskey, M.C. Nussenzweig, Convergent antibody responses to SARS-CoV-2 in convalescent individuals, Nature 584 (2020) 437–442, https://doi.org/10.1038/s41586-020-2456-9.
[14] S.P. Anand, J. Prévost, M. Nayrac, G. Beaudoin-Bussières, M. Benlarbi, R. Gasser, N. Brassard, A. Laumaea, S.Y. Gong, C. Bourassa, E. Brunet-Ratnasingham, H. Medjahed, G. Gendron-Lepage, G. Goyette, L. Gokool, C. Morrisseau, P. Bégin, V. Martel-Laferrière, C. Tremblay, J. Richard, R. Bazin, R. Duerr, D.E. Kaufmann, A. Finzi, Longitudinal analysis of humoral immunity against SARS-CoV-2 Spike in convalescent individuals up to 8 months post-symptom onset, BioRxiv (2021), https://doi.org/10.1101/2021.01.25.428097.
[15] K. Röltgen, A.E. Powell, O.F. Wirz, B.A. Stevens, C.A. Hogan, J. Najeeb, M. Hunter, H. Wang, M.K. Sahoo, C. Huang, F. Yamamoto, M. Manohar, J. Manalac, A. R. Otrelo-Cardoso, T.D. Pham, A. Rustagi, A.J. Rogers, N.H. Shah, C.A. Blish, J. R. Cochran, T.S. Jardetzky, J.L. Zehnder, T.T. Wang, B. Narasimhan, S. Gombar, R. Tibshirani, K.C. Nadeau, P.S. Kim, B.A. Pinsky, S.D. Boyd, Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome, Sci. Immunol. 5 (2020), https://doi.org/10.1126/sciimmunol.abe0240.
[16] C. Rydyznski Moderbacher, S.I. Ramirez, J.M. Dan, A. Grifoni, K.M. Hastie, D. Weiskopf, S. Belanger, R.K. Abbott, C. Kim, J. Choi, Y. Kato, E.G. Crotty, C. Kim, S.A. Rawlings, J. Mateus, L.P.V. Tse, A. Frazier, R. Baric, B. Peters, J. Greenbaum, E. Ollmann Saphire, D.M. Smith, A. Sette, S. Crotty, Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity, Cell 183 (2020) 996–1012, https://doi.org/10.1016/j.cell.2020.09.038, e19.
[17] C. Atyeo, S. Fischinger, T. Zohar, M.D. Slein, J. Burke, C. Loos, D.J. McCulloch, K. L. Newman, C. Wolf, J. Yu, K. Shuey, J. Feldman, B.M. Hauser, T. Caradonna, A. G. Schmidt, T.J. Suscovich, C. Linde, Y. Cai, D. Barouch, E.T. Ryan, R.C. Charles, D. Lauffenburger, H. Chu, G. Alter, Distinct early serological signatures track with SARS-CoV-2 survival, Immunity 53 (2020) 524–532, https://doi.org/10.1016/j.immuni.2020.07.020, e4.
[18] Q.-X. Long, B.-Z. Liu, H.-J. Deng, G.-C. Wu, K. Deng, Y.-K. Chen, P. Liao, J.-F. Qiu, Y. Lin, X.-F. Cai, D.-Q. Wang, Y. Hu, J.-H. Ren, N. Tang, Y.-Y. Xu, L.-H. Yu, Z. Mo, F. Gong, X.-L. Zhang, W.-G. Tian, L. Hu, X.-X. Zhang, J.-L. Xiang, H.-X. Du, H.-W. Liu, C.-H. Lang, X.-H. Luo, S.-B. Wu, X.-P. Cui, Z. Zhou, M.-M. Zhu, J. Wang, C.-

J. Xue, X.-F. Li, L. Wang, Z.-J. Li, K. Wang, C.-C. Niu, Q.-J. Yang, X.-J. Tang, Y. Zhang, X.-M. Liu, J.-J. Li, D.-C. Zhang, F. Zhang, P. Liu, J. Yuan, Q. Li, J.-L. Hu, J. Chen, A.-L. Huang, Antibody responses to SARS-CoV-2 in patients with COVID-19, Nat. Med. 26 (2020) 845–848, https://doi.org/10.1038/s41591-020-0897-1.

