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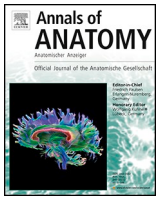

Minireview

# Spike protein-related proteinopathies: A focus on the neurological side of spikeopathies

Andreas Posa

*University Clinics and Outpatient Clinics for Radiology, Neuroradiology and Neurology, Martin Luther University Halle-Wittenberg, Ernst-Grube-Straße 40, Halle 06120, Germany*

A R T I C L E I N F O

*Keywords:*
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A B S T R A C T

*Background:* The spike protein (SP) is an outward-projecting transmembrane glycoprotein on viral surfaces. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), responsible for COVID-19 (Coronavirus Disease 2019), uses SP to infect cells that express angiotensin converting enzyme 2 (ACE2) on their membrane. Remarkably, SP has the ability to cross the blood-brain barrier (BBB) into the brain and cause cerebral damage through various pathomechanisms. To combat the COVID-19 pandemic, novel gene-based products have been used worldwide to induce human body cells to produce SP to stimulate the immune system. This artificial SP also has a harmful effect on the human nervous system.
*Study design:* Narrative review.
*Objective:* This narrative review presents the crucial role of SP in neurological complaints after SARS-CoV-2 infection, but also of SP derived from novel gene-based anti-SARS-CoV-2 products (ASP).
*Methods:* Literature searches using broad terms such as "SARS-CoV-2", "spike protein", "COVID-19", "COVID-19 pandemic", "vaccines", "COVID-19 vaccines", "post-vaccination syndrome", "post-COVID-19 vaccination syndrome" and "proteinopathy" were performed using PubMed. Google Scholar was used to search for topic-specific full-text keywords.
*Conclusions:* The toxic properties of SP presented in this review provide a good explanation for many of the neurological symptoms following SARS-CoV-2 infection and after injection of SP-producing ASP. Both SP entities (from infection and injection) interfere, among others, with ACE2 and act on different cells, tissues and organs. Both SPs are able to cross the BBB and can trigger acute and chronic neurological complaints. Such SP-associated pathologies (spikeopathies) are further neurological proteinopathies with thrombogenic, neurotoxic, neuroinflammatory and neurodegenerative potential for the human nervous system, particularly the central nervous system. The potential neurotoxicity of SP from ASP needs to be critically examined, as ASPs have been administered to millions of people worldwide.

## 1. SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

### 1.1. SARS-CoV-2: a new coronavirus

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2; genus: Betacoronavirus (Li et al., 2021a)) was discovered at the end of December 2019 in Wuhan, the capital of Hubei Province in central China (Tang et al., 2020), and is held responsible for COVID-19 (Coronavirus Disease 2019) (Theoharides and Kempuraj, 2023) and the pandemic declaration by the World Health Organization (WHO) on 11 March 2020 (Mistry et al., 2022). The complete genome sequence of SARS-CoV-2 showed a high nucleotide identity to bat SARS-related coronaviruses (RaTG13: 96.13 % (28720 / 29875) (Paraskevis et al., 2020; Zhou et al., 2020), BANAL-20–52: 96.85 % (28940 / 29881) (Temmam et al., 2022)), but a lower similarity to previous pandemic coronaviruses (SARS-CoV-1: about 79 %, MERS-CoV: about 50 %) (Lu et al., 2020; Gralinski and Menachery, 2020). The geographical origin of SARS-CoV-2 is currently located in Southeast Asia (Laos, Vietnam) and Southern China (Yunnan Province) (Chen et al., 2024).

### 1.2. SARS-CoV-2: special features

SARS-CoV-2 differs from other coronaviruses in several unique

*E-mail address:* andreas.posa@medizin.uni-halle.de.

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genomic, phylogenetic and structural features (Vkovski et al., 2021). These features mainly concern the spike protein (SP), with (1) special structural and mutational features in the (a) S protein receptor binding motif (RBM), (b) receptor binding domain (RBD), and (c) fusion domain (Cueno and Imai, 2021; Jaimes et al., 2020), (2) unique insertions and enhanced nuclear localisation signals (NLSs) in the nucleocapsid protein (Igyártó and Qin, 2024; Sattar et al., 2023), and (3) a unique (among all previously known Sarbecovirus strains) (Chen et al., 2024) RRAR sequence in its furin cleavage site (FCS) (Kumavath et al., 2021). In addition, SARS-CoV-2 is the only coronavirus with a prion-like domain found in the RBD of the S1 region of SP (Tetz and Tetz, 2022). These special features in SPs of SARS-CoV-2 are associated with (1) altered host switching from animals to humans (Gussow et al., 2020), (2) increased human-to-human transmissibility (Coutard et al., 2020), (3) altered ability to bind to angiotensin-converting enzyme 2 (ACE2) (Cao et al., 2020; Hatmal et al., 2020), (4) increased infectivity (Coutard et al., 2020) and (5) increased fatality rate (Gussow et al., 2020).

In addition, SARS-CoV-2 has other unique protein features, particularly in the proteins NSP3 (non-structural protein 3) and ORF9 (open reading frame 9), which also increase transmissibility and infectivity in humans (Cotten et al., 2021). In addition, compared to other coronaviruses, SARS-CoV-2 shows an altered activation of the IRE1α/XBP1 signalling pathway (endoplasmic reticulum stress signalling pathway; IRE1α: inositol-requiring enzyme 1 α; XBP-1: X box binding protein 1), which allows it to evade the host organism's immune system (Nguyen et al., 2022). In summary, these special, and in some cases unique features of SARS-CoV-2 influence its transmissibility, infectivity, immune defence and fatality rate. Devaux and Fantini (2023) further describe a possible contribution of rare alleles of human ACE2 in the emergence of SARS-CoV-2 variants escaping the immune response (Devaux and Fantini; 2023).

### 1.3. SARS-CoV-2: spike protein

The SPs of SARS-CoV-2 is an outward-projecting transmembrane glycoprotein peplomeric structure on the surface of the viral envelope (Cueno and Imai, 2021; Jaimes et al., 2020; Yao et al., 2020). It serves as a ligand for docking to the cell surface of the target cell and as a fusogenic protein for entry into the target cell (Wal et al., 2022). This aspect was already known from other coronaviruses prior to 2020 (Belouzard et al., 2012; Li, 2016). The term "spike" refers to the protruding peplomer structure visible under electron microscopy (as in coronaviruses, for example), in contrast to viruses that do not have such a prominent surface structure (Wrapp et al., 2020; Yao et al., 2020).

