Advanced Materials for SARS-CoV-2 Vaccines

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The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), has killed untold millions worldwide and has hurtled vaccines into the spotlight as a go-to approach to mitigate it. Advances in virology, genomics, structural biology, and vaccine technologies have enabled a rapid and unprecedented rollout of COVID-19 vaccines, although much of the developing world remains unvaccinated. Several new vaccine platforms have been developed or deployed against SARS-CoV-2, with most targeting the large viral Spike immunogen. Those that safely induce strong and durable antibody responses at low dosages are advantageous, as well are those that can be rapidly produced at a large scale. Virtually all COVID-19 vaccines and adjuvants possess nanoscale or microscale dimensions and represent diverse and unique biomaterials. Viral vector vaccine platforms, lipid nanoparticle mRNA vaccines and multimeric display technologies for subunit vaccines have received much attention. Nanoscale vaccine adjuvants have also been used in combination with other vaccines. To deal with the ongoing pandemic, and to be ready for potential future ones, advanced vaccine technologies will continue to be developed in the near future. Herein, the recent use of advanced materials used for developing COVID-19 vaccines is summarized.

1. Introduction

In two years, SARS-CoV-2 has reshaped the world, infecting hundreds of millions of people, killing millions, and severely impacting the entire human population. Vaccines are a centerpiece for strategies to overcome pandemics. They depend on delivering antigens to the immune system to trigger an adaptive immune response, effected in large part by cytotoxic CD8^{+} T cells that destroy infected cells, and virus neutralizing antibodies secreted by B cells. SARS-CoV-2 is a complex enveloped single-stranded RNA coronavirus encoding 11 open reading frames in its genome as illustrated in **Figure 1**A.[1] The Spike (S) glycoprotein has been the central focus for most vaccine

development, since it mediates viral entry and induces neutralizing antibody responses, which are predictive of protection from symptomatic SARS-CoV-2 infection.[2,3] As waves of new viral variants emerge, other targets such as the membrane (M), envelope (E), or nucleocapsid (N) proteins may emerge as complementary vaccine antigens to help increase breadth of protection.[4]

S forms a homotrimeric structure comprising two domains, S1 and S2, separated by a Furin cleavage site (FCS).[5,6] S1 contains the receptor binding domain (RBD) which binds to human angiotensin converting enzyme 2 (hACE2) on host cells. Subsequently, proteolytic cleavage by Furin and by Transmembrane protease serine 2 (TMPRSS2) at the FCS and just upstream of the fusion peptide, respectively, activates the S2 fusion machinery leading to viral entry.[7] S is a class I fusion glycoprotein that undergoes major structural rearrangements from prefusion to post-fusion conformation during viral fusion to host cell membranes. It was previously shown that prefusion-stabilized class I fusion protein antigens better preserve neutralization epitopes for viruses including respiratory syncytial virus (RSV) fusion (F) glycoprotein.[8] Similar to the Middle East respiratory syndrome coronavirus (MERS-CoV) S protein,[9] two proline substitutions (2P) at residues 986 and 987 at the C-terminal boundary of the first heptad repeat were found to stabilize SARS-CoV-2 S in its prefusion conformation.[10] These 2P stabilizing mutations have been widely adopted in many SARS-CoV-2 vaccines including the Moderna mRNA-1273 vaccine (Spikevax), the Pfizer/BioNTech BNT162b2 vaccine (Comirnaty), the Novavax NVX-CoV2373 vaccine (Nuvaxovid), and the Johnson and Johnson Ad26.CoV2.S vaccine (Janssen COVID-19 Vaccine).[11] In contrast, the AstraZeneca/Oxford ChAdOx1 nCoV-19/AZD1222 (Vaxzevria) antigen uses the wildtype SARS-CoV-2 S sequence and cells transduced with the adenovirus-vectored vaccine produce intact trimeric S, albeit with some proteolytic S degradation.[12] To mitigate this, another common antigen enhancement strategy used by NVX-CoV2373[13] and Ad26.CoV2.S[14] for example, is to insert mutations or deletions at the proteolytic-prone FCS to improve antigen stability and preserve immunogenicity.

As shown in the schematic illustration in Figure 1B, COVID-19 vaccines have taken on a wide variety of formats. **Table 1** lists some of the vaccine types that have reported peer-reviewed phase 3 clinical trial results so far.[16] Various advanced materials have emerged as vaccines for the S subunit antigen

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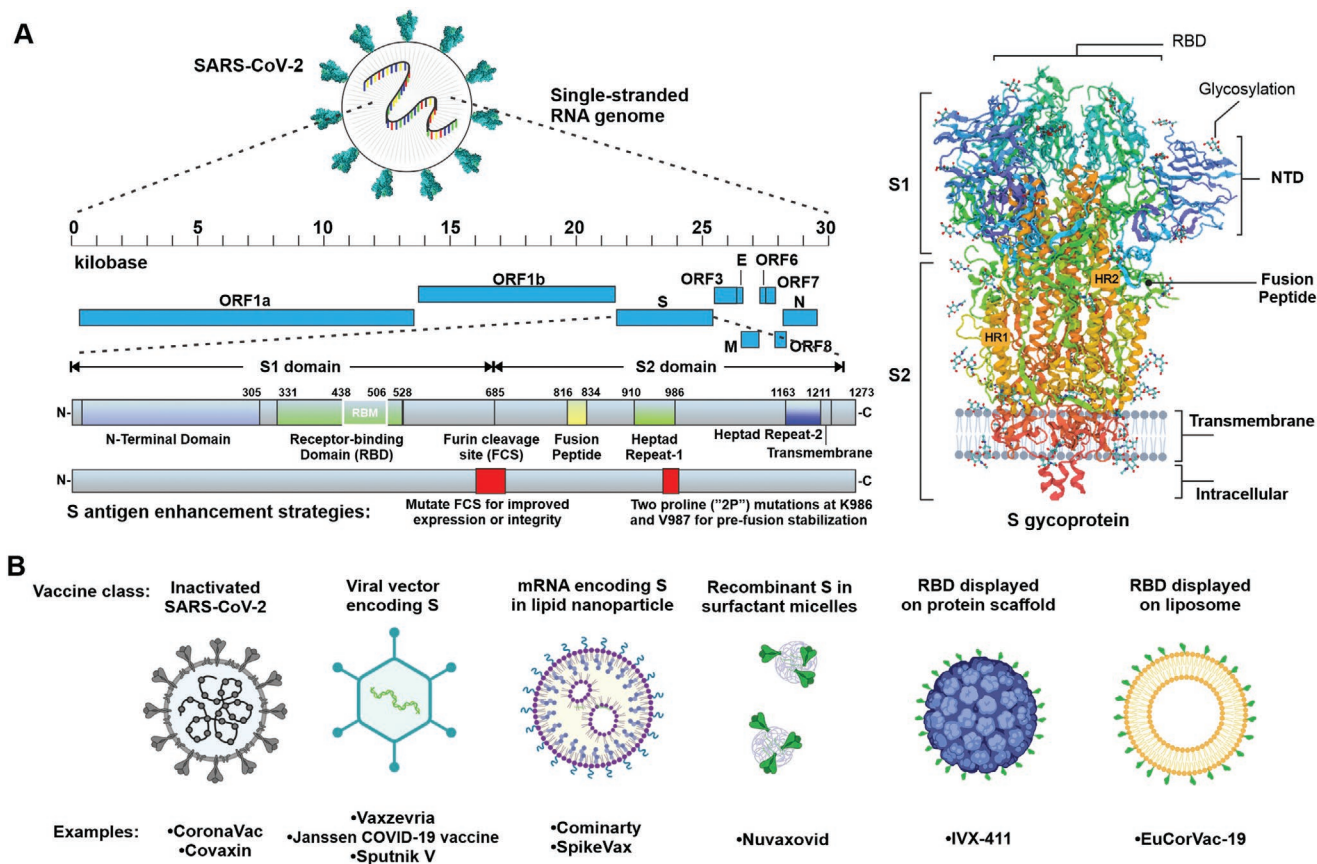
Figure 1. The SARS-CoV-2 genome, the S glycoprotein, and representative vaccine strategies. A) Schematic representation of the SARS-CoV-2 genome and its S glycoprotein with some notable features. The right panel indicates the structure of S (PDB ID: 6VXX). B) Representative SARS-CoV-2 vaccine classes. Trade name examples are provided below the schematic illustrations. The left part of (A) is adapted under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[15] Copyright 2020, The Authors, published by Frontiers. Parts of Figure 1 created with Biorender.com.

itself or the genetic code encoding for it, allowing in situ production of the protein inside the host cells.[17] Adjuvants have also been used to boost the immune reaction through multiple mechanisms including antigen depot effect, enhanced antigen presentation and cellular uptake through particle formation, induction of chemokines and cytokines, immune cell recruitment at the injection site, and promoting antigen transport to draining lymph nodes.[18,19]

Synthetic mRNA has emerged to greatly shape the COVID-19 vaccine response. mRNA can be used for in situ production of antigenic proteins in a safe and highly modular manner. Once a vaccine system is developed, developing a vaccine with a different nucleic acid sequence for a different target antigen is simpler and faster than for a recombinant protein. Although mRNA is less stable than DNA, it eliminates the need for nuclear targeting and in vivo transcription, as well

Table 1. COVID-19 vaccines with peer-reviewed phase III clinical trial data available.

Vaccine type	Names	Developer	Antigen	Adjuvant/excipient	Ref.
mRNA	BNT162b2/Comirnaty	Pfizer/BioNTech	S	Cationic lipid	[20]
	mRNA-1273/SpikeVax	Moderna			[21]
	CVnCoV	CureVac			[22]
Non-replicating adenovirus	AZD1222/Vaxzevria	AstraZeneca	S	None	[23]
	Sputnik V	Gamaleya			[24]
	Ad26.COV2.S/Janssen Covid-19 Vaccine	Johnson and Johnson			[25]
Inactivated Virus	BBIBP-CorV	Sinopharm	Whole virus	Alum	[26]
	CoronaVac	Sinovac			[27]
Protein subunit	Nuvaxovid/NVX-CoV2373	Novavax	S	Matrix-M	[28]

as the potential hazard of genetic integration.[29] mRNA technology has been investigated not for only vaccines, but also to generate virus-neutralizing ACE2 decoys.[30] The high molecular weight of nucleic acids and their strong negative charge impedes their delivery across the cell membranes, in addition to being prone to degradation in vivo. Thus, nucleic acid vaccines require delivery systems. Synthetic nanocarriers such as cationic polymers and lipid nanoparticles (LNPs) can be used for the delivery of mRNA vaccines across cell membranes.[31] The Pfizer/BioNTech mRNA-1273 and Moderna BNT162b2 vaccines have been highly successful, launching a new era of mRNA vaccines. The replication-incompetent adenovirus type viral-vector vaccines by Janssen and AstraZeneca have also seen global deployment as novel vaccine platforms. Over 15 different vaccines have been approved or authorized for emergency use worldwide, and the landscape is rapidly changing, with hundreds of candidates in various stages of clinical testing.[32] Not only are a wide variety of new vaccine technologies advancing through clinical trials, but clinical testing is also changing. Placebo controlled trials are becoming increasingly difficult to plan as populations become vaccinated and exposed to SARS-CoV-2, and thus some recent vaccine trials make use of an established comparator vaccine, with an endpoint of comparative neutralizing antibody titers. Current vaccines were designed against the S sequence of the Wuhan SARS-CoV-2 strain, and while vaccine-induced antibodies neutralize the prevalent circulating variants such as Beta and Delta, they do so with diminished potency.[33,34] As more mutated variants emerge in the future, redesigned antigens and accompanying new iterations of vaccines may be required to deal with them.

Several prior literature reviews have summarized COVID-19 vaccine design,[35–37] antigen design,[11,38] vaccine pipelines,[39–41] including with a focus on nanotechnology[42,43] and nanomaterials,[42,43] and biomimetic materials.[44] In this review, design and optimization of SARS-CoV-2 antigens and materials used for their delivery and adjuvantation are reviewed. Inactivated and viral vectored vaccine platforms, which are successful and important classes of COVID-19 vaccines are not discussed herein, given that their entirely viral nature shifts their discussion beyond the scope of antigen engineering or vaccine formulation using exogenous biomaterials.

2. Antigen Design

The SARS-CoV-2 lipid bilayer outer surface includes the M, E, and S structural proteins. The sera of mice immunized while M and E proteins show minimal neutralization activity, and these antigens are not currently being widely pursued.[45] The S glycoprotein, which forms trimeric structures of S1–S2 heterodimers on the virus surface is responsible for binding to hACE2 and cell entry. The S1 subunit contains the RBD which can adopts two distinct conformations: "up" or "down", and only the "up" conformation exposes the receptor-binding site ,[46] while the S2 subunit comprises the fusion peptide and heptad repeat (HR) regions 1 and 2 (Figure 1A). After receptor mediated endocytosis, S1 is cleaved away, which facilitates the fusion peptide insertion into the host cell membrane bringing HR1 and HR2 together which allows the fusion of the viral and host cell membranes.[47] The S glycoprotein is the main target antigen for most advanced vaccines.

Full-length S harbors multiple neutralizing epitopes[48] and T cell epitopes, is large (1200 amino acids), contains a hydrophobic transmembrane domain, and can present challenges for maintaining antigen integrity, relative to the smaller RBD.[38] The RBD is promising as a target for eliciting neutralizing antibodies as it is less glycosylated than S, which can increase its immunogenicity and it induces a high frequency of neutralizing antibodies.[49,50] On the other hand, the smaller molecular weight of RBD can decrease its immunogenicity, making it a target for multimerization strategies using advanced materials. Such delivery platforms should be flexible enough for rapid readjustment and adaptation to deal with viral variants with mutations that escape neutralization.[51] As shown in **Figure 2**, nanoparticulate vaccination approaches have several potential advantages. Compared to small and compact antigens, nanoparticles are better delivered through phagocytosis and endocytosis to immune cells in draining lymph nodes.[52] In addition, usually such multimeric display technologies are compatible with multivalent antigen display. For example, the SpyCatcher multimerization technology has been used to display multiple copies of the RBD from various beta-coronaviruses to induce broadly neutralizing antibodies.[53] Antigen density can often be tuned with nanoparticle-displayed antigens, which can lead to enhancement in B-cell receptor engagement and subsequent B cell activation.[54] Finally, some antigen display platforms enable the cellular co-delivery of antigens and adjuvants simultaneously. This presents potential advantages of activating the same antigen-presenting cells that take up the vaccine antigens, leading to more effective responses.