[19] A. Flemming, Deciphering the protective features of the antibody response, Nat. Rev. Immunol. 70 (21) (2021), https://doi.org/10.1038/s41577-020-00496-6.

[20] D.F. Gudbjartsson, G.L. Norddahl, P. Melsted, K. Gunnarsdottir, H. Holm, E. Eythorsson, et al., Humoral immune response to SARS-CoV-2 in Iceland, N. Engl. J. Med. 383 (2020) 1724–1734, https://doi.org/10.1056/NEJMoa2026116.

[21] B. Sun, Y. Feng, X. Mo, P. Zheng, Q. Wang, P. Li, P. Peng, X. Liu, Z. Chen, H. Huang, F. Zhang, W. Luo, X. Niu, P. Hu, L. Wang, H. Peng, Z. Huang, L. Feng, F. Li, F. Zhang, F. Li, N. Zhong, L. Chen, Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients, Emerg. Microbes Infect. 9 (2020) 940–948, https://doi.org/10.1080/22221751.2020.1762515.

[22] L.B. Rodda, J. Netland, L. Shehata, K.B. Pruner, P.A. Morawski, C.D. Thouvenel, K. K. Takehara, J. Eggenberger, E.A. Hemann, H.R. Waterman, M.L. Fahning, Y. Chen, M. Hale, J. Rathe, C. Stokes, S. Wrenn, B. Fiala, L. Carter, J.A. Hamerman, N. P. King, M. Gale, D.J. Campbell, D.J. Rawlings, M. Pepper, Functional SARS-CoV-2-Specific immune memory persists after mild COVID-19, Cell 184 (2021) 169–183, https://doi.org/10.1016/j.cell.2020.11.029, e17.

[23] C. Gaebler, Z. Wang, J.C.C. Lorenzi, F. Muecksch, S. Finkin, M. Tokuyama, A. Cho, M. Jankovic, D. Schaefer-Babajew, T.Y. Oliveira, M. Cipolla, C. Viant, C.O. Barnes, Y. Bram, G. Breton, T. Hägglöf, P. Mendoza, A. Hurley, M. Turroja, K. Gordon, K. G. Millard, V. Ramos, F. Schmidt, Y. Weisblum, D. Jha, M. Tankelevich, G. Martinez-Delgado, J. Yee, R. Patel, J. Dizon, C. Unson-O'Brien, I. Shimeliovich, D.F. Robbiani, Z. Zhao, A. Gazumyan, R.E. Schwartz, T. Hatziioannou, P. J. Bjorkman, S. Mehandru, P.D. Bieniasz, M. Caskey, M.C. Nussenzweig, Evolution of antibody immunity to SARS-CoV-2, Nature (2021), https://doi.org/10.1038/s41586-021-03207-w.

[24] I. Quast, D. Tarlinton, B cell memory: understanding COVID-19, Immunity 54 (2021) 205–210, https://doi.org/10.1016/j.immuni.2021.01.014.

[25] J.E. Kohlmeier, D.L. Woodland, Immunity to respiratory viruses, Annu. Rev. Immunol. 27 (2009) 61–82, https://doi.org/10.1146/annurev.immunol.021908.132625.

[26] K. Karikó, H. Muramatsu, F.A. Welsh, J. Ludwig, H. Kato, S. Akira, D. Weissman, Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability, Mol. Ther. 16 (2008) 1833–1840, https://doi.org/10.1038/mt.2008.200.

[27] N. Pardi, S. Tuyishime, H. Muramatsu, K. Kariko, B.L. Mui, Y.K. Tam, T.D. Madden, M.J. Hope, D. Weissman, Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes, J. Control. Release 217 (2015) 345–351, https://doi.org/10.1016/j.jconrel.2015.08.007.