The SP is a homotrimeric protein (Li et al., 2022a) and one of the four structural proteins of SARS-CoV-2 (Wang et al., 2020). There are 15–30 freely rotating homotrimers of SPs on the surface of a virion (Kadam et al., 2021). Each of the three identical monomers is cleaved into two subunits (S1 and S2) by proteolysis by a furin-like protease during viral transit (Jackson et al., 2021). The S1 subunit is located at the distal, outward-projecting end of SP and consists of an N-terminal domain and a trimer of three RBDs (Granados-Riveron and Aquino-Jarquin, 2021; Mittal et al., 2020; Parry et al., 2023). The S2 subunit consists mainly of a C-terminal region that forms the stalk of SP and is embedded proximally in the virus membrane (Granados-Riveron and Aquino-Jarquin, 2021; Mittal et al., 2020; Parry et al., 2023) (Fig. 1). The FCS in SP is crucial for the binding to and penetration of the virus into host cells (Coutard et al., 2020; Hasan et al., 2020; Hoffmann et al., 2020a). As already mentioned, SARS-CoV-2, in contrast to other coronaviruses (Chen et al., 2024; Örd et al., 2020), has the sequence RRAR on this FCS, which facilitates the cleavage of SP into its two subunits (Kumavath et al., 2021) and thus increases the transmissibility and infectivity of SARS-CoV-2 (Coutard et al., 2020). The SP determines the host and cell tropism of SARS-CoV-2 (Wang et al., 2020; Zhu et al., 2021), whereby the specific ACE2 binding of SP is achieved via the RBD on S1 (Colunga Biancatelli et al., 2021; Jackson et al., 2021).

### 1.4. SARS-CoV-2: ACE2 binding

SARS-CoV-2 (like other coronaviruses) (Petrosillo et al., 2020) uses SPs on its envelope surface to infect target cells that express ACE2 on their membrane, which acts as a receptor (Bellavite et al., 2023; Theoharides and Kempuraj, 2023). The penetration of SARS-CoV-2 into cells is mainly based on the interaction of SP with ACE2 (Bellavite et al., 2023; Jackson et al., 2021; Lan et al., 2020; Lei et al., 2021; Perrotta et al., 2020; Tai et al., 2020; Zhang et al., 2021) (Fig. 2). For cell entry, SARS-CoV-2 would also need a SP priming by the host cell transmembrane protease serine subtype 2 (TMPRSS2) (Cao et al., 2020;

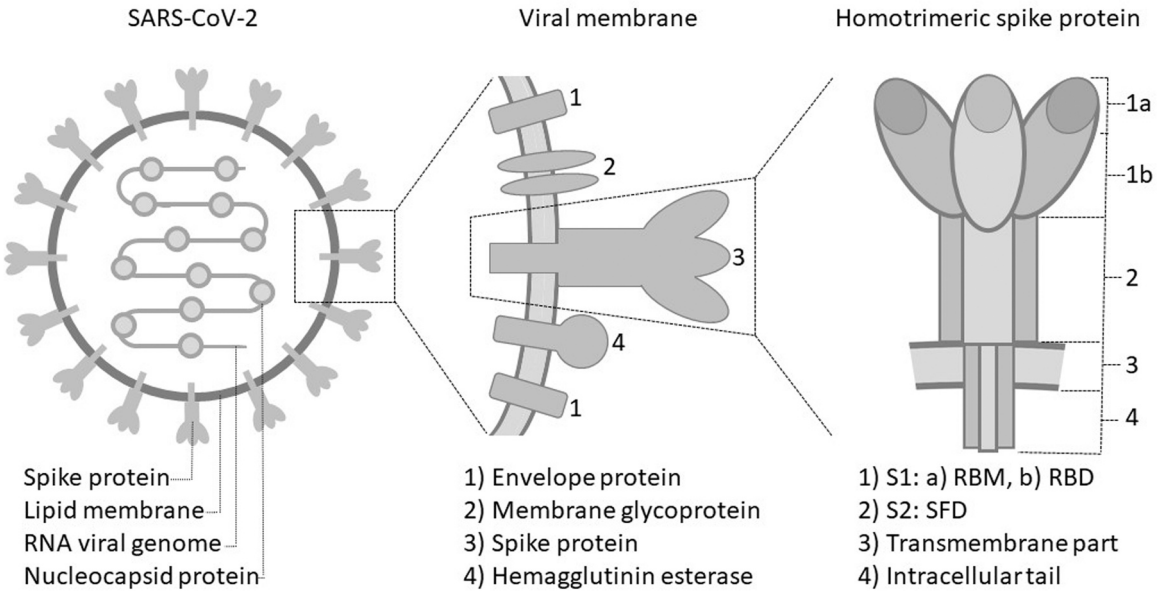


**Fig. 1.** Schematic representation of SARS-CoV-2 (left), the four structural proteins of the viral membrane (middle) and the homotrimeric spike protein (SP) (right) (modified from Mistry et al., 2022; Mittal et al., 2020). S1: S1 subunit at the distal, outward-projecting end of SP; RBM: receptor binding motif; RBD: receptor binding domain; S2: S2 subunit of a C-terminal region that forms the stalk of SP and is embedded proximal to the viral membrane; SFD: stalk fusion domain. RNA: ribonucleic acid.