2.1. mRNA Vaccines

mRNA vaccines emerged in the pandemic as effective and rapidly producible COVID-19 vaccines. The related DNA vaccines that preceded mRNA vaccines were in testing for several decades,[55] and the recent success mRNA vaccines has been enabled by gradual advances in mRNA modification, stabilization, and delivery methods.[56–58] mRNA vaccines will be a major focus for research and development efforts for the foreseeable future.[59] Compared to DNA, mRNA molecules are smaller, are transcribed in vitro, so they bypass the in vivo transcription process, but have been prone to biochemical degradation and induction of undesirable type I interferon immune responses. As shown in **Figure 3**, several mRNA modification strategies have emerged. The major features of an mRNA molecule, namely the 5′ cap, the 5′ untranslated region (UTR), the coding sequence, the 3′ UTR, and the polyadenenosine tail are all targets for optimization.[60] These modifications generally serve to improve the in vitro transcription, in vivo translation or stability of the molecule. In addition, the use of modified bases, especially N1-methylpseudouridine (N1mΨ) in place of uridine, used in both the Pfizer/BioNTech BNT162b2 and the Moderna mRNA-127 vaccines, diminishes the undesirable type I interferon immune response, in addition to improving stability.[61] An emerging approach to mRNA vaccines is the development of self-amplifying RNA (saRNA), which encodes a replicase sequence and holds potential to reduce the injection dose and possibly the number of required injections, by extending mRNA half-life.[62]

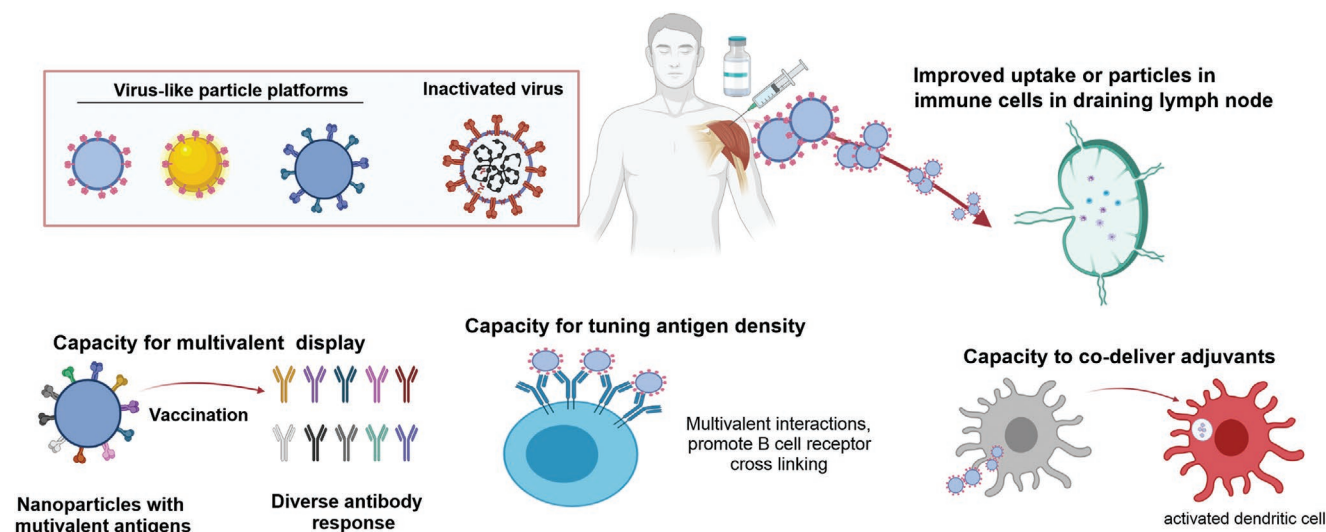Representative approaches for DNA and mRNA-based COVID-19 vaccines are listed in **Table 2**. The use of ionizable

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Figure 2. Nanoscale antigen delivery systems present potential advantages for vaccine delivery. Numerous vaccine platforms, including virus-like particles and inactivated viruses, have nanoscale dimensions and can exhibit enhanced uptake of antigen in immune cells in draining lymph nodes. In addition, antigen delivery systems can often facilitate multivalent antigen responses, have tunable antigen density and in some cases can co-deliver adjuvant along with antigen. Parts of Figure 2 created with Biorender.com.

cationic lipids for their delivery has been central for the success of the Pfizer/BioNTech BNT162b2 and the Moderna mRNA-1273 vaccines. However, numerous other materials have been used for formulation of mRNA. Although the first human approved mRNA was against COVID-19, mRNA vaccines have been in clinical testing for diseases such as HIV, rabies, influenza, and Zika virus for several years.[29]

2.2. Subunit Vaccines

Coronavirus subunit vaccines are developed based on specific viral antigenic fragments, produced as recombinant proteins.[69] Subunit vaccines have no risk of causing viral infection or genomic integration as they are devoid of genetic material. As such, subunit vaccines are generally considered to be safe and well-tolerated. The S glycoprotein and its RBD has been the subject of extensive research efforts for SARS-CoV-2 subunit vaccines. Some representative examples are shown in **Table 3**.

3. Virus-Like Particles

As a component of subunit vaccines, a protein scaffold utilizes a self-assembling protein to form a virus-like particle (VLP) which has defined size and number of monomers that can display the antigen of interest on its surface either by conjugation, genetic fusion or tag coupling.[81] As shown in **Figure 4**, the RBD in particular has been the subject of a great deal of VLP-related research, as the relatively small antigen tends to benefits from particulate presentation.

VLPs have attracted attention for infectious disease vaccines and a wide variety of nanoarchitectures can be used in their design.[85] The SpyTag/SpyCatcher technology is a method for irreversible protein ligation based on modification of domains from the surface proteins of *Streptococcus pyogenes* where an isopeptide bond can be formed specifically between the tag and the catcher.[86] Three generations of this technology have been developed with increased reaction speed.[87] The assembly of SARS-CoV-2 RBD on a SpyCatcher003-mi3 nanoparticle platform yielded 20 nm particles with no sign of aggregation (Figure 4A).[70] The resultant VLP showed binding to a range of neutralizing antibodies as well as ACE2, confirming that the RBD was displayed intact on the particle surface. RBD-SpyVLP showed stability against cold chain failures such as elevated temperatures up to 25 °C for 2 weeks and five freeze–thaw cycles. Upon immunization of mice or pigs, neutralizing humoral immune responses were observed against both S and RBD.

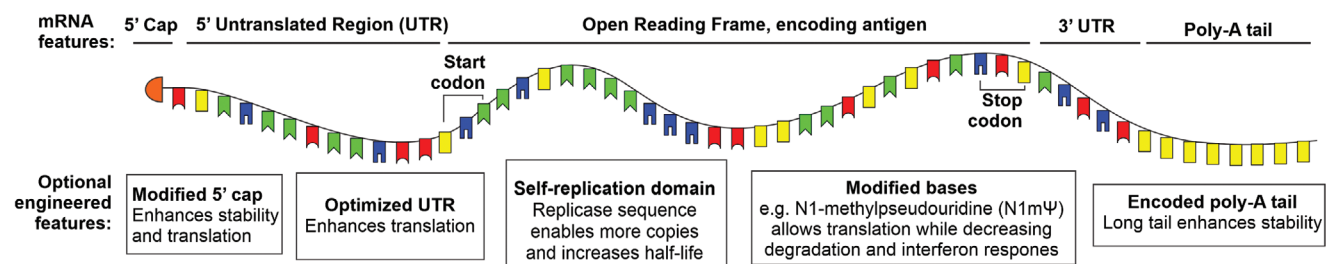To assess the effect of multiplexing of different RBDs on the same nanoparticle, mosaic nanoparticles were prepared to

Figure 3. Selected features of mRNA that can be engineered for improved vaccine efficacy.

Table 2. Representative approaches for nucleic-acid-based vaccines.

Antigen	Formulation technology	Notes	Ref.
S mRNA	Lipid nanoparticles	Safe and effective protection from COVID-19 in phase 3 clinical trials	[20,21]
RBD mRNA	Lipid nanoparticles	Single dose immunization protected hAce2 transgenic mice from SARS-CoV-2 challenge	[63]
RBD mRNA	Polyglucan–spermidine	Production of neutralizing antibodies in mice against RBD in mice	[64]
RBD mRNA	Polymeric micelle	Vitamin E succinate modified polyethyleneimine copolymer mRNA elicited antigen-specific antibodies	[65]
S DNA	Chitosan	Inhaled particles allowed cells to secrete S that competes with virus binding to ACE2 receptor	[66]
S DNA	Naked DNA	Various variants of S were used to immunize non-human primates	[67]
S DNA	Polymeric micelle	Deoxycholic acid polyethyenimine polymer encapsulated S for skin delivery and elicited neutralizing antibodies in mice	[68]

raise cross-reactive immune responses against zoonotic sarbecoviruses.[53] The RBDs were chosen based on sarbecovirus RBD receptor usage and cell tropism.[88] The chosen zoonotic RBDs were co-assembled into nanoparticles with or without SARS-CoV-2 RBD and compared to homotypic SARS-CoV-2 RBD using SpyTag/SpyCatcher technology where SpyTag003 was genetically fused to each single one and then assembled into SpyCatcher003-mi3. The resultant particles were used to immunize mice and compared to soluble RBD. Multimerizing the RBD on homotypic nanoparticles better-induced IgGs that can bind to zoonotic RBDs compared to soluble RBD or S, or natural infection.

The effect of conjugating the tag on N versus C terminus (RBDn vs RBDc) was investigated using the Tag/Catcher-AP205 platform.[71] Although both expressed well in monomeric forms, the C terminus conjugate VLP tended to aggregate while the N terminus one was monodisperse and stable. The soluble RBDs together with their VLPs were used to immunize mice and showed superior neutralization activity when in the particulate form with RBDn-VLP being superior to RBDc-VLP.

Chiba and co-workers used biotinylated variants of S so that it could be displayed on a streptavidin coated MS2 bacteriophage. The resulting S protein-coated particles were tested for immunogenicity in golden Syrian hamsters. After a single

dose, the vaccine generated neutralizing antibodies and protected hamsters from SARS-CoV-2 challenge.[80]

Artificial protein scaffolds make use of computationally designed proteins that can separate an individual protein folding subunit from the final macromolecular structure assembly. Recombinant proteins are traditionally expressed and purified, then self-assemble into VLPs when mixed. A two protein component (I53-50A and I53-50B) system was computationally designed to produce an icosahedral protein complex containing 120 subunits that assemble into 28 nm particles as shown in Figure 4B.[82] The self-assembling VLP was used to display either RBD[72] or S[73] by genetically fusing these with the I53-50A component. The RBD was genetically fused with variable linkers (RBD-8GS-, RBD-12GS-, and RBD-16GSI53-50).[72] The resultant RBD-displayed particles showed stable submicrometer size below 50 nm. Hydrogen/deuterium-exchange mass spectrometry and glycoproteomics confirmed the surface display of RBD with the native confirmation and glycosylation. The antigenicity and epitope accessibility of VLP-bound RBD were confirmed through its reactivity with human ACE2 ectodomain and two site-specific monoclonal antibodies. S protein fusions also resulted in stable nanoparticles (S-I53-50NPs) with size ≈30 nm. The VLPs were assessed in non-human primates that were immunized with 88 µg of RBD equivalent in

Table 3. Representative materials for nanoparticulate subunit vaccines.

Antigen	Binding technology	Notes	Ref.
RBD	SpyTag/SpyCatcher	Effective vaccine with 1 µg dose per mouse. Stabile with elevated temperatures and freeze–thaw cycles	[70]
Multiple RBDs		Co-display of SARS-CoV-2 and other RBDs on mosaic nanoparticles for broad antibody response	[53]
RBD		RBD particles generated with the Tag/Catcher-AP205 platform induced neutralizing antibodies	[71]
RBD	Artificial protein scaffold	RBD fusion proteins linked to I53-50A with 16 glycine and serine residues showed the best immunogenicity in the resulting particles	[72]
S		S-I53-50NPs protected macaques against dose viral challenge	[73]
RBD or S		AS03 was found to be a potent adjuvant when combined with RBD or prefusion S trimer nanoparticles	[74]
S	AuNP	Elicited anti-S antibodies in mice, but neutralizing activity was minimal	[75]
RBD peptide		S461-493-KLH conjugate induced anti-peptide antibodies	[76]
RBD	Ferritin cages	24-mer RBD self-assembling ferritin protein nanoparticles effectively induced strong neutralizing antibodies in mice	[77]
RBD		24-mer RBD bullfrog H. pylori ferritin protein nanoparticles protected ferrets from viral challenge	[78]
RBD	Cobalt liposomes	Display of RBD on liposome induced neutralizing antibodies in mice with 0.1 µg antigen doses	[79]
S	Streptavidin/biotin	MS2 bacteriophage scaffold coated with S conferred protection in hamsters after single injection of 60 µg	[80]