[28] M.A. Maier, M. Jayaraman, S. Matsuda, J. Liu, S. Barros, W. Querbes, Y.K. Tam, S. M. Ansell, V. Kumar, J. Qin, X. Zhang, Q. Wang, S. Panesar, R. Hutabarat, M. Carioto, J. Hettinger, P. Kandasamy, D. Butler, K.G. Rajeev, B. Pang, K. Charisse, K. Fitzgerald, B.L. Mui, X. Du, P. Cullis, T.D. Madden, M.J. Hope, M. Manoharan, A. Akinc, Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics, Mol. Ther. 21 (2013) 1570–1578, https://doi.org/10.1038/mt.2013.124.

[29] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.-L. Hsieh, O. Abiona, B. S. Graham, J.S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (2020) 1260–1263, https://doi.org/10.1126/science.abb2507.

[30] E.E. Walsh, R.W. Frenck, A.R. Falsey, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, K. Neuzil, M.J. Mulligan, R. Bailey, K.A. Swanson, P. Li, K. Koury, W. Kalina, D. Cooper, C. Fontes-Garfias, P.-Y. Shi, Ö. Türeci, K.R. Tompkins, K. E. Lyke, V. Raabe, P.R. Dormitzer, K.U. Jansen, U. Şahin, W.C. Gruber, Safety and immunogenicity of two RNA-Based Covid-19 vaccine candidates, N. Engl. J. Med. 383 (2020) 2439–2450, https://doi.org/10.1056/NEJMoa2027906.

[31] L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S. D. Schmidt, P.A. Swanson, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, J.H. Beigel, mRNA-1273 Study Group, An mRNA Vaccine against SARS-CoV-2 - Preliminary Report, N. Engl. J. Med. 383 (2020) 1920–1931, https://doi.org/10.1056/NEJMoa2022483.

[32] E.J. Anderson, N.G. Rouphael, A.T. Widge, L.A. Jackson, P.C. Roberts, M. Makhene, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. B. McDermott, B. Flach, B.C. Lin, N.A. Doria-Rose, S. O'Dell, S.D. Schmidt, K. S. Corbett, P.A. Swanson, M. Padilla, K.M. Neuzil, H. Bennett, B. Leav, M. Makowski, J. Albert, K. Cross, V.V. Edara, K. Floyd, M.S. Suthar, D.R. Martinez, R. Baric, W. Buchanan, C.J. Luke, V.K. Phadke, C.A. Rostad, J.E. Ledgerwood, B. S. Graham, J.H. Beigel, mRNA-1273 study group, safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults, N. Engl. J. Med. 383 (2020) 2427–2438, https://doi.org/10.1056/NEJMoa2028436.

[33] S. Amit, G. Regev-Yochay, A. Afek, Y. Kreiss, E. Leshem, Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients, Lancet (2021), https://doi.org/10.1016/S0140-6736(21)00448-7.

[34] H. Rossman, S. Shilo, T. Meir, M. Gorfine, U. Shalit, E. Segal, Patterns of COVID-19 pandemic dynamics following deployment of a broad national immunization program, MedRxiv (2021), https://doi.org/10.1101/2021.02.08.21251325, 2021.02.08.21251325.

[35] C. Pawlowski, P. Lenehan, A. Puranik, V. Agarwal, A.J. Venkatakrishnan, M. J. Niesen, J.C.O. Horo, A.D. Badley, J. Halamka, V. Soundararajan, FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system, MedRxiv (2021), https://doi.org/10.1101/2021.02.15.21251623, 2021.02.15.21251623.

[36] G. Nemerow, J. Flint, Lessons learned from adenovirus (1970–2019), FEBS Lett. 593 (2019) 3395–3418, https://doi.org/10.1002/1873-3468.13700.

[37] I. Khatun, Adenoviral Vectors, Materials and Methods, 2020. /method/Adenoviral-Vectors.html.