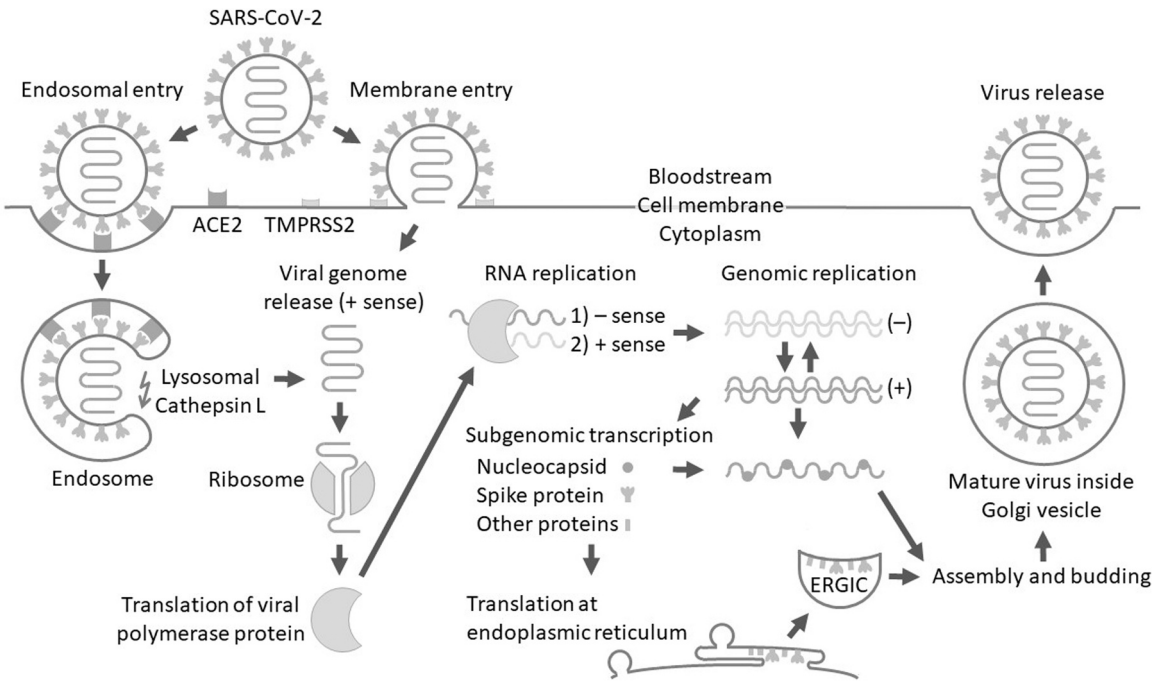


**Fig. 2.** Schematic representation of the SARS-CoV-2 lifecycle (modified from Duan et al., 2020; Harrison et al., 2020). ACE2: angiotensin-converting enzyme 2, TMPRSS2: transmembrane protease serine 2, ERGIC: endoplasmic-reticulum-Golgi intermediate compartment. RNA: ribonucleic acid.

Hoffmann et al., 2020b) (Fig. 2). ACE2 occurs in membrane-bound form on various cell types, including upper respiratory and gastrointestinal mucosa, kidney, heart, endothelium, blood vessels, platelets and in soluble form in the plasma (Bellavite et al., 2023; Cao et al., 2020; Lamers et al., 2020; Ortiz et al., 2020; Verdecchia et al., 2020; Zhang et al., 2020a). According to current knowledge, there are multiple interactions between different SP options (soluble vs. cell-bound; whole protein vs. peptide fragments) and different ACE2 options (soluble vs. cell-bound) (Trougakos et al., 2022). This can lead to internalisation and degradation of ACE2 throughout the organism (Deshotels et al., 2014; Gao et al., 2022a; Ramos et al., 2021), with destabilising consequences for the renin-angiotensin-aldosterone system (RAAS) (vascular and cardiac dysregulation, inflammatory and thrombogenic responses) (Cao et al., 2020; Tabarsi et al., 2022a, b; Trougakos et al., 2021; Verdecchia et al., 2020; Zhang et al., 2020a) and other body regions (Angeli et al., 2022; Barton et al., 2021; Bellavite et al., 2023; Colunga Biancatelli et al., 2021; Partridge et al., 2021; Taka et al., 2020; Zhu et al., 2021a). RAAS plays a central role in the human immune response to SARS-CoV-2 by acting on macrophages and monocytes, which are essential for proper immune homeostasis (Cao et al., 2020). Dysregulation of this ACE2-RAAS axis contributes to various SARS-CoV-2 pathologies, including chaotic immune responses (Cao et al., 2020).

In addition to its high ACE2 affinity, SP also binds to p53, BP1, and BRCA1 and 2, allowing for a wide range of potential biological and carcinogenic interference (Parry et al., 2023; Singh and Singh, 2020). Furthermore, SP inhibits various DNA repair processes (Jiang and Mei, 2021), with corresponding carcinogenic effects in the mouse model (Lai et al., 2021). Moreover, SPs have been shown in cell lines and experimental mouse models to release lipids from membranes and interfere with membrane lipid exchange, negatively affecting membrane stability (Correa et al., 2021).

### 1.5. *SARS-CoV-2: blood-brain barrier permeability*

Autopsy studies on COVID-19 patients have shown that SARS-CoV-2 infects not only the respiratory tract but also other non-respiratory cells, fluids, tissues, vascular endothelia (at physiological barriers) and organs, including the brain (Elsoukkary et al., 2021; Schurink et al., 2020; Stein et al., 2022; Tian et al., 2020; Xu et al., 2020; Yao et al., 2021). Thus, COVID-19 has respiratory and non-respiratory manifestations. Although autopsy studies have shown that the most common immediate cause of COVID-19 death was diffuse pulmonary alveolar damage, followed by multiorgan failure (von Stillfried et al., 2022). Even at the beginning of the COVID-19 pandemic, SARS-CoV-2 was detected in the human brain in post-mortem studies (Matschke et al., 2020). Olfactory transmucosal SARS-CoV-2 invasion has been described as a possible route of entry into the brain (Meinhardt et al., 2021). Further, it has been shown that SARS-CoV-2 RNA can persist in the human body for up to 230 days after the onset of COVID-19 symptoms, including the brain (Stein et al., 2022). The neuronal damage patterns of SARS-CoV-2 in the brain are diverse, complex (Spudich and Nath, 2022; Varatharaj et al., 2020) and have also been described for other coronaviruses (Kase and Okano, 2021). It has been shown that SARS-CoV-2 infection causes neuron-neuron, neuron-glia and glia-glia fusion in murine hippocampal cultures and in human-derived brain organoids (Martínez-Mármol et al., 2023). This fusion impairs neuronal activity and communication and is one mechanism by which SARS-CoV-2 damages the nervous system and causes neuropathological disorders (Martínez-Mármol et al., 2023). Theoharides and Kempuraj (2023) described possible pathomechanisms of SARS-CoV-2 associated Neuro-COVID (Theoharides and Kempuraj, 2023). Although SARS-CoV-2 is primarily considered a respiratory pathogen, it also acts as a neurotropic pathogen. Here, immune activation and inflammation within the central nervous system (CNS) are the main drivers of neurological diseases in Neuro-COVID (Spudich and Nath, 2022). Autopsy studies of COVID-19 patients show infiltration of macrophages, CD8 + T lymphocytes in perivascular regions, and widespread microglial activation throughout the brain (Matschke et al., 2020). Interestingly, single-cell analysis of brain tissue demonstrated CD8 + T lymphocyte infiltration and microglial activation, but without evidence of viral RNA detection in brain parenchyma cells (Fullard et al., 2021).