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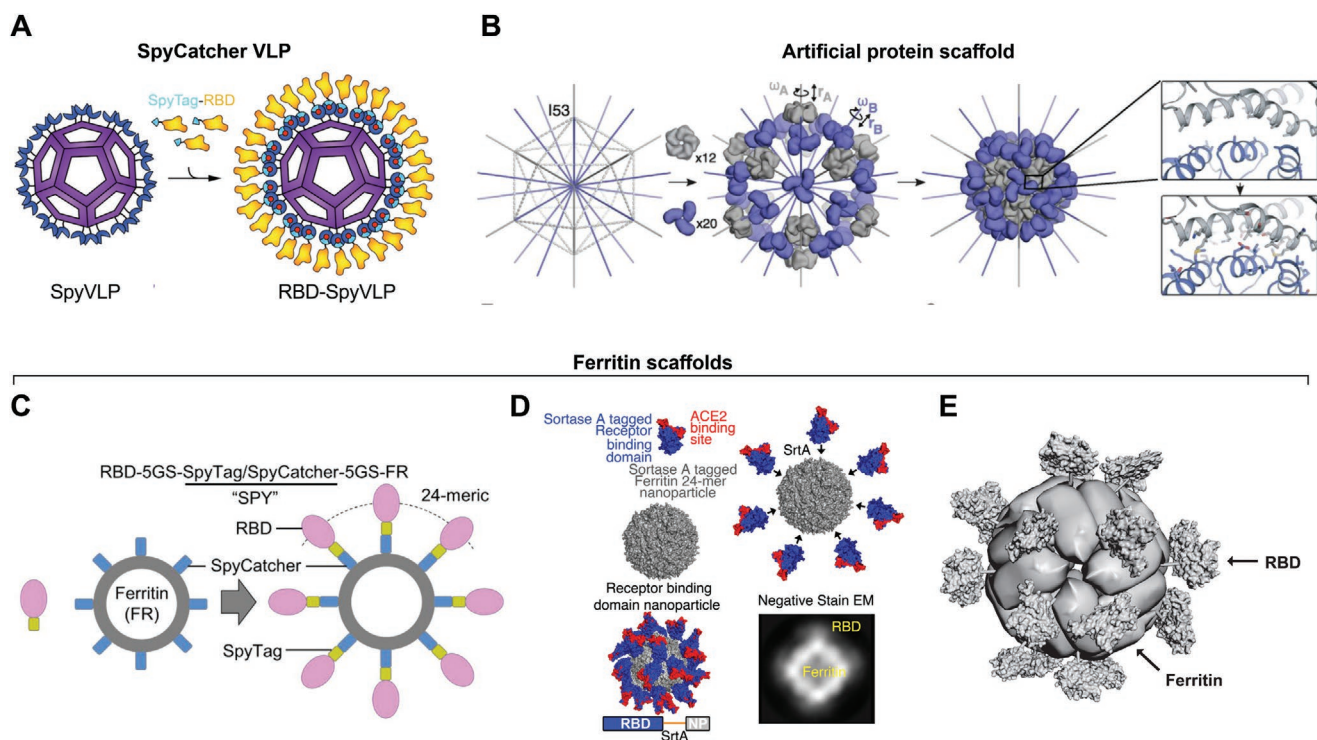www.advancedsciencenews.com

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Figure 4. Protein nanoparticles for RBD delivery. A) The RBD-SpyVLP vaccine candidate consists of SpyCatcher003-VLP conjugated with SpyTag-RBD.[70] B) The I53 protein icosahedron architecture, with the fivefold symmetry through each vertex and threefold symmetry through each face of the icosahedron with 12 pentamers and 20 trimers are aligned along the fivefold and threefold symmetry axes.[82] C) Conjugating the RBD to the 24-meric ferritin particles using the SpyTag/SpyCatcher (SPY) system.[83] D) SARS-CoV-2 RBD nanoparticles were constructed by expressing RBD with a C-terminal sortase A donor sequence and a *H. pylori* ferritin nanoparticle.[84] E) Modeling of an RBD nanoparticle based on *H. pylori* ferritin and the RBD.[78] A) Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license.[70] Copyright 2021, The Authors, published by Springer Nature. B) Reproduced with permission.[82] Copyright 2016, American Association for the Advancement of Science. C) Reproduced with permission.[83] Copyright 2021, The Authors, published by American Society for the Advancement of Science. Reprinted/adapted from ref. [83]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. D) Reproduced with permission.[84] Copyright 2021, The Authors, published by Springer Nature. E) Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license.[78] Copyright 2021, The Authors, published by ASM Journals.

the RBD-12GS-I53-50 formulation in a 4-week prime-boost regime that resulted in induction of protective neutralizing antibodies.[72] S-I53-50NPs was used to immunize mice, rabbits, and cynomolgus macaques showing strong immune responses in all species and protecting macaques against viral challenge.[73] Furthermore, RBD or S nanoparticles were combined with the adjuvants Essai O/W 1 849 101, AS03, AS37, CpG1018-alum or alum and benchmarked in their ability to elicit protective immunity against SARS-CoV-2 infection in rhesus macaques.[74] RBD-16GSI53-50 immunizations showed that AS03 was best able to produce a mixed Th1–Th2 response while other adjuvants were biased to either Th1 or Th2. Upon identifying AS03 as the preferred adjuvant, the RBD was compared to Hexa-Pro, a stable variant of the prefusion S trimer,[10] in its soluble and nanoparticulate form with I53-50. AS03 was a potent adjuvant with either immunogen, resulting in a neutralizing immune response.[74] The icosahedral protein scaffold with RBD fusion decoration has advanced into phase three clinical testing with the GBP510 vaccine (ClinicalTrials.gov # NCT05007951).

Ferritin is the primary iron storage protein and naturally assembles into nanonanocages, which can be genetically engineered to functionalize its surface.[89] Multiple copies of RBD were displayed on the surface of ferritin nanoparticles

consisting of either 24-mer or 60-mers composed of an inner layer of locking domains and a cluster of T cell epitopes, as shown in Figure 4C.[83] The CR3022 monoclonal antibody was used for immunoaffinity separation as it can bind to both SARS-CoV-1/2 RBDs. SARS-CoV-1/2 RBDs ("RBD-up" conformation) were attached to protein nanoparticles using the SpyTag/SpyCatcher system. In the same manner to compare antigens, RBD was compared to heptad repeats[90] and it was found that heptad repeats conjugated to ferritin nanoparticles through Spytag/Spycatcher technology not only produced neutralizing humoral and cellular responses but also these neutralizing antibodies were able to neutralize other coronaviruses providing cross-protection. In another approach, the RBD was displayed on the surface of ferritin nanoparticles through sortase A enzyme as represented in Figure 4D.[84] The vaccine elicited neutralizing antibodies in non-human primates.

Helicobacter pylori-bullfrog ferritin nanoparticles were used to produce RBD self-assembling protein-based vaccine. The conjugated ferritin RBD self-assembled into 24-mer nanoparticles as described in (Figure 4E) that were able to protect ferrets against SARS-CoV-2 challenge after three injections of 15 μg doses with AddaVax adjuvant.[78] A ferritin cage with surface S or RBD were able to produce detectable antibodies level after single dose,
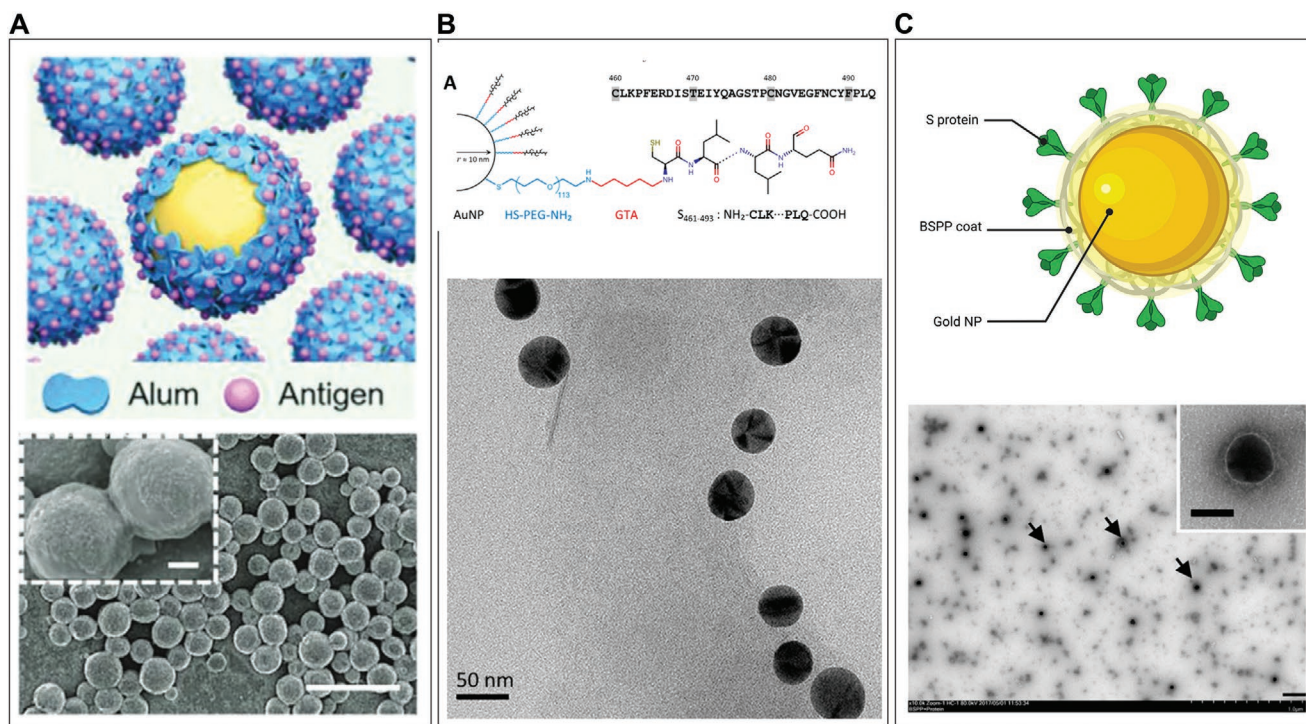
Figure 5. Inorganic materials. A) An alum-stabilized Pickering emulsion schematic (top) and scanning electron microscopy image (bottom) after solidification by replacing squalene with paraffin wax. The scale bars represent 10 μm and 200 nm (inset).[98] B) Schematic (top) and electron microscopy image (bottom) of gold nanoparticles (AuNP) after functionalization with thiol–poly(ethylene glycol)–amine, activation with glutaraldehyde (GTA) and conjugation with an S$_{461-493}$ peptide.[76] C) Illustration (top) and electron microscopy image (bottom) of AuNP coated with Bis(p-sulfonatophenyl) phenylphosphine dihydrate dipotassium salt (BSPP) and S. The arrows show S bound AuNPs. Scale bar: 200 or 20 nm (inset).[75] A) Reproduced with permission.[98] Copyright 2020, Wiley-VCH. B) Reproduced with permission.[76] Copyright 2021, Elsevier. C) Bottom: Reproduced with permission.[75] Copyright 2019, The Societies and John Wiley & Sons Australia, Ltd.

but can even get higher levels after a second booster dose.[91] Ferritin-RBD nanoparticles were also able to induce long-term memory in mice when compared to soluble RBD.[92]

To compare three protein scaffolds, Kang and co-workers displayed RBD on three different protein nanoparticle via SpyTag-SpyCatcher system, Ferritin (24-mer), mi3 (60-mer), and I53–50 (120-mer).[93] The sera from immunized mice showed that when adjuvanted with Addavax, all three nanoparticles resulted in high neutralizing antibodies levels which were significantly higher than the monomeric RBD immunized mice. In a similar comparative approach, Lainšček et al. compared RBD genetic fusions presented using various nanoscaffolds including foldons, ferritin, lumazine synthase, and β-annulus peptides, encoded by a DNA vaccine.[94] The small β-annulus peptide scaffold induced the best virus neutralization in mice.

Medicago uses plants to produce VLP vaccines. Plant-based platforms in theory enable rapid and scaled product development. AS03-adjuvant, squalene-based adjuvant, or CpG1018, toll-like receptor 9 (TLR9) agonist adjuvants, were used with a plant-based VLP displaying the S glycoprotein to vaccinate healthy individuals with single or two doses of 3.75, 7.5, or 15 μg VLP. AS03 showed a balanced Th1/Th2 response after two injections with enhancement in neutralizing antibodies level at higher doses.[95] To durability and cross reactivity of the produced antibodies, AS03 were used as adjuvant of choice to immunize 20 healthy individuals with two doses of 3.75 μg VLP 21 days apart.[96] At day 201, sera from vaccinated individuals showed

durable neutralizing antibody response against SARS-CoV-2 with significant cross reactivity between in some individuals against SARS-CoV but not MERS-CoV. Plant viruses themselves can be used as a VLP scaffold. SARS-CoV-2 derived peptides were directly conjugated in a trivalent fashion onto cow pea mosaic virus (CPMV), generating neutralizing antibodies.[97]

4. Inorganic Materials

Aluminum salts have been regarded as a safe vaccine adjuvant for over 70 years. A Pickering emulsion (PAPE) was developed using a microgel squalene-in-water system stabilized with alum as shown in **Figure 5**A.[98] The resultant microparticles had spherical morphology with antigen at the surface with stability for at least 120 days at 37 °C. About 90% of the RBD was adsorbed to the microparticles after incubation with PAPE for 30 min at room temperature. The vaccine produced a mixed Th1/Th2 response in mice. Gold nanoparticles (AuNP) are one of the most widely used inorganic biomaterial.[99] Sekimukai et al. found that although S protein/AuNP could be formed as shown in Figure 5B and induced a strong IgG response, the vaccine failed to induce protective antibodies or limit eosinophilic infiltration in lungs.[75] An S derived peptide (S$_{461-493}$) was chosen based on BepiPred-2.0: Sequential B-Cell Epitope Predictor tool and conjugated to keyhole limpet hemocyaninon (KLH) to increase immunogenicity and the conjugate was displayed on the surface of 10 nm AuNP as shown in

Figure 5C.[76] The resultant particles elicited antibodies against the peptide but were not tested for neutralization or protective efficacy.