[38] A. Ricobaraza, M. Gonzalez-Aparicio, L. Mora-Jimenez, S. Lumbreras, R. Hernandez-Alcoceba, High-capacity adenoviral vectors: expanding the scope of gene therapy, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21103643.

[39] S. Zhang, W. Huang, X. Zhou, Q. Zhao, Q. Wang, B. Jia, Seroprevalence of neutralizing antibodies to human adenoviruses type-5 and type-26 and chimpanzee adenovirus type-68 in healthy Chinese adults, J. Med. Virol. 85 (2013) 1077–1084, https://doi.org/10.1002/jmv.23546.

[40] J. Ersching, M.I.M. Hernandez, F.S. Cezarotto, J.D.S. Ferreira, A.B. Martins, W. M. Switzer, Z. Xiang, H.C.J. Ertl, C.R. Zanetti, A.R. Pinto, Neutralizing antibodies to human and simian adenoviruses in humans and New-World monkeys, Virology 407 (2010) 1–6, https://doi.org/10.1016/j.virol.2010.07.043.

[41] P. Abbink, A.A.C. Lemckert, B.A. Ewald, D.M. Lynch, M. Denholtz, S. Smits, L. Holterman, I. Damen, R. Vogels, A.R. Thorner, K.L. O'Brien, A. Carville, K. G. Mansfield, J. Goudsmit, M.J.E. Havenga, D.H. Barouch, Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D, J. Virol. 81 (2007) 4654–4663, https://doi.org/10.1128/JVI.02696-06.

[42] F.-C. Zhu, X.-H. Guan, Y.-H. Li, J.-Y. Huang, T. Jiang, L.-H. Hou, J.-X. Li, B.-F. Yang, L. Wang, W.-J. Wang, S.-P. Wu, Z. Wang, X.-H. Wu, J.-J. Xu, Z. Zhang, S.-Y. Jia, B.-S. Wang, Y. Hu, J.-J. Liu, J. Zhang, X.-A. Qian, Q. Li, H.-X. Pan, H.-D. Jiang, P. Deng, J.-B. Gou, X.-W. Wang, X.-H. Wang, W. Chen, Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial, Lancet 396 (2020) 479–488, https://doi.org/10.1016/S0140-6736(20)31605-6.

[43] D.Y. Logunov, I.V. Dolzhikova, O.V. Zubkova, A.I. Tukhvatulin, D. V. Shcheblyakov, A.S. Dzharullaeva, D.M. Grousova, A.S. Erokhova, A. V. Kovyrshina, A.G. Botikov, F.M. Izhaeva, O. Popova, T.A. Ozharovskaya, I. B. Esmagambetov, I.A. Favorskaya, D.I. Zrelkin, D.V. Voronina, D.N. Shcherbinin, A.S. Semikhin, Y.V. Simakova, E.A. Tokarskaya, N.L. Lubenets, D.A. Egorova, M. M. Shmarov, N.A. Nikitenko, L.F. Morozova, E.A. Smolyarchuk, E.V. Kryukov, V. F. Babira, S.V. Borisevich, B.S. Naroditsky, A.L. Gintsburg, Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia, Lancet 396 (2020) 887–897, https://doi.org/10.1016/S0140-6736(20)31866-3.

[44] J. Sadoff, M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A.M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P.-J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K.E. Stephenson, S.C. De Rosa, K.W. Cohen, M.J. McElrath, E. Cormier, G. Scheper, D.H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, H. Schuitemaker, Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine, N. Engl. J. Med. (2021), https://doi.org/10.1056/NEJMoa2034201.

[45] N.A. Hutnick, D. Carnathan, K. Demers, G. Makedonas, H.C.J. Ertl, M.R. Betts, Adenovirus-specific human T cells are pervasive, polyfunctional, and cross-reactive, Vaccine 28 (2010) 1932–1941, https://doi.org/10.1016/j.vaccine.2009.10.091.