In particular, S1 of SP can cross the blood-brain barrier (BBB) and enter the brain in animal studies, as described in 2020 (Rhea et al., 2020). This was also demonstrated in human cell culture models, where

SP effectively crossed the human brain endothelial cell barrier (Petrovszki et al., 2022). Studies in mouse models and human post-mortem tissues have shown that SARS-CoV-2 SP accumulates in the cranial skull marrow, brain meninges, and brain parenchyma (Rong et al., 2023). The SP crosses the BBB by adsorptive transcytosis (Rhea et al., 2020), in which the interaction with ACE2 plays an important role (DeOre et al., 2021; Rong et al., 2023). It disrupts the function of the BBB by dysregulating ACE2 expression and RhoA proteins, leading to a loss of BBB integrity, thus facilitating the passage of SP (and other substances) into the brain (Buzhdygan et al., 2020; DeOre et al., 2021; Lei et al., 2021; Kim et al., 2021a).

The endothelial cells of the brain (on which ACE2 is also physiologically expressed) (Chen et al., 2021a) are one of the most important components of the BBB and represent a major barrier to the entry of pathogenic or infectious agents into the brain (Kim et al., 2021a). However, this BBB is not an obstacle for SP (Roh et al., 2024) (Fig. 3). Once in the brain, SP can damage the CNS in a variety of ways, which will be described in more detail below. Knowledge of SP's unique ability to cross the BBB has significant and essential implications for the understanding of acute and chronic neurological and neuropsychiatric symptoms following a SARS-CoV-2 infection (especially Long-COVID disease) (Rong et al., 2023; Spudich and Nath, 2022; Theoharides, 2022), but also, as will be shown, following administration of anti-SARS-CoV-2 products (ASPs).

## 2. Spike protein and the central nervous system

### 2.1. Spike protein: Thrombogenic damage

The SP can lead to thrombotic events in a variety of ways. The high ACE2 affinity of SP induces platelet aggregation, thrombosis and blood clot-promoting inflammation (Angeli et al., 2021, 2022), which was already demonstrated in the mouse model at the beginning of the pandemic (Zhang et al., 2020b). In particular, the unbound free SP interacts with platelet integrins and triggers platelet deformation and coagulation via filopodia induction (Kuhn et al., 2023). The SP also dysregulates antithrombin (Zheng et al., 2021) and fibrinolysis (Ryu et al., 2021) and can promote platelet coagulation-promoting hyperreactivity via an inhibitory interaction with the α7-nicotinic acetylcholine receptor (α7nAchR) (Changeux et al., 2020; OBrien et al., 2023). In addition, SP has been shown to induce erythrocyte haemagglutination, probably via shape and function-altering electrostatic interpolation of positive charges on SP with negative charges on erythrocytes (Boschi et al., 2022). The complement system may also be affected by SP, resulting in increased coagulopathy (Parry et al., 2023; Perico et al., 2022; Rong et al., 2023). The influences of SP on endothelial cell function and inflammatory and immune responses described below also have a thrombogenic potential.

### 2.2. Spike protein: cerebral tissue and endothelial cell damage

In addition to the direct neurotoxic damage to brain tissue caused by SP, including cell death (Rong et al., 2023), SP primarily have a damaging effect on cerebral endothelial cells in blood vessels (Kim et al., 2021a; Nuovo et al., 2021) as well as on microvascular homeostasis (Panigrahi et al., 2021; Perico et al., 2022). This can occur in a variety of ways: (1) Induction of the degradation of the junctional proteins (a) vascular endothelial (VE) cadherin, (b) junctional adhesion molecule (JAM) A, (c) connexin-43, and (d) platelet endothelial cell adhesion molecule (PECAM) 1 (Raghavan et al., 2021). (2) Activation of (a) integrin α5β1, (b) NF-κB (nuclear factor 'kappa-light-chain-enhancer' of activated B cells) (Cosentino and Marino, 2022; Olajide et al., 2022; Robles et al., 2021), (c) toll-like receptors (TLR2 & 4) and (d) the RAAS (Burnett et al., 2023; Cosentino and Marino, 2022; Fontes-Dantas et al., 2023; Sariol and Perlman, 2021; Vargas et al., 2020). (3) Increased expression of leukocyte adhesion molecules (Robles et al., 2021). (4) Mitochondrial damage through metabolic and molecular dysregulation in brain endothelial cells (Kim et al., 2021a).

All of these SP-related pathomechanisms lead to (1) pro-inflammatory and (2) apoptotic reactions in endothelial cells, (3) increased vascular permeability, (4) reduced vascular density, (5) impaired endothelial cell barrier function in BBB, and (6) reduced cerebral blood flow in the brain (Buzhdygan et al., 2020; Jeong et al., 2022; Erickson et al., 2021; Kim et al., 2021a; Raghavan et al., 2021; Robles et al., 2021; Theoharides and Kempuraj, 2023), as demonstrated in in vitro studies using BBB models (Buzhdygan et al., 2020) and in animal models using humanized ACE2 mice (Burnett et al., 2023; Foster et al., 2023; Jabi et al., 2022). The resulting neurological and vascular consequences are cerebrovascular and brain tissue rarefaction and cognitive dysfunction (Foster et al., 2023; Jabi et al., 2022; Rong et al., 2023). Post-mortem studies described cerebral morphological changes, neuronal necrosis, and loss in the capillaries of the choroid plexus in COVID-19 patients (Gomes et al., 2021; Yang et al., 2021a).