5. Lipid Materials for Vaccines

5.1. Lipid-Based Nanoparticles for mRNA Vaccines

Lipid delivery systems are the most widely used tool for mRNA vaccine delivery as they offer advantages of in vivo stabilization, enhanced cell permeability and endosomal escape.[100,101] The process of delivery of mRNA through endomembranes via multiple mechanisms is illustrated in **Figure 6**A.[102] The tunable nature of such systems that incorporate multiple lipid components lends itself to modification and optimization (Figure 6B).[102] For example, Elia et al., tested several ionizable lipids to optimize a design of an mRNA vaccine encoding SARS-CoV-2 human Fc-conjugated receptor binding domain (RBD-hFc).[103] After escaping the endosome, the mRNA is translated into the corresponding protein. Near complete protection in

hACE2 transgenic mice was achieved after a single injection of mRNA-RBD as well as robust humoral and cellular responses that lasted for at over 6 months in BALB/c mice.[63]

RBD and S1 subunit mRNA formulations were compared using the GenVoy-ILM lipid system, an ionizable lipid mix to generate LNPs. Sera from mice groups injected with 30 µg of mRNA of either S1 subunit or RBD formulations showed high levels of neutralizing antibodies with the RBD being superior to S1 subunit. RBD immunized mice had enhanced cellular response when compared to those with S1 subunit.[105]

One or two doses of an RBD mRNA LNP formulation (termed ARCoV) elicited neutralizing antibodies against multiple SARS-CoV-2 strains in mice and non-human primates.[104] The formulation showed homogenous morphology with regular size distribution (Figure 6C) and was able to retain 85% of its activity when stored at 37 °C for 7 days. Alternatively, a self-amplifying RNA encoding a prefusion stabilized SARS-CoV-2 S was formulated with LNP and dose titration (0.01–10 µg) was tested for humoral and cellular immunogenicity and neutralization activity in mice.[106] All doses resulted in mice sera with
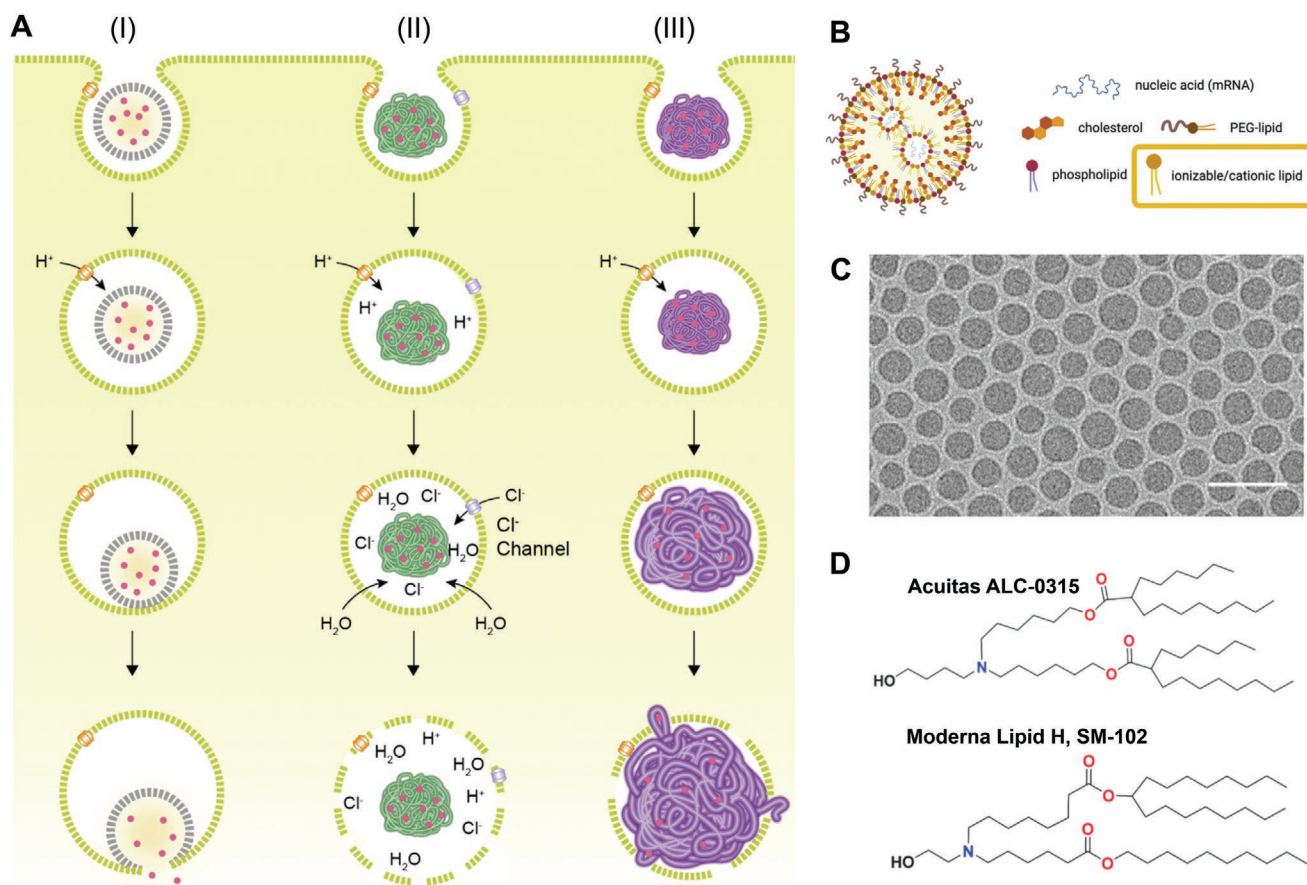

Figure 6. Lipid nanoparticles for mRNA delivery. A) Putative mechanisms of endosomal escape of nanocarriers. I) Nanocarriers induce destabilization of endosomal membranes for cytosolic release of genetic cargos. II) Nanocarriers, particularly polyplexes, scavenge protons and become cationic in acidic lumens of endosome compartments, resulting in the inflow of more protons and counter ions. This osmotic gradient induces influx of water to the endosomes, causing endosome rupture. III) Nanocarriers swell in acidic pH due to the electrostatic repulsion and physically rupture the endosome.[102] B) General structure of lipid nanoparticles. Ionizable or cationic lipids are the main component responsible for the encapsulation of nucleic acid and intracellular delivery.[102] C) Cryo-transmission electron microscopy images of ARCoV particles showing homogeneous morphologies of solid spheres that lack an aqueous core. Scale bar: 200 nm.[104] D) Structures of ionizable lipids used in the Pfizer/BioNTech BNT162b2 vaccine and the Moderna mRNA-1273 vaccine.[100] A,B) Reproduced with permission.[102] Copyright 2020, Elsevier. C) Reproduced with permission.[104] Copyright 2020, Elsevier.

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higher quantities of neutralizing IgG compared to convalescent sera.

Overall, mRNA and LNP formulation is an emerging practice with many optimization methodologies to consider.[107] The ionizable lipids used by in mRNA vaccines play a substantial role in their efficacy. Pfizer/BioNTech's Comirnaty vaccine uses an amino lipid termed ALC-0315, while Moderna's SpikeVax vaccine uses lipid H.[108] Their chemical structures are similar and are shown in Figure 6D.

Although LNPs have emerged as the current carrier of choice for advanced mRNA vaccines, other non-lipid approaches are viable and are mentioned briefly here. They typically involve cationic polymers instead of lipids. For example, a polyglucin:spermidine conjugate was investigated as a potential carrier for a mRNA-RBD vaccine and induced neutralizing antibodies in mice.[64] Chitosan was used to produce a DNA vaccine encoding a secreted S portion that has the potential for treatment and vaccination as well by acting as a competitive antagonist at the ACE2 receptor.[66] Full length S protein encoding mRNA was successfully encapsulated into a core–shell structured lipopolyplex nanoparticles.[109] A cationic polymer termed SW-01 was used to condense the mRNA into the core and then coated with a shell of ionized and non-ionized lipids using microfluidics. The resultant vaccine, SW0123, produced neutralizing antibodies in both C57BL/6 and BALB/c mice. SW0123 is now under evaluation in a Phase I clinical trial in China (SW0123 is now under evaluation in a Phase I clinical trial in China (Chinese Clinical Trial Registry, CTR20210542).

5.2. Liposome and Micelle Adjuvants

Liposome-based vaccine delivery systems hold the advantages of human safety track record, ease of manufacture, and control over lipid composition. They can also be designed to control parameters such as vesicle charge and size which impact entrapment efficiency. Liposome-based vaccines can be used for delivering different kinds of antigens, either proteins or nucleic acids, which can be adsorbed at the surface, or be entrapped in the aqueous core of liposomes. Lipophilic compounds including several immune stimulants can be incorporated into the lipid bilayer. For instance, AS01, a liposomal adjuvant system incorporating two molecular adjuvants (a monophosphoryl lipid A (MPLA) and a saponin molecule (QS-21)) stimulates humoral and cell-mediated immune responses when coadministration with antigens.[110] The effectiveness and safety of AS01 has led it to being widely, used even with inactivated viruses.[111] GlaxoSmithKline (GSK), which produces AS01, has engaged in several partnerships to embed its pandemic adjuvant AS03, an adjuvant system composed of α-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion with SARS-CoV-2-protein-based vaccines such as the Medicago CoVLP (ClinicalTrials.gov # NCT04636697) and the GBP510 (ClinicalTrials.gov # NCT05007951) vaccines.

In another approach to further enhance immunogenicity of liposomal adjuvant systems, his-tagged protein antigens were engineered to bind on the bilayer surface based on interaction with immobilized cobalt ions in the bilayer through a novel porphyrin phospholipid conjugate (termed CoPoP),
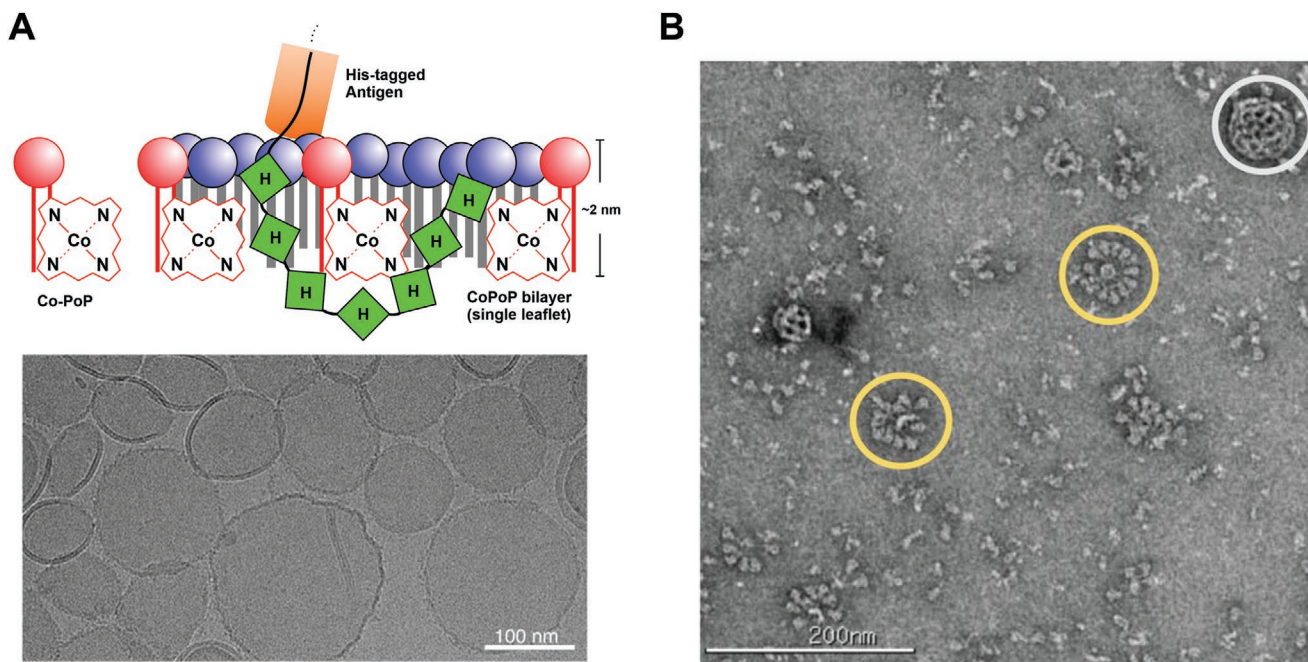

Figure 7. Lipids for protein antigen particles. A) Top: A peptide with a his-tag (green) binding to pre-formed CoPoP liposomes in an aqueous solution with simple admixing.[112] Bottom: Cryo-electron microscopy image of the RBD displayed on immunogenic CoPoP liposomes. B) Electron microscopy images of SARS-CoV-2 3Q-2P-FL, formulated in polysorbate 80 surfactant in the presence of Matrix-M adjuvant (Novavax). S rosettes are circled in yellow and Matrix-M adjuvant cages are circled in white. Matrix-M does not appear to interact with the S nanoparticles.[116] A) Top: Reproduced with permission.[112] Copyright 2015, Springer Nature. Bottom: Reproduced with permission.[79] Copyright 2020, Wiley-VCH. B) Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[116] Copyright 2020, American Association for the Advancement of Science.

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allowing enhanced antigen presentation and uptake as shown in **Figure 7**A.[112] RBD presentation on the surface of these liposomes resulted in a potent neutralizing antibody response in mice with just 0.1 μg dose per mouse. This technology has recently advanced to clinical trials (ClinicalTrials.gov # NCT04783311) under the tradename EuCorVac-19.[79]

Another saponin based adjuvant, Matrix-M, is made of Quillaja saponins that are formulated into nanoparticles together with cholesterol and phospholipids.[113] Matrix-M enhances Th1 and Th2 responses as well as inducing multiple antibody subclasses.[114,115] Matrix-M, a key component of the Novavax Nuvaxovid vaccine, increases the immunogenicity of full-length recombinant SARS-CoV-2 S nanoparticle vaccine shown in Figure 7B.[13]

6. Materials for Vaccine Storage and Delivery

There are many challenges when it comes to a pandemic mass vaccination. One is the logistics of vaccine storage and global distribution that require active cold chains to enable shipments, including low temperature storage conditions or a narrow range of storage temperatures. For example, some mRNA vaccines require shipment and long-term storage at −80 °C. Liposomal vaccines can aggregate if frozen and thus should not be stored below 0 °C.[117] Another challenge can be the lack of available trained health care workers who can administer vaccines. A vaccine delivery platform that can break cold chain limitations

and allow for self-administration could improve efficient worldwide vaccination in both developed and developing countries.