[46] K.J. Ewer, J.R. Barrett, S. Belij-Rammerstorfer, H. Sharpe, R. Makinson, R. Morter, A. Flaxman, D. Wright, D. Bellamy, M. Bittaye, C. Dold, N.M. Provine, J. Aboagye, J. Fowler, S.E. Silk, J. Alderson, P.K. Aley, B. Angus, E. Berrie, S. Bibi, P. Cicconi, E. A. Clutterbuck, I. Chelysheva, P.M. Folegatti, M. Fuskova, C.M. Green, D. Jenkin, S. Kerridge, A. Lawrie, A.M. Minassian, M. Moore, Y. Mujadidi, E. Plested, I. Poulton, M.N. Ramasamy, H. Robinson, R. Song, M.D. Snape, R. Tarrant, M. Voysey, M.E.E. Watson, A.D. Douglas, A.V.S. Hill, S.C. Gilbert, A.J. Pollard, T. Lambe, Oxford COVID Vaccine Trial Group, T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial, Nat. Med. (2020), https://doi.org/10.1038/s41591-020-01194-5.

[47] J.R. Barrett, S. Belij-Rammerstorfer, C. Dold, K.J. Ewer, P.M. Folegatti, C. Gilbride, R. Halkerston, J. Hill, D. Jenkin, L. Stockdale, M.K. Verheul, P.K. Aley, B. Angus, D. Bellamy, E. Berrie, S. Bibi, M. Bittaye, M.W. Carroll, B. Cavell, E.A. Clutterbuck, N. Edwards, A. Flaxman, M. Fuskova, A. Gorringe, B. Hallis, S. Kerridge, A. M. Lawrie, A. Linder, X. Liu, M. Madhavan, R. Makinson, J. Mellors, A. Minassian, M. Moore, Y. Mujadidi, E. Plested, I. Poulton, M.N. Ramasamy, H. Robinson, C. S. Rollier, R. Song, M.D. Snape, R. Tarrant, S. Taylor, K.M. Thomas, M. Voysey, M. E.E. Watson, D. Wright, A.D. Douglas, C.M. Green, A.V.S. Hill, T. Lambe, S. Gilbert, A.J. Pollard, Oxford COVID Vaccine Trial Group, Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses, Nat. Med. (2020), https://doi.org/10.1038/s41591-020-01179-4.

[48] M. Voysey, S.A. Costa Clemens, S.A. Madhi, L.Y. Weckx, P.M. Folegatti, P.K. Aley, et al., Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK, Lancet 397 (2012) 99–111, https://doi.org/10.1016/S0140-6736(20)32661-1.

[49] M.N. Ramasamy, A.M. Minassian, K.J. Ewer, A.L. Flaxman, P.M. Folegatti, D. R. Owens, M. Voysey, P.K. Aley, B. Angus, G. Babbage, S. Belij-Rammerstorfer, L. Berry, S. Bibi, M. Bittaye, K. Cathie, H. Chappell, S. Charlton, P. Cicconi, E. A. Clutterbuck, R. Colin-Jones, C. Dold, K.R.W. Emary, S. Fedosyuk, M. Fuskova, D. Gbesemete, C. Green, B. Hallis, M.M. Hou, D. Jenkin, C.C.D. Joe, E.J. Kelly, S. Kerridge, A.M. Lawrie, A. Lelliott, M.N. Lwin, R. Makinson, N.G. Marchevsky, Y. Mujadidi, A.P.S. Munro, M. Pacurar, E. Plested, J. Rand, T. Rawlinson, S. Rhead,

H. Robinson, A.J. Ritchie, A.L. Ross-Russell, S. Saich, N. Singh, C.C. Smith, M. D. Snape, R. Song, R. Tarrant, Y. Themistocleous, K.M. Thomas, T.L. Villafana, S. C. Warren, M.E.E. Watson, A.D. Douglas, A.V.S. Hill, T. Lambe, S.C. Gilbert, S. N. Faust, A.J. Pollard, Oxford COVID Vaccine Trial Group, Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial, Lancet 396 (2021) 1979–1993, https://doi.org/10.1016/S0140-6736(20)32466-1.