### 2.3. Spike protein: neuroinflammatory damage

In addition to endothelial inflammatory reactions, SP can cause further neuroinflammatory damage in a variety of ways (Kim et al., 2021a; Kumar et al., 2021; Li et al., 2021b; Rahman et al., 2021; Zhu et al., 2021b). For example, it activates (1) microglial purinergic signalling (Alves et al., 2023), (2) microglia / macrophages (e.g. activation of caspase-1 in BV-2 microglial cells) (Cao et al., 2021; Frank et al., 2022; Jeong et al., 2022; Olajide et al., 2022; Theoharides and Kempuraj, 2023), and (3) vascular pericytes (Khaddaj-Mallat et al., 2021), with corresponding neuroinflammatory consequences. A neuropathological analysis of the brains of 52 patients with COVID-19 showed perivascular inflammation with lymphocytic and microglial infiltration (Wierzba-Bobrowicz et al., 2021). In addition, post-mortem reports of

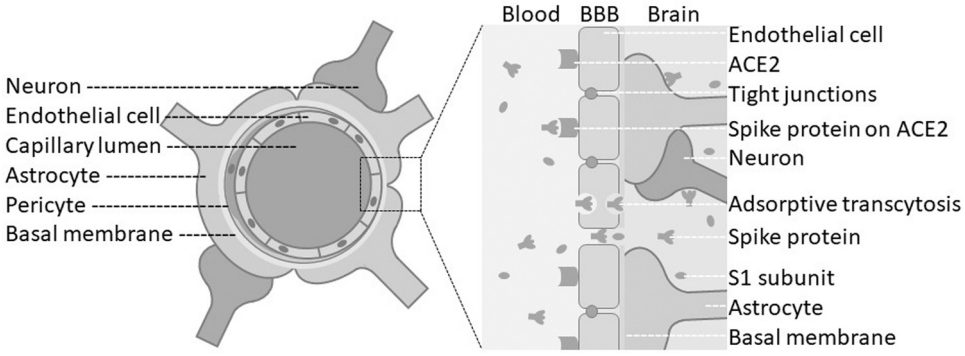


**Fig. 3.** Schematic representation of a cross-section through a cerebral capillary (left) and the blood-brain barrier (BBB) (right) (modified from Stefanou et al., 2022). To illustrate the passage of the spike protein and its S1 subunit across the BBB. ACE2: angiotensin-converting enzyme 2.

COVID-19 patients also showed significant cerebral neuroinflammation (Boroujeni et al., 2021; Dixon et al., 2020; Radhakrishnan and Kandasamy, 2022; Shen et al., 2022; Theoharides and Kempuraj, 2023). An important role in this context is played by pro-inflammatory factors such as TNF-α (tumor necrosis factor alpha), IL 1β / 6 / 18 (interleukins), NF-κB (nuclear factor 'kappa-light-chain-enhancer' of activated B cells), NRF2 (nuclear factor erythroid 2-related factor 2) (Cosentino and Marino, 2022; Khan et al., 2021; Oka et al., 2021; Olajide et al., 2022; Saha et al., 2022; Theoharides and Kempuraj, 2023; Tsilioni and Theoharides, 2023; Wang et al., 2007), T-cell receptors (TCR) and superantigens (Cheng et al., 2020). Furthermore, SP (particularly S1) functions as a pathogen-associated molecular pattern (PAMP), which induces neuroinflammation in animal studies in rats via the activation of pattern recognition receptors, independent of viral infection (Frank et al., 2022). In addition, SP may trigger neuroinflammatory processes due to their prion-like properties (see below) by stimulating the accumulation of toxic prion-like fibrils in neurons (Idrees and Kumar, 2021; Seneff et al., 2023).

### 2.4. Spike protein: neurodegenerative damage

Neurodegenerative and neuroinflammatory processes often go hand in hand (Guzmán-Martínez et al., 2019). Misfolded proteins are a hallmark of neurodegenerative diseases (Tsoi et al., 2023). Pathological protein misfolding can be exacerbated by external factors, such as viral infections (Hetz and Saxena, 2017).

SP can trigger neurodegenerative damage in the CNS via various mechanisms. SP has been shown to bind to amyloidogenic proteins such as amyloid-beta (Aβ), alpha-synuclein (α-syn), tau, prion and TDP-43, accelerating their aggregation and misfolding and leading to neurodegeneration (Cao et al., 2023; Idrees and Kumar, 2021; Nyström and Hammarström, 2022; Trougakos et al., 2022). Aβ1–42 in particular has a high affinity for S1 of SP (Hsu et al., 2021). Aβ1–42 increases the binding and thus the effect of S1 on ACE2 (Hsu et al., 2021). In the presence of S1, there is also a reduced clearance of Aβ1–42 (Hsu et al., 2021). These aspects suggest that SP tends to act as a functional amyloid and form toxic aggregates (Tavassoly et al., 2020).

SP has also been shown to have prion-like properties. It contains sequences that are characteristic of prion-like proteins and facilitates the accumulation of toxic, prion-like fibrils in neurons, contributing to neurodegenerative changes in the CNS (Kyriakopoulos et al., 2022; Perez et al., 2023; Seneff et al., 2023). In 2022, Tetz and Tetz identified the presence of prion-like domains in the SARS-CoV-2 SP (Tetz and Tetz, 2022). Interestingly, SP from other coronaviruses do not show such prion-like properties of their RBD (Tetz and Tetz, 2022; Parry et al., 2023). In the context of prion similarity, S1 also shows a "glycine zipper" motif, which is associated with susceptibility to misfolding and thus prion formation (Parry et al., 2023). SP can also induce the expression of prion protein (PrP) in the brain via hyperinflammation (Parry et al., 2023). The increase in prion glycoproteins (PrPC) can lead to misfolding of the prion conformation and generate prions and prion-related diseases (Norrby, 2011). In addition, SP activates signalling pathways such as mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), which are involved in neurotoxicity and prion-like disease processes (Kyriakopoulos et al., 2022; Suzuki et al., 2021). And it affects the transmembrane glycoprotein CD147, which can also promote neurodegenerative processes (Cosentino and Marino, 2022).

Furthermore, in vitro cell culture experiments have shown that SP is involved in the increased expression of α-Syn, a protein that tends to aggregate (Wu et al., 2022), which is thought to be responsible for a number of neurodegenerative diseases (Brás et al., 2020). In addition, the inhibitory effect of SP on the α7-nAChR of the cholinergic system has been demonstrated (Changeux et al., 2020; OBrien et al., 2023; Parry et al., 2023; Tillman et al., 2023). In the human nervous system (HNS), α7-nAChRs are highly expressed, especially in the hippocampus, cortex and limbic regions, and are involved in cognition, sensory information processing, attention, working memory and reward pathways (Parry et al., 2023). The inhibitory interaction of SP with CNS α7-nAChRs can also be considered pro-neurodegenerative, as the important role of α7-nAChRs in the pathogenesis of Alzheimer's disease (reduction of α7-nAChRs in the brain, especially in the hippocampus) has long been known (Ma and Qian, 2019; Parri et al., 2011).