6.1. Thermostability

Next generations of COVID-19 vaccines should consider global distribution efficiency, and thus reduced cold chain requirements could be a significant advantage.[118] One of the main approaches to increasing the thermostability of a vaccine is to remove its aqueous solvent. Many drying techniques are available for vaccines such as spray and freeze drying (lyophilization). Although spray drying is fast and can produce free flowing powder which can be desirable in industry, lyophilization is a preferred technique for the drying of biologics it does not subject the vaccine to heating stress. Moreover, it can retain the sterility of the sample during the process. Freezing stress can have problematic effects on nanoparticulate vaccines, necessitating the use of cryoprotectants.[119] A hybrid drying technique between both spray and freeze drying (spray freeze drying) can be adapted to produce freeze dried spherical free flowing powder rather than cake. The large-scale production process of a lyophilized vaccine is substantially different than a liquid vaccine, therefore consideration of vaccine production capacity is important.

Lyophilization is frequently used to improve protein storage stability. Liposome-displayed S and RBD were lyophilized with a 7.5% sucrose cryoprotectant that was found effective in inhibiting liposomal aggregation upon reconstitution.[120] The
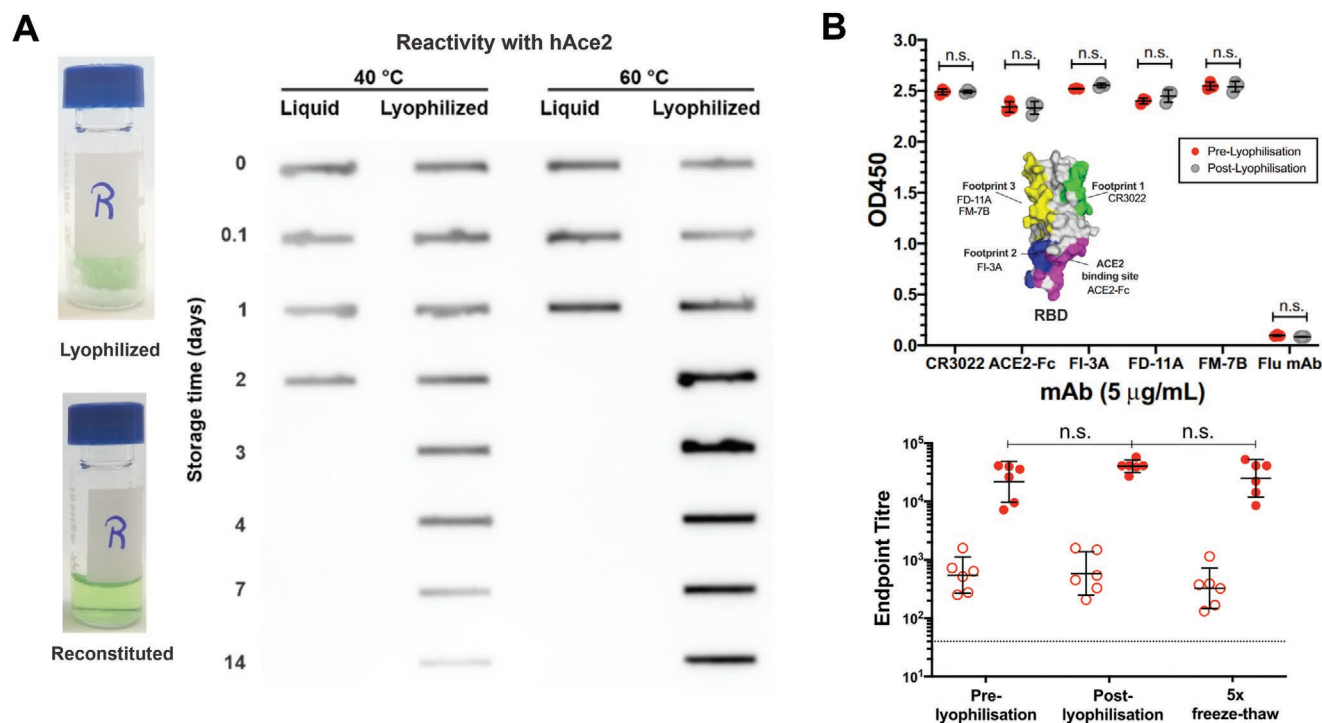

Figure 8. Stability of lyophilized RBD vaccines. A) RBD-decorated liposomes are shown before and after lyophilization (left). RBD stability, as gauged by reactivity with hACE2 was then assessed for the liquid or lyophilized vaccines (right).[120] B) RBD-SpyVLPs reactivity with various conformational monoclonal antibodies and hACE2 is maintained with lyophilization (top). Upon immunization with either pre- or post-lyophilized or five times freeze thawed RBD-SpyVLPs, mice effectively induced antibodies before and after boosting (bottom). A) Adapted under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[120] Copyright 2021, The Authors, published by American Association for the Advancement of Science. B) Adapted under the terms of the CC-BY Creative Commons 4.0 International license (https://creativecommons.org/licenses/by/4.0).[70] Copyright 2021, The Authors, published by Springer Nature.
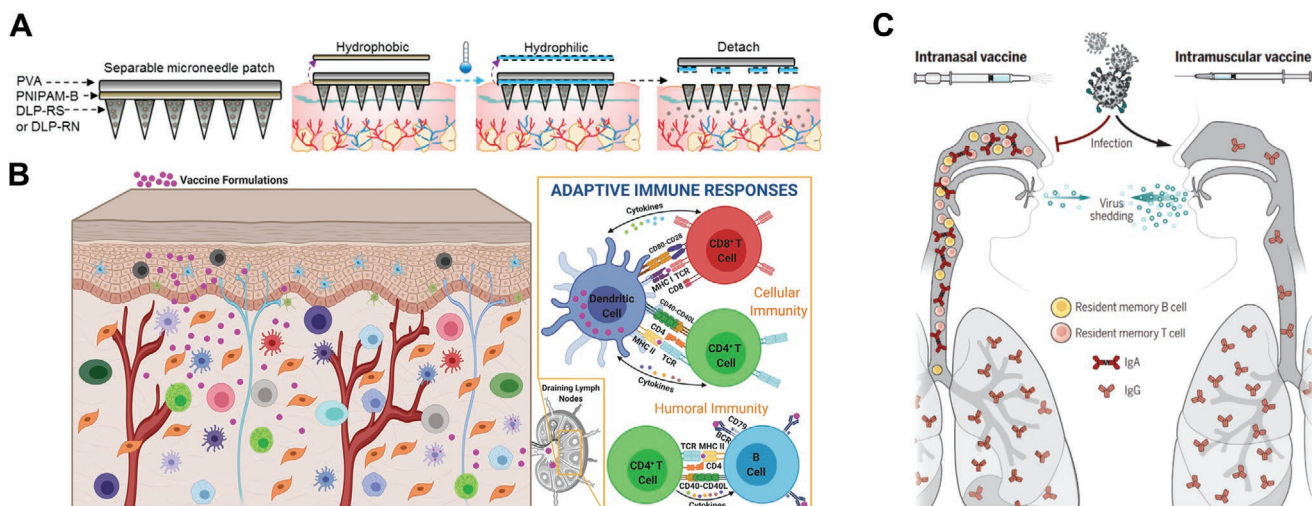
Figure 9. Needle-free vaccine delivery. A) The design of separable microneedle patches for skin delivery where a thermal responsive "PNIPAM-B" polymer was inserted between the backing layer and microneedles containing Resiquimod loaded deoxycholic acid polyethylenimine micelles with surface condensed DNA encoding for either S protein "DLP-RS" or N protein "DLP-RN." PNIPAM-B polymer is hydrophobic at room temperature and transfers to hydrophilic if the temperature is lower than the LCST (14–16 °C).[123] Thus, the backing layer of SMN can be separated from skin and leave the microneedles embedded. B) Skin vaccination induces antigen-specific cellular and humoral immune responses as the introduction of vaccine components into the skin microenvironment results in antigen loading and functional skewing of skin-resident APCs capable of directly or indirectly inducing T cell responses in the draining lymph nodes. The magnitude, breadth, and longevity of these responses are influenced by vaccine dose, spatiotemporal vaccine release kinetics, and immunoregulatory signals delivered with the antigen or released by other skin cells.[122] C) IgA and resident memory B and T cells in the nasal passages and upper airways are elicited by intranasal vaccination and prevent infection and reduce virus shedding. Serum IgG elicited by intramuscular vaccination transudates into the lungs and prevents pulmonary infection but allows infection in the nasal passages and virus shedding. shedding.[131] A) Reproduced with permission.[123] Copyright 2021, American Chemical Society. B) Reproduced with permission.[122] Copyright 2021, The Authors. Published by Elsevier. C) Reproduced with permission.[131] Copyright 2021, American Association for the Advancement of Science.

powdered vaccine was able to withstand elevated temperatures (60°C) for at least 2 weeks in terms of antigen stability when tested for conformational stability via slot blot and colloidal stability of the liposomes when measured with dynamic light scattering.[120] Lyophilization of RBD-SpyVLP rendered it thermostable without a loss in immunogenicity. The vaccine was able to withstand five freeze–thawing cycles retaining its correct conformation and immunogenicity (**Figure 8**B).[70]

Lyophilization of mRNA also can enhance its stability. A lyophilized RNA platform developed by CureVac as a rabies vaccine was able to withstand storage temperatures 5–25 °C for 3 years and was stable for ≈6 months at 40 °C.[121] A lipid-based delivery system for mRNA-RBD vaccine (named ARCoV) was tested for its thermostability for 7 days at different temperatures. The results showed that the system can protect its mRNA cargo at 37 °C retaining about 85% of its activity in liquid form.[104]

6.2. Delivery Methods

Intramuscular injection is the most used delivery method for COVID-19 vaccine administration and is chosen due to reproducible dose delivery and historic precedent.[122] Besides the need to be administered with trained personnel, the use of needles carries the hazard of infection and vaccine hesitance, and also can cause supply chain shortages. Other vaccine delivery methods have gained interest, namely intradermal and intranasal or inhalable.

Microarray patches offer an attractive means of delivery of biologics through the skin allowing controlled release of vaccine components intradermally or intracutaneously. Skin science advances provide evidence that these immuniza-

tions can induce sustained humoral and cellular immune responses.[122] For example, a poly(vinyl acetate) separable microneedle patch was prepared via micromolding technology to deliver a low molecular weight polyethylenimine nanoparticles encapsulating DNA encoding for either S or N proteins. poly(*N*-isopropylacrylamide-*co*-butyl acrylate) was used as a separable layer thanks to its thermoresponsive properties, where it becomes hydrophilic and easily separated at 14–16 °C (**Figure 9**A). The nanoparticles were able to encapsulate a hydrophobic immunostimulant, Resiquimod, only after chemical conjugation of deoxycholic acid to polyethyleneimine forming an amphiphilic self-assembling polymer that DNA can be condensed on its surface via electrostatic condensation.[123] Both formulations induced significant cellular and humoral response in mice when compared to naïve groups but only the S protein encoding formulation sera was tested for neutralization activity with pseudotyped virus showing significant neutralizing activity. A carboxymethyl cellulose dissolving microneedle array incorporating the S1 subunit from S was fabricated using a tip-loading 3-stage manufacturing strategy. A 2 week prime-boost regimen resulted in eliciting neutralizing antibodies for at least 4 weeks in mice.[124] A needle free jet injector was used to immunize Rhesus macaques using 1 or 2 mg ZyCoV-D (naked plasmid DNA) and compared with intradermal injections and it was found that it was able to produce comparable neutralizing antibodies to intradermal injection. Electroporation was used to administer Inovio Pharma (INO-4800)[125] which was previously used to administer MERS,[126] Ebola,[127] and Zika virus vaccines.[128] In general, microarray patches are among the most promising skin-targeted vaccine delivery systems with the advantages of self-administration,

elimination of needle hazard are painless and can effectively induce immune response (Figure 9B).[130,131]

Another delivery route of interest is inhalation or intranasal administration. Compared to intramuscular or subcutaneous injections, vaccines targeted to the lungs can boost the local immune response and produce mucosal immunity from secreted IgA and tissue resident immune cells that can prevent the infection onset as shown in Figure 9C.[132] In one study, a chimpanzee adenovirus-vectored vaccine encoding a prefusion stabilized S was found to be effective when administered intranasally dose induced high levels of neutralizing antibodies, promoted systemic and mucosal IgA and T cell responses, and prevented SARS-CoV-2 infection in both the upper and lower respiratory tracts.[133] In another study, two doses of aerosolized adenovirus type-5 vector-based COVID-19 vaccine was found to be well tolerated in adult humans and was able to elicited neutralizing antibody responses, similar to one dose of intramuscular injection.[134] In another approach, targeted phage-based vaccination was developed against SARS-CoV-2 where a dual ligand peptide-targeted phage was engineered based on a structure-guided antigen design.[135] One of these engineered epitopes was displayed on the major capsid protein pVIII of the phage and induced a specific and sustained humoral response when injected in mice. Moreover, the peptide CAKSMGDIVC was co-displayed on the phages (on the minor capsid protein pIII) which enables their transport across the lung epithelium and into the systemic circulation. As a result, aerosolization of these phages into the lungs of mice generated a systemic and specific antibody response.[135] Taken together, intranasal delivery shows promise, but further data is required to show a compelling advantage over traditional intramuscular administration.

7. Conclusion

Advanced materials have emerged to shape vaccines that have mitigated the severity of the COVID-19 pandemic. Cationic lipid materials for mRNA delivery in particular have been instrumental in being developed quickly to generate safe and effective vaccines. Self-assembly technologies for subunit vaccines have emerged and have been advanced to the point of clinical testing. Moving forward, more information will emerge about long-term efficacy and safety of these vaccine candidates, which will be helpful in shaping future vaccine design, both for the ongoing COVID-19 pandemic and for other infectious disease targets. The ability to have vaccine platforms that can be easily manipulated to fit new antigens or viral variants is of importance. Thermostable platform technologies are desirable to decrease the cost of shipment and storage and facilitates worldwide distribution. Overall, advanced vaccine materials have made great headway in the past couple of years, and are poised for further research and development breakthroughs in the near future.