[50] J. Yu, S. Zhao, H. Rao, Whole genomic analysis of a potential recombinant human adenovirus type 1 in Qinghai plateau, China, Virol. J. 17 (2020) 111, https://doi.org/10.1186/s12985-020-01387-x.

[51] W. Zhang, L. Huang, Genome analysis of a novel recombinant human adenovirus type 1 in China, Sci. Rep. 9 (2019) 4298, https://doi.org/10.1038/s41598-018-37756-4.

[52] Y. Wang, Y. Li, R. Lu, Y. Zhao, Z. Xie, J. Shen, W. Tan, Phylogenetic evidence for intratypic recombinant events in a novel human adenovirus C that causes severe acute respiratory infection in children, Sci. Rep. 6 (2016) 23014, https://doi.org/10.1038/srep23014.

[53] C. Keech, G. Albert, I. Cho, A. Robertson, P. Reed, S. Neal, J.S. Plested, M. Zhu, S. Cloney-Clark, H. Zhou, G. Smith, N. Patel, M.B. Frieman, R.E. Haupt, J. Logue, M. McGrath, S. Weston, P.A. Piedra, C. Desai, K. Callahan, M. Lewis, P. Price-Abbott, N. Formica, V. Shinde, L. Fries, J.D. Lickliter, P. Griffin, B. Wilkinson, G. M. Glenn, Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine, N. Engl. J. Med. 383 (2020) 2320–2332, https://doi.org/10.1056/NEJMoa2026920.

[54] S. Xia, Y. Zhang, Y. Wang, H. Wang, Y. Yang, G.F. Gao, W. Tan, G. Wu, M. Xu, Z. Lou, W. Huang, W. Xu, B. Huang, H. Wang, W. Wang, W. Zhang, N. Li, Z. Xie, L. Ding, W. You, Y. Zhao, X. Yang, Y. Liu, Q. Wang, L. Huang, Y. Yang, G. Xu, B. Luo, W. Wang, P. Liu, W. Guo, X. Yang, Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial, Lancet Infect. Dis. 21 (2021) 39–51, https://doi.org/10.1016/S1473-3099(20)30831-8.

[55] S. Perlman, A.A. Dandekar, Immunopathogenesis of coronavirus infections: implications for SARS, Nat. Rev. Immunol. 5 (2005) 917–927, https://doi.org/10.1038/nri1732.

[56] M.S. Yip, N.H.L. Leung, C.Y. Cheung, P.H. Li, H.H.Y. Lee, M. Daëron, J.S.M. Peiris, R. Bruzzone, M. Jaume, Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus, Virol. J. 11 (2014) 82, https://doi.org/10.1186/1743-422X-11-82.

[57] L. Liu, Q. Wei, Q. Lin, J. Fang, H. Wang, H. Kwok, H. Tang, K. Nishiura, J. Peng, Z. Tan, T. Wu, K.-W. Cheung, K.-H. Chan, X. Alvarez, C. Qin, A. Lackner, S. Perlman, K.-Y. Yuen, Z. Chen, Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection, JCI Insight 4 (2019), https://doi.org/10.1172/jci.insight.123158.

[58] A.M. Arvin, K. Fink, M.A. Schmid, A. Cathcart, R. Spreafico, C. Havenar-Daughton, A. Lanzavecchia, D. Corti, H.W. Virgin, A perspective on potential antibody-dependent enhancement of SARS-CoV-2, Nature 584 (2020) 353–363, https://doi.org/10.1038/s41586-020-2538-8.

[59] W.S. Lee, A.K. Wheatley, S.J. Kent, B.J. DeKosky, Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies, Nat. Microbiol. 5 (2020) 1185–1191, https://doi.org/10.1038/s41564-020-00789-5.