## 3. Vaccines and the COVID-19 pandemic

Vaccines have been used since the late 18th century, with development in the laboratory beginning in the late 19th century and continuing on an immunological basis in the 20th century (D'Amelio et al., 2016; Plotkin, 2014). Although corresponding concepts have been considered since ancient times (Hussein et al., 2015), the widespread use of vaccines was achieved by the English physician Edward Anthony Jenner (1749–1823) in the 1790 s with the first vaccine against smallpox (Plotkin, 2003; Sern and Markel, 2005).

### 3.1. Vaccines: neurological post-vaccination syndrome

In addition to their estimated (Ioannidis et al., 2022; Parry et al., 2023; Roussel et al., 2020; Watson et al., 2022) and attributed benefits (Pezzotti et al., 2018; Rappuoli et al., 2014), vaccines and other immunostimulating drugs are known to have adverse effects on the organism. The term post-vaccination syndrome (PVS) has been established for conventional vaccines that have been used regularly to date. It encompasses a number of adverse effects and has long been known as a vaccine complication. PVS was first described in the early 20th century. Specifically, the first cases of post-vaccinal encephalitis were documented in Sweden in 1924 following smallpox vaccination (Heinertz, 1948), followed by others (Dodge, 1961). A significant increase in Guillain-Barre syndrome (GBS) was observed in the USA in 1976–1977 as part of a national flu vaccination program (Schonberger et al., 1979). More recent descriptions include post-HPV (human papillomavirus) vaccination syndrome (Martínez-Lavín, 2018; Martínez-Lavín and Tejada-Ruiz, 2020) and other autoimmune and inflammatory syndromes triggered primarily by adjuvants, which are referred to as ASIA syndrome (autoimmune syndromes induced by adjuvants) (Iremli et al., 2021; Shoenfeld and Agmon-Levin, 2011).

The effects of PVS can vary greatly in severity and type and include autoimmune and inflammatory reactions, neurological symptoms and other systemic reactions, with clinical symptoms including chronic pain, fatigue and cognitive impairment (Blitshteyn et al., 2018; Iremli et al., 2021; Martínez-Lavín and Tejada-Ruiz, 2020; Rosipal et al., 2014; Vera-Lastra et al., 2021). People with a conspicuous history of autoimmune diseases, allergic or convulsive reactions and a family history of these have an increased risk of PVS (Soriano et al., 2015). The administration of multiple vaccinations within a short period of time may increase the risk of developing PVS in vulnerable individuals (Martínez-Lavín and Tejada-Ruiz, 2020).

Neurological PVS can be demyelinating processes in the CNS (Karussis and Petrou, 2014). These include acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, attacks of multiple sclerosis (MS), Miller-Fisher syndrome and neuromyelitis optica spectrum disorders (NMOSD) (Kumar et al., 2019; Shoamanesh, 2012). In addition, cases of seizures following vaccination have been reported, particularly in children (Nacharova et al., 2021).

### 3.2. Anti-SARS-CoV-2 products: historical review

During the so-called COVID-19 pandemic (Rehman et al., 2020), the issue of vaccines received broad medical, political and social attention and relevance worldwide (Bhagat et al., 2020). In particular, gene-based medicines came into focus (Corbett et al., 2020), and it was only through this pandemic that their broad global clinical application and establishment was achieved (Mulligan et al., 2020; Rijkers et al., 2021).

Previously, mRNA / DNA-based technologies were mainly the subject of experimental scientific research, especially in cancer (Maruggi et al., 2019; Pardi et al., 2018; Schlake et al., 2012). Prior to the COVID-19 pandemic, mRNA products with the aim of immunizing against a respiratory infectious disease had never been approved for public use (Dolgin, 2021). Viral vector DNA products had also only been used to a limited extent against Ebola, dengue fever and Japanese encephalitis (McCann et al., 2022).

After the genetic sequence of SARS-CoV-2 was announced, the pharmaceutical science industry focused on the sequence regions encoding the gene message for SP. Almost all ASPs are based on SP from the original Wuhan Hu-1 strain (Jackson et al., 2021; Trougakos et al., 2022). The development of such gene-based products involved technical processes that had been available for a long time (Malone et al., 1989), but had never been used on a large or even global scale for human use (Bellavite et al., 2023). Originally, mRNA technology was primarily intended to replace or deliver a therapeutic protein (Pardi et al., 2015). To combat SARS-CoV-2, novel gene-based products were used, whose genetic material (mRNA/DNA) encodes the SP, the main surface protein of SARS-CoV-2 (Jackson et al., 2021). Other viral SARS-CoV-2 structures, such as for example the comparatively harmless nucleocapsid, would have been equally good candidates for immunisation from the outset (see below). ASPs are specified to transfect human cells to efficiently produce SARS-CoV-2 SP for an immune response (Kämmerer et al., 2024). This is intended to induce neutralising antibodies against SARS-CoV-2 in the host organism in order to prevent SP-ACE2-binding (Bellavite et al., 2023; Kämmerer et al., 2024).

### 3.3. Anti-SARS-CoV-2 products: product types

Several types of ASPs are currently available and in use worldwide (Bellavite et al., 2023). According to the WHO, more than 350 ASPs are in preclinical or clinical development, and ten (as of 2023) have been approved by the WHO for global use (Scholkmann and May, 2023). These products can be divided into four different types of mechanism: (1) “inactivated virus products” (Sinopharm’s Covilo, Sinovac’s CoronaVac; Bharat Biotech’s Covaxin), (2) “adjuvanted protein products” (Novavax’s Nuvaxovid and Covovax NVXCoV2373), (3) “messenger RNA (mRNA) products” (Moderna’s Spikevax mRNA-1273; Pfizer–BioNTech’s Comirnaty BNT162b2), and (4) “adenovirus vector–based DNA products” (AstraZeneca’s Vaxzevria and Covishield ChAdOx1, Johnson & Johnson–Janssen’s Ad26. COV2. S, Sputnik V and EpiVacCorona (Russia), iNCOVACC (India), Convidecia (China)) (Barouch, 2022). The gene-based products of Pfizer-BioNTech (BNT162b2, Comirnaty) (Oliver et al., 2020) and Moderna (mRNA-1273, Spikevax) (Oliver et al., 2021) were among the first substances to be approved (for emergency use) in December 2020 and are currently the most widely used substances in the US and Europe (Bellavite et al., 2023). Both products use a lipid nanoparticle platform to deliver the synthetic mRNA information to instruct the synthesis of SP in the infiltrated / transfected host cell.