Acknowledgements

Conflict of Interest

W.C.H. and J.F.L. hold interest in POP Biotechnologies. The other authors declare no conflict.

Keywords

[1] N. Chazal, *Front. Microbiol.* **2021**, *12*, 2677.
[2] D. S. Khoury, D. Cromer, A. Reynaldi, T. E. Schlub, A. K. Wheatley, J. A. Juno, K. Subbarao, S. J. Kent, J. A. Triccas, M. P. Davenport, *Nat. Med.* **2021**, *27*, 1205.
[3] V. V. Edara, W. H. Hudson, X. Xie, R. Ahmed, M. S. Suthar, *JAMA, J. Am. Med. Assoc.* **2021**, *325*, 1896.
[4] G. A. Poland, I. G. Ovsyannikova, R. B. Kennedy, *Vaccine* **2021**, *39*, 4239.
[5] A. C. Walls, Y.-J. Park, M. A. Tortorici, A. Wall, A. T. Mcguire, D. Veesler, *Cell* **2020**, *181*, 281.
[6] M. Hoffmann, H. Kleine-Weber, S. Pöhlmann, *Mol. Cell* **2020**, *78*, 779.
[7] D. Bestle, M. R. Heindl, H. Limburg, T. Van Lam Van, O. Pilgram, H. Moulton, D. A. Stein, K. Hardes, M. Eickmann, O. Dolnik, C. Rohde, H.-D. Klenk, W. Garten, T. Steinmetzer, E. Böttcher-Friebertshäuser, *Life Sci. Alliance* **2020**, *3*, e202000786.
[8] J. S. Mclellan, M. Chen, M. G. Joyce, M. Sastry, G. B. E. Stewart-Jones, Y. Yang, B. Zhang, L. Chen, S. Srivatsan, A. Zheng, T. Zhou, K. W. Graepel, A. Kumar, S. Moin, J. C. Boyington, G.-Y. Chuang, C. Soto, U. Baxa, A. Q. Bakker, H. Spits, T. Beaumont, Z. Zheng, N. Xia, S.-Y. Ko, J.-P. Todd, S. Rao, B. S. Graham, P. D. Kwong, *Science* **2013**, *342*, 592.
[9] J. Pallesen, N. Wang, K. S. Corbett, D. Wrapp, R. N. Kirchdoerfer, H. L. Turner, C. A. Cottrell, M. M. Becker, L. Wang, W. Shi, W.-P. Kong, E. L. Andres, A. N. Kettenbach, M. R. Denison, J. D. Chappell, B. S. Graham, A. B. Ward, J. S. Mclellan, *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, E7348.
[10] C.-L. Hsieh, J. A. Goldsmith, J. M. Schaub, A. M. Divenere, H.-C. Kuo, K. Javanmardi, K. C. Le, D. Wrapp, A. G. Lee, Y. Liu, C.-W. Chou, P. O. Byrne, C. K. Hjorth, N. V. Johnson, J. Ludes-Meyers, A. W. Nguyen, J. Park, N. Wang, D. Amengor, J. J. Lavinder, G. C. Ippolito, J. A. Maynard, I. J. Finkelstein, J. S. Mclellan, *Science* **2020**, *369*, 1501.
[11] L. Dai, G. F. Gao, *Nat. Rev. Immunol.* **2021**, *21*, 73.
[12] Y. Watanabe, L. Mendonça, E. R. Allen, A. Howe, M. Lee, J. D. Allen, H. Chawla, F. Pulido, F. Donnellan, H. Davies, M. Ulaszewska, S. Belij-Rammerstorfer, S. Morris, A.-S. Krebs, W. Dejnirattisai, J. Mongkolsapaya, P. Supasa, G. R. Screaton, C. M. Green, T. Lambe, P. Zhang, S. C. Gilbert, M. Crispin, *ACS Cent. Sci.* **2021**, *7*, 594.
[13] J.-H. Tian, N. Patel, R. Haupt, H. Zhou, S. Weston, H. Hammond, J. Logue, A. D. Portnoff, J. Norton, M. Guebre-Xabier, B. Zhou, K. Jacobson, S. Maciejewski, R. Khatoon, M. Wisniewska, W. Moffitt, S. Kluepfel-Stahl, B. Ekechukwu, J. Papin, S. Boddapati, C. J. Wong, P. A. Piedra, M. B. Frieman, M. J. Massare, L. Fries, K. L. Bengtsson, L. Stertman, L. Ellingsworth, G. Glenn, G. Smith, *Nat. Commun.* **2021**, *12*, 372.
[14] R. Bos, L. Rutten, J. E. M. van der Lubbe, M. J. G. Bakkers, G. Hardenberg, F. Wegmann, D. Zuijdgeest, A. H. de Wilde, A. Koornneef, A. Verwilligen, D. van Manen, T. Kwaks, R. Vogels, T. J. Dalebout, S. K. Myeni, M. Kikkert, E. J. Snijder, Z. Li,

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D. H. Barouch, J. Vellinga, J. P. M. Langedijk, R. C. Zahn, J. Custers, H. Schuitemaker, *npj Vaccines* **2020**, *5*, 91.

[15] L. Duan, Q. Zheng, H. Zhang, Y. Niu, Y. Lou, H. Wang, *Front. Immunol.* **2020**, *11*, 2593.

[16] A. S. Omrani, I. M. Tleyjeh, *Clin. Microbiol. Infect.* **2021**, *27*, 1729.

[17] N. P. Restifo, H. Ying, L. Hwang, W. W. Leitner, *Gene Ther.* **2000**, *7*, 89.

[18] S. Awate, L. A. Babiuk, G. Mutwiri, *Front. Immunol.* **2013**, *4*, 114.

[19] Z. Liang, H. Zhu, X. Wang, B. Jing, Z. Li, X. Xia, H. Sun, Y. Yang, W. Zhang, L. Shi, *Front. Immunology* **2020**, *11*, 2896.

[20] F. P. Polack, S. J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G. Pérez Marc, E. D. Moreira, C. Zerbini, R. Bailey, K. A. Swanson, S. Roychoudhury, K. Koury, P. Li, W. V. Kalina, D. Cooper, R. W. Frenck, L. L. Hammitt, Ö. Türeci, H. Nell, A. Schaefer, S. Ünal, D. B. Tresnan, S. Mather, P. R. Dormitzer, U. Şahin, K. U. Jansen, W. C. Gruber, *N. Engl. J. Med.* **2020**, *383*, 2603.

[21] L. R. Baden, H. M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S. A. Spector, N. Rouphael, C. B. Creech, J. Mcgettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B. S. Graham, H. Bennett, R. Pajon, C. Knightly, et al., *N. Engl. J. Med.* **2020**, *384*, 403.

[22] P. G. Kremsner, R. A. Ahuad Guerrero, E. Arana-Arri, G. J. Aroca Martinez, M. Bonten, R. Chandler, G. Corral, E. J. L. De Block, L. Ecker, J. J. Gabor, C. A. Garcia Lopez, L. Gonzales, M. A. Granados González, N. Gorini, M. P. Grobusch, A. D. Hrabar, H. Junker, A. Kimura, C. F. Lanata, C. Lehmann, I. Leroux-Roels, P. Mann, M. F. Martinez-Reséndez, T. J. Ochoa, C. A. Poy, M. J. Reyes Fentanes, L. M. Rivera Mejia, V. V. Ruiz Herrera, X. Sáez-Llorens, O. Schönborn-Kellenberger, et al., *Lancet Infect. Dis.* **2021**, https://doi.org/10.1016/s1473-3099(21)00677-0.

[23] M. Voysey, S. A. C. Clemens, S. A. Madhi, L. Y. Weckx, P. M. Folegatti, P. K. Aley, B. Angus, V. L. Baillie, S. L. Barnabas, Q. E. Bhorat, S. Bibi, C. Briner, P. Cicconi, A. M. Collins, R. Colin-Jones, C. L. Cutland, T. C. Darton, K. Dheda, C. J. A. Duncan, K. R. W. Emary, K. J. Ewer, L. Fairlie, S. N. Faust, S. Feng, D. M. Ferreira, A. Finn, A. L. Goodman, C. M. Green, C. A. Green, P. T. Heath, on behalf of the Oxford COVID Vaccine Trial Group, *Lancet* **2021**, *397*, 99.

[24] D. Y. Logunov, I. V. Dolzhikova, D. V. Shcheblyakov, A. I. Tukhvatulin, O. V. Zubkova, A. S. Dzharullaeva, A. V. Kovyrshina, N. L. Lubenets, D. M. Grousova, A. S. Erokhova, 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, D. A. Egorova, M. M. Shmarov, N. A. Nikitenko, V. A. Gushchin, E. A. Smolyarchuk, S. K. Zyryanov, S. V. Borisevich, B. S. Naroditsky, et al., *Lancet* **2021**, *397*, 671.

[25] J. Sadoff, G. Gray, A. Vandebosch, V. Cárdenas, G. Shukarev, B. Grinsztejn, P. A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, K. Offergeld, G. Scheper, K. L. Taylor, M. L. Robb, J. Treanor, D. H. Barouch, J. Stoddard, M. F. Ryser, M. A. Marovich, K. M. Neuzil, L. Corey, N. Cauwenberghs, T. Tanner, K. Hardt, J. Ruiz-Guiñazú, M. Le Gars, H. Schuitemaker, J. Van Hoof, F. Struyf, M. Douoguih, *N. Engl. J. Med.* **2021**, *384*, 2187.

[26] N. Al Kaabi, Y. Zhang, S. Xia, Y. Yang, M. M. Al Qahtani, N. Abdulrazzaq, M. Al Nusair, M. Hassany, J. S. Jawad, J. Abdalla, S. E. Hussein, S. K. Al Mazrouei, M. Al Karam, X. Li, X. Yang, W. Wang, B. Lai, W. Chen, S. Huang, Q. Wang, T. Yang, Y. Liu, R. Ma, Z. M. Hussain, T. Khan, M. Saifuddin Fasihuddin, W. You, Z. Xie, Y. Zhao, et al., *JAMA, J. Am. Med. Assoc.* **2021**, *326*, 35.

[27] M. D. Tanriover, H. L. Doğanay, M. Akova, H. R. Güner, A. Azap, S. Akhan, Ş. Köse, F. Ş. Erdinç, E. H. Akalın,

Ö. F. Tabak, H. Pullukçu, Ö. Batum, S. Şimşek Yavuz, Ö. Turhan, M. T. Yıldırmak, I. Köksal, Y. Taşova, V. Korten, G. Yılmaz, M. K. Çelen, S. Altın, I. Çelik, Y. Bayındır, I. Karaoğlan, A. Yılmaz, A. Özkul, H. Gür, S. Unal, CoronaVac Study Group, *Lancet* **2021**, *398*, 213.

[28] P. T. Heath, E. P. Galiza, D. N. Baxter, M. Boffito, D. Browne, F. Burns, D. R. Chadwick, R. Clark, C. Cosgrove, J. Galloway, A. L. Goodman, A. Heer, A. Higham, S. Iyengar, A. Jamal, C. Jeanes, P. A. Kalra, C. Kyriakidou, D. F. Mcauley, A. Meyrick, A. M. Minassian, J. Minton, P. Moore, I. Munsoor, H. Nicholls, O. Osanlou, J. Packham, C. H. Pretswell, A. San Francisco Ramos, D. Saralaya, et al. for the 2019nCoV-302 Study Group, *N. Engl. J. Med.* **2021**, *385*, 1172.

[29] N. Pardi, M. J. Hogan, F. W. Porter, D. Weissman, *Nat. Rev. Drug Discovery* **2018**, *17*, 261.

[30] M. Li, S. Li, Y. Huang, H. Chen, S. Zhang, Z. Zhang, W. Wu, X. Zeng, B. Zhou, B. Li, *Adv. Mater.* **2021**, *33*, 2107707.

[31] J. Yao, Y. Fan, Y. Li, L. Huang, *J. Drug Targeting* **2013**, *21*, 926.

[32] F. Thienemann, G. Chakafana, D. Piñeiro, F. J. Pinto, P. Perel, K. Singh, J.-L. Eiselé, D. Prabhakaran, K. Sliwa, *Global Heart* **2021**, *16*, 29.

[33] D. Planas, D. Veyer, A. Baidaliuk, I. Staropoli, F. Guivel-Benhassine, M. M. Rajah, C. Planchais, F. Porrot, N. Robillard, J. Puech, M. Prot, F. Gallais, P. Gantner, A. Velay, J. Le Guen, N. Kassis-Chikhani, D. Edriss, L. Belec, A. Seve, L. Courtellemont, H. Péré, L. Hocqueloux, S. Fafi-Kremer, T. Prazuck, H. Mouquet, T. Bruel, E. Simon-Lorière, F. A. Rey, O. Schwartz, *Nature* **2021**, *596*, 276.

[34] T. A. Bates, H. C. Leier, Z. L. Lyski, S. K. Mcbride, F. J. Coulter, J. B. Weinstein, J. R. Goodman, Z. Lu, S. A. R. Siegel, P. Sullivan, M. Strnad, A. E. Brunton, D. X. Lee, A. C. Adey, B. N. Bimber, B. J. O'Roak, M. E. Curlin, W. B. Messer, F. G. Tafesse, *Nat. Commun.* **2021**, *12*, 5135.

[35] D. R. Burton, L. M. Walker, *Cell Host Microbe* **2020**, *27*, 695.

[36] M. F. Haidere, Z. A. Ratan, S. Nowroz, S. B. Zaman, Y.-J. Jung, H. Hosseinzadeh, J. Y. Cho, *Biomol. Ther.* **2021**, *29*, https://doi.org/10.4062/biomolther.2020.178.

[37] C. J. Batty, M. T. Heise, E. M. Bachelder, K. M. Ainslie, *Adv. Drug Delivery Rev.* **2021**, *169*, 168.

[38] P. Lee, C.-U. Kim, S. H. Seo, D.-J. Kim, *Immune Network* **2021**, *21*, e4.

[39] M. D. Shin, S. Shukla, Y. H. Chung, V. Beiss, S. K. Chan, O. A. Ortega-Rivera, D. M. Wirth, A. Chen, M. Sack, J. K. Pokorski, N. F. Steinmetz, *Nat. Nanotechnol.* **2020**, *15*, 646.