[60] J.K. DeMarco, W. Severson, D. DeMarco, G. Pogue, J.D. Gabbard, K.E. Palmer, At the intersection between SARS-CoV-2, macrophages and the adaptive immune response: a key role for antibody-dependent pathogenesis but not enhancement of infection in COVID-19, BioRxiv (2021), https://doi.org/10.1101/2021.02.22.432407, 2021.02.22.432407.

[61] S. Sridhar, A. Luedtke, E. Langevin, M. Zhu, M. Bonaparte, T. Machabert, S. Savarino, B. Zambrano, A. Moureau, A. Khromava, Z. Moodie, T. Westling, C. Mascareñas, C. Frago, M. Cortés, D. Chansinghakul, F. Noriega, A. Bouckenooghe, J. Chen, S.-P. Ng, P.B. Gilbert, S. Gurunathan, C. A. DiazGranados, Effect of dengue serostatus on dengue vaccine safety and efficacy, N. Engl. J. Med. 379 (2018) 327–340, https://doi.org/10.1056/NEJMoa1800820.

[62] P.M. Taylor, B.A. Askonas, Influenza nucleoprotein-specific cytotoxic T-cell clones are protective in vivo, Immunology 58 (1986) 417–420.

[63] B.S. Graham, L.A. Bunton, P.F. Wright, D.T. Karzon, Role of T lymphocyte subsets in the pathogenesis of primary infection and rechallenge with respiratory syncytial virus in mice, J. Clin. Invest. 88 (1991) 1026–1033, https://doi.org/10.1172/JCI115362.

[64] J. Zhao, J. Zhao, S. Perlman, T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice, J. Virol. 84 (2010) 9318–9325, https://doi.org/10.1128/JVI.01049-10.

[65] A. Grifoni, D. Weiskopf, S.I. Ramirez, J. Mateus, J.M. Dan, C.R. Moderbacher, S. A. Rawlings, A. Sutherland, L. Premkumar, R.S. Jadi, D. Marrama, A.M. de Silva, A. Frazier, A.F. Carlin, J.A. Greenbaum, B. Peters, F. Krammer, D.M. Smith, S. Crotty, A. Sette, Targets of t cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals, Cell 181 (2020) 1489–1501, https://doi.org/10.1016/j.cell.2020.05.015, e15.

[66] J. Braun, L. Loyal, M. Frentsch, D. Wendisch, P. Georg, F. Kurth, S. Hippenstiel, M. Dingeldey, B. Kruse, F. Fauchere, E. Baysal, M. Mangold, L. Henze, R. Lauster, M.A. Mall, K. Beyer, J. Röhmel, S. Voigt, J. Schmitz, S. Miltenyi, I. Demuth, M. A. Müller, A. Hocke, M. Witzenrath, N. Suttorp, F. Kern, U. Reimer, H. Wenschuh, C. Drosten, V.M. Corman, C. Giesecke-Thiel, L.E. Sander, A. Thiel, SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19, Nature 587 (2020) 270–274, https://doi.org/10.1038/s41586-020-2598-9.

[67] L. Ni, F. Ye, M.-L. Cheng, Y. Feng, Y.-Q. Deng, H. Zhao, P. Wei, J. Ge, M. Gou, X. Li, L. Sun, T. Cao, P. Wang, C. Zhou, R. Zhang, P. Liang, H. Guo, X. Wang, C.-F. Qin, F. Chen, C. Dong, Detection of SARS-CoV-2-Specific humoral and cellular immunity in COVID-19 convalescent individuals, Immunity 52 (2020) 971–977, https://doi.org/10.1016/j.immuni.2020.04.023, e3.

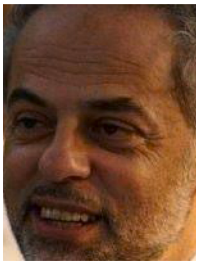
[68] D. Weiskopf, K.S. Schmitz, M.P. Raadsen, A. Grifoni, N.M.A. Okba, H. Endeman, J. P.C. van den Akker, R. Molenkamp, M.P.G. Koopmans, E.C.M. van Gorp, B. L. Haagmans, R.L. de Swart, A. Sette, R.D. de Vries, Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome, Sci. Immunol. 5 (2020), https://doi.org/10.1126/sciimmunol.abd2071.