Interestingly, in non-Western countries, traditional protein-based (CinnaGen/SpikoGen (Covax-19)) or inactivated virus vaccines (Bharat Biotech (Covaxin), Sinovac (CoronaVac)) were used for most ASP (Parry et al., 2023). In contrast, the novel gene-based products (mRNA and adenovirus DNA) were preferred in most Western countries (Igyártó and Qin, 2024; Parry et al., 2023). Nevertheless, it should be clearly emphasized at this point that all ASPs introduce the foreign SP into the human body, whether as inactivated virus product, as adjuvanted protein product, or as a gene-based product of injected mRNA or adenovirus vector-based DNA.

### 3.4. Anti-SARS-CoV-2 products: approval situation

Although the approval of the genetically engineered ASPs for worldwide clinical use in humans was formally granted surprisingly quickly (“warp speed”) (Gee et al., 2021; Kämmerer et al., 2024; Patel et al., 2022; Winch et al., 2021), further evidence of the qualitative and quantitative efficacy and, above all, the safety of such novel gene-based products must be provided on the basis of the experimental studies of phase 3 (Higdon et al., 2022; Kämmerer et al., 2024) and the observational studies of phase 4 that are still ongoing (Bellavite et al., 2023). In particular, since the proclaimed goal of immunizing large population groups (Dolgin and Ledford, 2023), healthy people (Sadeghalvad et al., 2022) and even adolescents and children (Tian and Yang, 2022) are affected by such measures. At this point, it must be clearly emphasized that at the time of approval and deployment of ASPs, phase 3 trials were still ongoing. Final results from completed and evaluated ASP studies were therefore not available. The final benefit-risk analysis, the safety, efficacy, and side effect profile, and the long-term effects of ASPs were therefore unknown and unpredictable. Despite this lack of data, millions of people worldwide received ASPs, including non-risk groups such as healthy adults, adolescents, and children.

It is now known that prior to their global launch in 2020, the novel gene-based ASPs had not undergone all the necessary product analyses required for Good Manufacturing Practices (GMP) regulation of a drug (according to the guidelines of the EMA (European Medicines Agency) (EMA, 2001) or the WHO (World Health Organisation) (WHO, 2005)). Many of the regularly required, lengthy and complex safety tests and toxicological analyses were bypassed in order to obtain the emergency approval status (Lalani et al., 2023; Parry et al., 2023). In addition, the placebo group of the approval trials was unblinded at the time of the emergency approval for ethical reasons (Stoehr et al., 2021), i.e. the group of untreated people was dissolved (Tsiatis and Davidian, 2021). This unblinding led to changes in the study protocols and to complex problems in assessing, in particular, the long-term efficacy and safety of such novel ASPs (Tsiatis and Davidian, 2021). In drug trials, a placebo control group is considered necessary in order to assess the efficacy of a new treatment in an unbiased manner and, most importantly, to create a basis for comparison (Jensen et al., 2017; Laursen et al., 2023; Streiner, 1999). It should also be noted that for large-scale mRNA-based ASP production, the manufacturing process was changed. This was followed by the mass production of DNA matrices using cloned shuttle vectors, which can be easily multiplied in bacterial cell culture systems (Kämmerer et al., 2024). However, this manufacturing process was not the same as the original one.

Furthermore, it is noteworthy that before 2020 there were no specific regulations for ASPs due to their novelty (Banoun, 2023). The WHO even admitted at the time that no detailed information was available at that time for the standardized manufacturing, safety and efficacy control of corresponding products (Liu et al., 2022).

### 3.5. Anti-SARS-CoV-2 products: immunostimulatory gene-based prodrugs

The novel gene-based ASPs used worldwide do not work like conventional protein-based vaccines or inactivated viral components in the proclaimed activation of the protective immune system (Banoun, 2023). This is because they deliver their immunisation message in the form of mRNA / DNA directly into various host cell types in multiple organ systems, which are then supposed to produce SP themselves (similar to SARS-CoV-2) in order to present it on their surface membrane (from which it can be secreted in soluble form and distributed systemically in the human body). This is intended to secondarily activate the immune system (Bellavite et al., 2023; Kämmerer et al., 2024; Trougakos et al., 2022) (Fig. 4). The body’s own, non-immune cells thus become antigen-presenting cells, with the potential risk of a cytopathic autoimmune reaction against cells that express foreign spike antigens (Parry et al., 2023). The host cell, pharmacologically transfected by gene-based ASPs, can produce large amounts of SP and / or its subunits / peptide fragments (Trougakos et al., 2022) and release them into the bloodstream (Cosentino and Marino, 2022; Heinz and Stiasny, 2021; Jackson et al., 2021), which can then spread throughout the body (Trougakos