[40] E. Tanzi, C. Genovese, M. Tettamanzi, C. Fappani, M. C. Raviglione, A. Amendola, *J. Prev. Med. Hyg.* **2021**, *62*, E18.

[41] K. Rawat, P. Kumari, L. Saha, *Eur. J. Pharmacol.* **2021**, *892*, 173751.

[42] P. Hassanzadeh, *J. Controlled Release* **2020**, *328*, 112.

[43] C. Zeng, X. Hou, M. Bohmer, Y. Dong, *View* **2021**, *2*, 20200180.

[44] S. Wu, Y. Xia, Y. Hu, G. Ma, *Adv. Drug Delivery Rev.* **2021**, *176*, 113871.

[45] J. Sun, Z. Zhuang, J. Zheng, K. Li, R. L.-Y. Wong, D. Liu, J. Huang, J. He, A. Zhu, J. Zhao, X. Li, Y. Xi, R. Chen, A. N. Alshukairi, Z. Chen, Z. Zhang, C. Chen, X. Huang, F. Li, X. Lai, D. Chen, L. Wen, J. Zhuo, Y. Zhang, Y. Wang, S. Huang, J. Dai, Y. Shi, K. Zheng, M. R. Leidinger, et al., *Cell* **2020**, *182*, 734.

[46] R. Yan, Y. Zhang, Y. Li, F. Ye, Y. Guo, L. Xia, X. Zhong, X. Chi, Q. Zhou, *Cell Res.* **2021**, *31*, 717.

[47] J. Shang, Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, F. Li, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 11727.

[48] L. Du, Y. He, Y. Zhou, S. Liu, B.-J. Zheng, S. Jiang, *Nat. Rev. Microbiol.* **2009**, *7*, 226.

[49] O. C. Grant, D. Montgomery, K. Ito, R. J. Woods, *Sci. Rep.* **2020**, *10*.

[50] H. Kleanthous, J. M. Silverman, K. W. Makar, I.-K. Yoon, N. Jackson, D. W. Vaughn, *npj Vaccines* **2021**, *6*, 128.

[51] W. F. Garcia-Beltran, E. C. Lam, K. St 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, *Cell* **2021**, *184*, 2372.

[52] W.-C. Huang, B. Deng, C. Lin, K. A. Carter, J. Geng, A. Razi, X. He, U. Chitgupi, J. Federizon, B. Sun, C. A. Long, J. Ortega, S. Dutta, C. R. King, K. Miura, S.-M. Lee, J. F. Lovell, *Nat. Nanotechnol.* **2018**, *13*, 1174.

[53] A. A. Cohen, P. N. P. Gnanapragasam, Y. E. Lee, P. R. Hoffman, S. Ou, L. M. Kakutani, J. R. Keeffe, H.-J. Wu, M. Howarth, A. P. West, C. O. Barnes, M. C. Nussenzweig, P. J. Bjorkman, *Science* **2021**, *371*, 735.

[54] H. G. Kelly, S. J. Kent, A. K. Wheatley, *Expert Rev. Vaccines* **2019**, *18*, 269.

[55] M. A. Liu, *J. Intern. Med.* **2003**, *253*, 402.

[56] S. H. Boo, Y. K. Kim, *Exp. Mol. Med.* **2020**, *52*, 400.

[57] P. S. Kowalski, A. Rudra, L. Miao, D. G. Anderson, *Mol. Ther.* **2019**, *27*, 710.

[58] N. Chaudhary, D. Weissman, K. A. Whitehead, *Nat. Rev. Drug Discovery* **2021**, *20*, 817.

[59] M. J. Hogan, N. Pardi, *Annu. Rev. Med.* **2022**, *73*, https://doi.org/10.1146/annurev-med-042420-112725.

[60] N. A. C. Jackson, K. E. Kester, D. Casimiro, S. Gurunathan, F. Derosa, *npj Vaccines* **2020**, *5*, 11.

[61] K. D. Nance, J. L. Meier, *ACS Cent. Sci.* **2021**, *7*, 748.

[62] N. N. Sanders, *Mol. Ther.* **2021**, *29*, 1944.

[63] Q. Huang, K. Ji, S. Tian, F. Wang, B. Huang, Z. Tong, S. Tan, J. Hao, Q. Wang, W. Tan, G. F. Gao, J. Yan, *Nat. Commun.* **2021**, *12*, 2355.

[64] L. I. Karpenko, A. P. Rudometov, S. V. Sharabrin, D. N. Shcherbakov, M. B. Borgoyakova, S. I. Bazhan, E. A. Volosnikova, N. B. Rudometova, L. A. Orlova, I. A. Pyshnaya, B. N. Zaitsev, N. V. Volkova, M. S. Azaev, A. V. Zaykovskaya, O. V. Pyankov, A. A. Ilyichev, *Vaccines* **2021**, *9*, 76.

[65] J. Ren, Y. Cao, L. Li, X. Wang, H. Lu, J. Yang, S. Wang, *J. Controlled Release* **2021**, *338*, 537.

[66] D. Tatlow, C. Tatlow, S. Tatlow, S. Tatlow, *Clin. Exp. Pharmacol. Physiol.* **2020**, *47*, 1874.

[67] J. Yu, L. H. Tostanoski, L. Peter, N. B. Mercado, K. Mcmahan, S. H. Mahrokhian, J. P. Nkolola, J. Liu, Z. Li, A. Chandrashekar, D. R. Martinez, C. Loos, C. Atyeo, S. Fischinger, J. S. Burke, M. D. Slein, Y. Chen, A. Zuiani, F. J. N. Lelis, M. Travers, S. Habibi, L. Pessaint, A. Van Ry, K. Blade, R. Brown, A. Cook, B. Finneyfrock, A. Dodson, E. Teow, J. Velasco, et al., *Science* **2020**, *369*, 806.

[68] Y. Yin, W. Su, J. Zhang, W. Huang, X. Li, H. Ma, M. Tan, H. Song, G. Cao, S. Yu, D. Yu, J. H. Jeong, X. Zhao, H. Li, G. Nie, H. Wang, *ACS Nano* **2021**, *15*, 14347.

[69] N. Wang, J. Shang, S. Jiang, L. Du, *Front. Microbiol.* **2020**, *11*, 298.

[70] T. K. Tan, P. Rijal, R. Rahikainen, A. H. Keeble, L. Schimanski, S. Hussain, R. Harvey, J. W. P. Hayes, J. C. Edwards, R. K. McLean, V. Martini, M. Pedrera, N. Thakur, C. Conceicao, I. Dietrich, H. Shelton, A. Ludi, G. Wilsden, C. Browning, A. K. Zagrajek, D. Bialy, S. Bhat, P. Stevenson-Leggett, P. Hollinghurst, M. Tully, K. Moffat, C. Chiu, R. Waters, A. Gray, M. Azhar, et al., *Nat. Commun.* **2021**, *12*, 542.

[71] C. Fougeroux, L. Goksøyr, M. Idorn, V. Soroka, S. K. Myeni, R. Dagil, C. M. Janitzek, M. Søgaard, K.-L. Aves, E. W. Horsted, S. M. Erdoğan, T. Gustavsson, J. Dorosz, S. Clemmensen, L. Fredsgaard, S. Thrane, E. E. Vidal-Calvo, P. Khalifé, T. M. Hulen, S. Choudhary, M. Theisen, S. K. Singh, S. Garcia-Senosiain, L. Van Oosten, G. Pijlman, B. Hierzberger, T. Domeyer, B. W. Nalewajek, A. Strøbæk, M. Skrzypczak, et al., *Nat. Commun.* **2021**, *12*, 324.

[72] A. C. Walls, B. Fiala, A. Schäfer, S. Wrenn, M. N. Pham, M. Murphy, L. V. Tse, L. Shehata, M. A. O'connor, C. Chen, M. J. Navarro, M. C. Miranda, D. Pettie, R. Ravichandran, J. C. Kraft, C. Ogohara, A. Palser, S. Chalk, E.-C. Lee, K. Guerriero, E. Kepl, C. M. Chow, C. Sydeman, E. A. Hodge, B. Brown, J. T. Fuller, K. H. Dinnon, L. E. Gralinski, S. R. Leist, K. L. Gully, et al., *Cell* **2020**, *183*, 1367.

[73] P. J. M. Brouwer, M. Brinkkemper, P. Maisonnasse, N. Dereuddre-Bosquet, M. Grobben, M. Claireaux, M. De Gast, R. Marlin, V. Chesnais, S. Diry, J. D. Allen, Y. Watanabe, J. M. Giezen, G. Kerster, H. L. Turner, K. Van Der Straten, C. A. Van Der Linden, Y. Aldon, T. Naninck, I. Bontjer, J. A. Burger, M. Poniman, A. Z. Mykytyn, N. M. A. Okba, E. E. Schermer, M. J. Van Breemen, R. Ravichandran, T. G. Caniels, J. Van Schooten, N. Kahlaoui, et al., *Cell* **2021**, *184*, 1188.

[74] P. S. Arunachalam, A. C. Walls, N. Golden, C. Atyeo, S. Fischinger, C. Li, P. Aye, M. J. Navarro, L. Lai, V. V. Edara, K. Röltgen, K. Rogers, L. Shirreff, D. E. Ferrell, S. Wrenn, D. Pettie, J. C. Kraft, M. C. Miranda, E. Kepl, C. Sydeman, N. Brunette, M. Murphy, B. Fiala, L. Carter, A. G. White, M. Trisal, C.-L. Hsieh, K. Russell-Lodrigue, C. Monjure, J. Dufour, et al., *Nature* **2021**, *594*, 253.

[75] H. Sekimukai, N. Iwata-Yoshikawa, S. Fukushi, H. Tani, M. Kataoka, T. Suzuki, H. Hasegawa, K. Niikura, K. Arai, N. Nagata, *Microbiol. Immunol.* **2020**, *64*, 33.

[76] S. Farfán-Castro, M. J. García-Soto, M. Comas-García, J. I. Arévalo-Villalobos, G. Palestino, O. González-Ortega, S. Rosales-Mendoza, *Nanomed.: Nanotechnol. Biol. Med.* **2021**, *34*, 102372.

[77] L. He, X. Lin, Y. Wang, C. Abraham, C. Sou, T. Ngo, Y. Zhang, I. A. Wilson, J. Zhu, *Sci. Adv.* **2021**, *7*, eabf1591.

[78] Y.-I. Kim, D. Kim, K.-M. Yu, H. D. Seo, S.-A. Lee, M. A. B. Casel, S.-G. Jang, S. Kim, W. Jung, C.-J. Lai, *Mbio* **2021**, *12*, e00230.

[79] W.-.C. Huang, S. Zhou, X. He, K. Chiem, M. T. Mabrouk, R. H. Nissly, I. M. Bird, M. Strauss, S. Sambhara, J. Ortega, E. A. Wohlfert, L. Martinez-Sobrido, S. V. Kuchipudi, B. A. Davidson, J. F. Lovell, *Adv. Mater.* **2020**, *32*, 2005637.

[80] S. Chiba, S. J. Frey, P. J. Halfmann, M. Kuroda, T. Maemura, J. E. Yang, E. R. Wright, Y. Kawaoka, R. S. Kane, *Commun. Biol.* **2021**, *4*, 597.

[81] B. Nguyen, N. H. Tolia, *npj Vaccines* **2021**, *7*, eabf1591.

[82] J. B. Bale, S. Gonen, Y. Liu, W. Sheffler, D. Ellis, C. Thomas, D. Cascio, T. O. Yeates, T. Gonen, N. P. King, D. Baker, *Science* **2016**, *353*, 389.

[83] L. He, X. Lin, Y. Wang, C. Abraham, C. Sou, T. Ngo, Y. Zhang, I. A. Wilson, J. Zhu, *Sci. Adv.* **2021**, *7*, eabf1591.

[84] K. O. Saunders, E. Lee, R. Parks, D. R. Martinez, D. Li, H. Chen, R. J. Edwards, S. Gobeil, M. Barr, K. Mansouri, S. M. Alam, L. L. Sutherland, F. Cai, A. M. Sanzone, M. Berry, K. Manne, K. W. Bock, M. Minai, B. M. Nagata, A. B. Kapingidza, M. Azoitei, L. B. Tse, T. D. Scobey, R. L. Spreng, R. W. Rountree, C. T. DeMarco, T. N. Denny, C. W. Woods, E. W. Petzold, J. Tang, et al., *Nature* **2021**, *594*, 553.

[85] R. A. Hills, M. Howarth, *Curr. Opin. Biotechnol.* **2022**, *73*, 346.

[86] B. Zakeri, J. O. Fierer, E. Celik, E. C. Chittock, U. Schwarz-Linek, V. T. Moy, M. Howarth, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E690.

[87] D. Hatlem, T. Trunk, D. Linke, J. C. Leo, *Int. J. Mol. Sci.* **2019**, *20*, 2129.

[88] M. Letko, A. Marzi, V. Munster, *Nat. Microbiol.* **2020**, *5*, 562.

[89] Z. Wang, H. Gao, Y. Zhang, G. Liu, G. Niu, X. Chen, *Front. Chem. Sci. Eng.* **2017**, *11*, 633.

[90] X. Ma, F. Zou, F. Yu, R. Li, Y. Yuan, Y. Zhang, X. Zhang, J. Deng, T. Chen, Z. Song, Y. Qiao, Y. Zhan, J. Liu, J. Zhang, X. Zhang, Z. Peng, Y. Li, Y. Lin, L. Liang, G. Wang, Y. Chen, Q. Chen, T. Pan, X. He, H. Zhang, *Immunity* **2020**, *53*, 1315.

[91] A. E. Powell, K. Zhang, M. Sanyal, S. Tang, P. A. Weidenbacher, S. Li, T. D. Pham, J. E. Pak, W. Chiu, P. S. Kim, *ACS Cent. Sci.* **2021**, *7*, 183.

[92] W. Wang, B. Huang, Y. Zhu, W. Tan, M. Zhu, *Cell Mol. Immunol.* **2021**, *18*, 749.