[69] T. Sekine, A. Perez-Potti, O. Rivera-Ballesteros, K. Strålin, J.-B. Gorin, A. Olsson, S. Llewellyn-Lacey, H. Kamal, G. Bogdanovic, S. Muschiol, D.J. Wullimann, T. Kammann, J. Emgård, T. Parrot, E. Folkesson, Karolinska COVID-19 Study Group, O. Rooyackers, L.I. Eriksson, J.-I. Henter, A. Sönnerborg, T. Allander, J. Albert, M. Nielsen, J. Klingström, S. Gredmark-Russ, N.K. Björkström, J. K. Sandberg, D.A. Price, H.-G. Ljunggren, S. Aleman, M. Buggert, Robust t cell immunity in convalescent individuals with asymptomatic or mild COVID-19, Cell 183 (2020) 158–168, https://doi.org/10.1016/j.cell.2020.08.017, e14.

[70] N. Le Bert, A.T. Tan, K. Kunasegaran, C.Y.L. Tham, M. Hafezi, A. Chia, M.H. Y. Chng, M. Lin, N. Tan, M. Linster, W.N. Chia, M.I.-C. Chen, L.-F. Wang, E.E. Ooi, S. Kalimuddin, P.A. Tambyah, J.G.-H. Low, Y.-J. Tan, A. Bertoletti, SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls, Nature 584 (2020) 457–462, https://doi.org/10.1038/s41586-020-2550-z.

[71] W.F. Garcia-Beltran, E.C. Lam, K.S. Denis, A.D. Nitido, Z.H. Garcia, B.M. Hauser, J. Feldman, M.N. Pavlovic, D.J. Gregory, M.C. Poznansky, A. Sigal, A.G. Schmidt, A.J. Iafrate, V. Naranbhai, A.B. Balazs, Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity, MedRxiv (2021), https://doi.org/10.1101/2021.02.14.21251704, 2021.02.14.21251704.

[72] D. Planas, T. Bruel, L. Grzelak, F. Guivel-Benhassine, I. Staropoli, F. Porrot, C. Planchais, J. Buchrieser, M. M. Rajah, E. Bishop, M. Albert, F. Donati, S. Behillil, V. Enouf, M. Maquart, M. Gonzalez, J. De Sèze, H. Péré, D. Veyer, A. Sève, E. Simon Lorière, S. Fafi-Kremer, K. Stefic, H. Mouquet, L. Hocqueloux, S. van der Werf, T. Prazuck, O. Schwartz, Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies bioRxiv, (n.d.). https://www.biorxiv.org/content/10.1101/2021.02.12.430472v1.



Maurizio Federico started his scientific career in the Virology Laboratory at the Istituto Superiore di Sanità (ISS), Rome, Italy, headed by Prof. G.B. Rossi. He spent the first 5 years studying the antiviral/differentiation effects of interferon, as well as different molecular aspects of the erythroleukemia differentiation. Afterwards, as part of the Virology laboratory of the Italian Ministry of Health, he actively contributed to the isolation and characterization of HIV-1 isolates circulating in Italy. In this context, he decisively participated to the first molecular cloning and sequencing of an HIV-1 isolate from an Italian patient. In the late' 90, he became leader of a scientific team focused on HIV basic research at the Virology Department of the ISS. Recently, he developed both basic and translational investigations on exosomes and extracellular vesicles, with the goal to understand their role in HIV-1 pathogenesis. In addition, these activities represented a starting point for the implementation of an original platform for the production of CTL vaccines against infectious diseases (included SARS-CoV-2) and tumors based on the unique molecular characteristics of an HIV-1 Nef mutant. At the present he acts as Director of the National Center for Global Health at ISS.