[93] Y.-F. Kang, C. Sun, Z. Zhuang, R.-Y. Yuan, Q. Zheng, J.-P. Li, P.-P. Zhou, X.-C. Chen, Z. Liu, X. Zhang, X.-H. Yu, X.-W. Kong,

Q.-Y. Zhu, Q. Zhong, M. Xu, N.-S. Zhong, Y.-X. Zeng, G.-K. Feng, C. Ke, J.-C. Zhao, M.-S. Zeng, *ACS Nano* **2021**, *15*, 2738.

[94] D. Lainšček, T. Fink, V. Forstnerič, I. Hafner-Bratkovič, S. Orehek, Ž. Strmšek, M. Manček-Keber, P. Pečan, H. Esih, Š. Malenšek, J. Aupič, P. Dekleva, T. Plaper, S. Vidmar, L. Kadunc, M. Benčina, N. Omersa, G. Anderluh, F. Pojer, K. Lau, D. Hacker, B. E. Correia, D. Peterhoff, R. Wagner, V. Bergant, A. Herrmann, A. Pichlmair, R. Jerala, *Vaccines* **2021**, *9*, 431.

[95] B. J. Ward, P. Gobeil, A. Séguin, J. Atkins, I. Boulay, P.-Y. Charbonneau, M. Couture, M.-A. D'aoust, J. Dhaliwall, C. Finkle, K. Hager, A. Mahmood, A. Makarkov, M. P. Cheng, S. Pillet, P. Schimke, S. St-Martin, S. Trépanier, N. Landry, *Nat. Med.* **2021**, *27*, 1071.

[96] P. A. Gobeil, S. Pillet, I. Boulay, N. Charland, A. Lorin, M. Cheng, D. Vinh, P. Boutet, R. Van Der Most, F. Roman, M. De los Angeles Ceregido Perez, M.-A. D'Aoust, N. Landry, B. J. Ward, *medRxiv* **2021**, https://doi.org/10.1101/2021.08.04.21261507.

[97] O. A. Ortega-Rivera, M. D. Shin, A. Chen, V. Beiss, M. A. Moreno-Gonzalez, M. A. Lopez-Ramirez, M. Reynoso, H. Wang, B. L. Hurst, J. Wang, J. K. Pokorski, N. F. Steinmetz, *J. Am. Chem. Soc.* **2021**, *143*, 14748.

[98] S. Peng, F. Cao, Y. Xia, X.-D. Gao, L. Dai, J. Yan, G. Ma, *Adv. Mater.* **2020**, *32*, 2004210.

[99] A. Sasidharan, N. A. Monteiro-Riviere, *Nanomed. Nanobiotechnol.* **2015**, *7*, 779.

[100] X. Hou, T. Zaks, R. Langer, Y. Dong, *Nat. Rev. Mater.* **2021**, *6*, 1078.

[101] Y. Zhang, C. Sun, C. Wang, K. E. Jankovic, Y. Dong, *Chem. Rev.* **2021**, *121*, 12181.

[102] J. Kim, Y. Eygeris, M. Gupta, G. Sahay, *Adv. Drug Delivery Rev.* **2021**, *170*, 83.

[103] U. Elia, S. Ramishetti, R. Rosenfeld, N. Dammes, E. Bar-Haim, G. S. Naidu, E. Makdasi, Y. Yahalom-Ronen, H. Tamir, N. Paran, O. Cohen, D. Peer, *ACS Nano* **2021**, *15*, 9627.

[104] N.-N. Zhang, X.-F. Li, Y.-Q. Deng, H. Zhao, Y.-J. Huang, G. Yang, W.-J. Huang, P. Gao, C. Zhou, R.-R. Zhang, Y. Guo, S.-H. Sun, H. Fan, S.-L. Zu, Q. Chen, Q. He, T.-S. Cao, X.-Y. Huang, H.-Y. Qiu, J.-H. Nie, Y. Jiang, H.-Y. Yan, Q. Ye, X. Zhong, X.-L. Xue, Z.-Y. Zha, D. Zhou, X. Yang, Y.-C. Wang, B. Ying, et al., *Cell* **2020**, *182*, 1271.

[105] W. Tai, X. Zhang, A. Drelich, J. Shi, J. C. Hsu, L. Luchsinger, C. D. Hillyer, C.-T. K. Tseng, S. Jiang, L. Du, *Cell Res.* **2020**, *30*, 932.

[106] P. F. McKay, K. Hu, A. K. Blakney, K. Samnuan, J. C. Brown, R. Penn, J. Zhou, C. R. Bouton, P. Rogers, K. Polra, P. J. C. Lin, C. Barbosa, Y. K. Tam, W. S. Barclay, R. J. Shattock, *Nat. Commun.* **2020**, *11*, 3523.

[107] X. Xia, *Vaccines* **2021**, *9*, 734.

[108] M. D. Buschmann, M. J. Carrasco, S. Alishetty, M. Paige, M. G. Alameh, D. Weissman, *Vaccines* **2021**, *9*, 65.

[109] R. Yang, Y. Deng, B. Huang, L. Huang, A. Lin, Y. Li, W. I/, J Liu, S. Lu, Z. Zhan, Y. Wang, R A, W. Wang, P. Niu, L. Zhao, S. Li, X. Ma, L. Zhang, Y. Zhang, W. Yao, X. Liang, J. Zhao, Z. Liu, X. Peng, H. Li, W. Tan, *Signal Transduction Targeted Ther.* **2021**, *6*, 213.

[110] V. S. Moorthy, W. R. Ballou, *Malaria J.* **2009**, *8*.

[111] A. Roberts, E. W. Lamirande, L. Vogel, B. Baras, G. Goossens, I. Knott, J. Chen, J. M. Ward, V. Vassilev, K. Subbarao, *Viral Immunol.* **2010**, *23*, 509.

[112] S. Shao, J. Geng, H. Ah Yi, S. Gogia, S. Neelamegham, A. Jacobs, J. F. Lovell, *Nat. Chem.* **2015**, *7*, 438.

[113] S. E. Magnusson, A. F. Altenburg, K. L. Bengtsson, F. Bosman, R. D. De Vries, G. F. Rimmelzwaan, L. Stertman, *Immunol. Res.* **2018**, *66*, 224.

[114] S. E. Magnusson, J. M. Reimer, K. H. Karlsson, L. Lilja, K. L. Bengtsson, L. Stertman, *Vaccine* **2013**, *31*, 1725.

[115] J. M. Reimer, K. H. Karlsson, K. Lövgren-Bengtsson, S. E. Magnusson, A. Fuentes, L. Stertman, *PLoS One* **2012**, *7*, e41451.

[116] S. Bangaru, G. Ozorowski, H. L. Turner, A. Antanasijevic, D. Huang, X. Wang, J. L. Torres, J. K. Diedrich, J.-H. Tian, A. D. Portnoff, N. Patel, M. J. Massare, J. R. Yates, D. Nemazee, J. C. Paulson, G. Glenn, G. Smith, A. B. Ward, *Science* **2020**, *370*, 1089.

[117] World Health Organization & United Nations Children's Fund (UNICEF) COVID-19 Vaccination: Supply and Logistics Guidance: Interim Guidance, 12 February **2021**, World Health Organization, https://apps.who.int/iris/handle/10665/339561.

[118] K. AboulFotouh, Z. Cui, R. O. Williams, *AAPS PharmSciTech* **2021**, *22*, 126.

[119] M. T. Mabrouk, W.-C. Huang, B. Deng, N. Li-Purcell, A. Seffouh, J. Ortega, G. Ekin Atilla-Gokcumen, C. A. Long, K. Miura, J. F. Lovell, *Int. J. Pharm.* **2020**, *589*, 119843.

[120] M. T. Mabrouk, K. Chiem, E. Rujas, W.-C. Huang, D. Jahagirdar, B. Quinn, M. Surendran Nair, R. H. Nissly, V. S. Cavener, N. R. Boyle, T. A. Sornberger, S. V. Kuchipudi, J. Ortega, J.-P. Julien, L. Martinez-Sobrido, J. Lovell, *Sci. Adv.* **2021**, *7*, eabj1476.

[121] M. Alberer, U. Gnad-Vogt, H. S. Hong, K. T. Mehr, L. Backert, G. Finak, R. Gottardo, M. A. Bica, A. Garofano, S. D. Koch, M. Fotin-Mleczek, I. Hoerr, R. Clemens, F. Von Sonnenburg, *Lancet* **2017**, *390*, 1511.

[122] E. Korkmaz, S. C. Balmert, T. L. Sumpter, C. D. Carey, G. Erdos, L. D. Falo, *Adv. Drug Delivery Rev.* **2021**, *171*, 164.

[123] Y. Yin, W. Su, J. Zhang, W. Huang, X. Li, H. Ma, M. Tan, H. Song, G. Cao, S. Yu, D. Yu, J. H. Jeong, X. Zhao, H. Li, G. Nie, H. Wang, *ACS Nano* **2021**, *15*, 14347.

[124] E. Kim, G. Erdos, S. Huang, T. W. Kenniston, S. C. Balmert, C. D. Carey, V. S. Raj, M. W. Epperly, W. B. Klimstra, B. L. Haagmans, E. Korkmaz, L. D. Falo, A. Gambotto, *EBioMedicine* **2020**, *55*, 102743.

[125] P. Tebas, S. Yang, J. D. Boyer, E. L. Reuschel, A. Patel, A. Christensen-Quick, V. M. Andrade, M. P. Morrow, K. Kraynyak, J. Agnes, M. Purwar, A. Sylvester, J. Pawlicki, E. Gillespie, I. Maricic, F. I. Zaidi, K. Y. Kim, Y. Dia, D. Frase, P. Pezzoli, K. Schultheis, T. R. F. Smith, S. J. Ramos, T. Mcmullan, K. Buttigieg, M. W. Carroll, J. Ervin, M. C. Diehl, E. Blackwood, M. P. Mammen, et al., *EClinicalMedicine* **2021**, *31*, 100689.

[126] K. Modjarrad, C. C. Roberts, K. T. Mills, A. R. Castellano, K. Paolino, K. Muthumani, E. L. Reuschel, M. L. Robb, T. Racine, M.-D. Oh, C. Lamarre, F. I. Zaidi, J. Boyer, S. B. Kudchodkar, M. Jeong, J. M. Darden, Y. K. Park, P. T. Scott, C. Remigio, A. P. Parikh, M. C. Wise, A. Patel, E. K. Duperret, K. Y. Kim, H. Choi, S. White, M. Bagarazzi, J. M. May, D. Kane, H. Lee, et al., *Lancet Infect. Dis.* **2019**, *19*, 1013.

[127] P. Tebas, K. A. Kraynyak, A. Patel, J. N. Maslow, M. P. Morrow, A. J. Sylvester, D. Knoblock, E. Gillespie, D. Amante, T. Racine, T. Mcmullan, M. Jeong, C. C. Roberts, Y. K. Park, J. Boyer, K. E. Broderick, G. P. Kobinger, M. Bagarazzi, D. B. Weiner, N. Y. Sardesai, S. M. White, *J. Infect. Dis.* **2019**, *220*, 400.

[128] P. Tebas, C. C. Roberts, K. Muthumani, E. L. Reuschel, S. B. Kudchodkar, F. I. Zaidi, S. White, A. S. Khan, T. Racine, H. Choi, J. Boyer, Y. K. Park, S. Trottier, C. Remigio, D. Krieger, S. E. Spruill, M. Bagarazzi, G. P. Kobinger, D. B. Weiner, J. N. Maslow, *N. Engl. J. Med.* **2021**, *385*, e35.

[129] K. Badizadegan, J. L. Goodson, P. A. Rota, K. M. Thompson, *Expert Rev. Vaccines* **2020**, *19*, 175.

[130] E. Korkmaz, S. C. Balmert, C. D. Carey, G. Erdos, L. D. Falo, *Expert Opin. Drug Delivery* **2021**, *18*, 151.

[131] F. E. Lund, T. D. Randall, *Science* **2021**, *373*, 397.

[132] W. F. Tonnis, G. F. Kersten, H. W. Frijlink, W. L. J. Hinrichs, A. H. De Boer, J.-P. Amorij, *J. Aerosol Med. Pulm. Drug Delivery* **2012**, *25*, 249.

[133] A. O. Hassan, N. M. Kafai, I. P. Dmitriev, J. M. Fox, B. K. Smith, I. B. Harvey, R. E. Chen, E. S. Winkler,

A. W. Wessel, J. B. Case, E. Kashentseva, B. T. Mccune, A. L. Bailey, H. Zhao, L. A. Vanblargan, Y.-N. Dai, M. Ma, L. J. Adams, S. Shrihari, J. E. Danis, L. E. Gralinski, Y. J. Hou, A. Schäfer, A. S. Kim, S. P. Keeler, D. Weiskopf, R. S. Baric, M. J. Holtzman, D. H. Fremont, D. T. Curiel, et al., *Cell* **2020**, *183*, 169.

[134] S. Wu, J. Huang, Z. Zhang, J. Wu, J. Zhang, H. Hu, T. Zhu, J. Zhang, L. Luo, P. Fan, B. Wang, C. Chen, Y. Chen, X. Song, Y. Wang, W. Si, T. Sun, X. Wang, L. Hou, W. Chen, *Lancet Infect. Dis.* **2021**, *21*, 1654.

[135] D. I. Staquicini, F. H. F. Tang, C. Markosian, V. J. Yao, F. I. Staquicini, E. Dodero-Rojas, V. G. Contessoto, D. Davis, P. O'brien, N. Habib, T. L. Smith, N. Bruiners, R. L. Sidman, M. L. Gennaro, E. C. Lattime, S. K. Libutti, P. C. Whitford, S. K. Burley, J. N. Onuchic, W. Arap, R. Pasqualini, *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2105739118.

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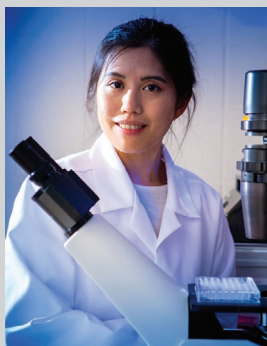
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