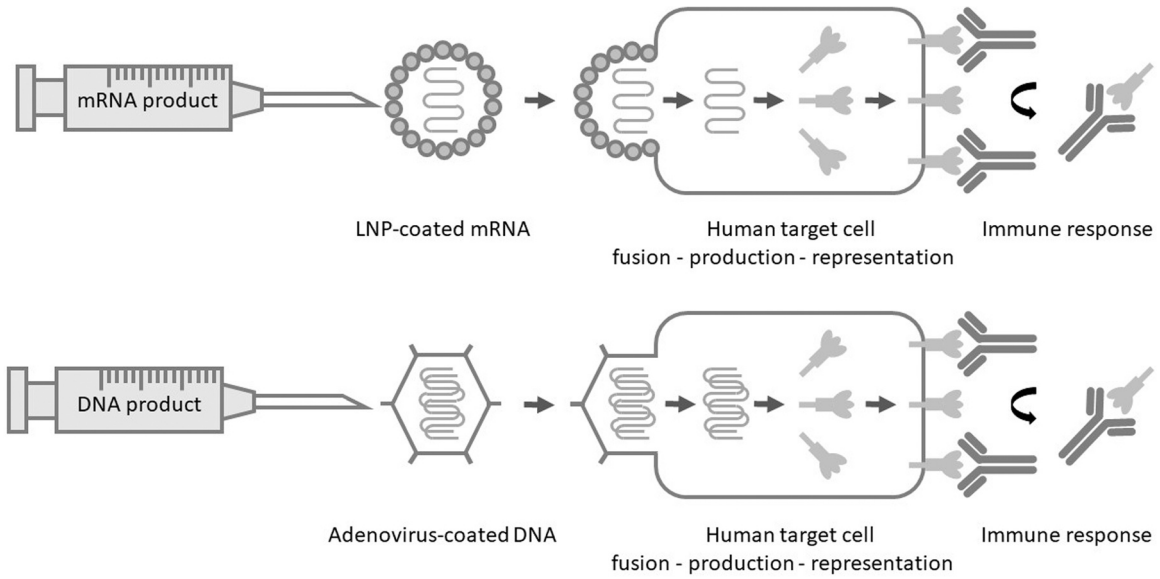


**Fig. 4.** Schematic representation of the functional mechanism of anti-SARS-CoV-2 products (ASPs) (top: mRNA products; bottom: adenovirus vector-based DNA products). Following ASP injection into the human body, the product reaches the human target cell (HTC), fuses with it and releases the genomic ASP material into the HTC. From this, the HTC itself produces the viral spike protein (SP). SP is then attached to the HTC surface and presented to the human immune system (HIS). This stimulates an immune response. The HIS thus comes into contact with SP (a viral surface protein). The aim of this immunisation is to enable the pre-formed HIS to respond more quickly and effectively to an invasion by SARS-CoV-2 viruses. RNA: ribonucleic acid. DNA: deoxyribonucleic acid. LNP: lipid nanoparticle.

et al., 2022). In addition, such gene-based products have been shown to induce neurogenetic responses (Trougakos et al., 2022), including epigenetic reprogramming of, for example, monocyte populations (Arunachalam et al., 2021).

ASPs, especially of the mRNA / DNA type, have been designed to induce a robust and sustained immune response (Li et al., 2022b). For this purpose, these products have been genetically stabilised (e.g. by poly(A) tail (Kyriakopoulos and McCullough, 2021; Sahin et al., 2014) and 3′ untranslated region (3′UTR) of human globin (Orlandini von Niessen et al., 2019)) in such a way that the transfected host cell is able to produce SP over a longer period of time (Bellavite et al., 2023), which are more stably incorporated into the host cell plasma membrane and thus presented by a further genetic modification (leader sequence for translation) (Bellavite et al., 2023). It is noteworthy in this context that mRNA from gene-based products has a higher guanine / cytosine (GC) content than the natural native SARS-CoV-2 mRNA (53 % BNT162b2 / 61 % mRNA-1273 vs. 36 %) (McKernan et al., 2021), which contributes to a further increase in SP production (Mauro and Chappell, 2014). It has long been known that high GC content increases mRNA levels in mammalian cells (Kudla et al., 2006). It has thus been shown that gene-based ASPs, due to their pharmacokinetics, produce a larger number of SPs in the body than the SARS-CoV-2 virus (Banoun, 2023; McKernan et al., 2021). Corresponding spike products can circulate continuously throughout the body (Trougakos et al., 2022).

In addition, unlike natural mRNA, ASP mRNA (nucleoside-modified mRNA, mod-mRNA, m-mRNA) can remain intact for days, allowing long-term expression of SPs (Granados-Riveron and Aquino-Jarquin, 2021; Igyártó and Qin, 2024; Kämmerer et al., 2024; Sahin et al., 2014). The SP can bind in different ways to (among others) different ACE2 types (cell-bound vs. soluble) and act on different cells, tissues and organs (Trougakos et al., 2022). In addition, it is noteworthy that the gene sequence of the ASPs contains the same FCS as the viral SARS-CoV-2 mRNA sequence (a section of the four basic amino acids Arg-Arg-Ala-Arg at the S1-S2 junction), which has an impact on the generation of the soluble S1 (as a product of ASPs) (Bellavite et al., 2023; Heinz and Stiasny, 2021; Trougakos et al., 2022; Zhang et al., 2020c).

The SP determines the host and cell tropism of SARS-CoV-2 (Wang et al., 2020; Zhu et al., 2021), whereby the specific ACE2 binding of SP is achieved via RBD on S1 (Jackson et al., 2021; Colunga Biancatelli et al., 2021). SP from ASPs shows a native-like mimicry with respect to receptor binding functionality and prefusion structure of SP from SARS-CoV-2 infection (Watanabe et al., 2021; Zhu et al., 2021). Thus, the main pathogen of SARS-CoV-2 infection (Jackson et al., 2021) is mimicked by the product (SP) of a health intervention (ASP). Thus, both types of SP (from SARS-CoV-2 infection as well as from ASP injection (in particular the mRNA products BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)) (Bellavite et al., 2023)) intervene in ACE2-controlled regulatory circuits. The undesirable effects of these SPs on, among others, the ACE2-controlled renin-angiotensin-aldosterone, inflammatory, coagulation, immune, cardiac, and circulatory systems (Almas et al., 2022; Angeli et al., 2021; Athyros and Doumas, 2022; Bellavite et al., 2023; Karlstad et al., 2022; Kim et al., 2021b; Kouhpayeh and Ansari, 2022; Lei et al., 2021; Sun et al., 2022; Zhu et al., 2021), but also on other systems in the human body are well known (Mahroum et al., 2022; Mingot-Castellano et al., 2022; Mohseni Afshar et al., 2023; Nunez-Castilla et al., 2022; Pour Mohammad et al., 2022; Shafiq et al., 2021).

Due to these novel mechanisms at the gene level, it is controversial whether these genetically engineered pharmaceuticals even meet the definition of a “vaccine” or should rather be considered “immunostimulatory gene-based prodrugs” (Bellavite et al., 2023; Cosentino and Marino, 2022). There has been and continues to be a complex medical, scientific, regulatory, and legal debate regarding the respective classifications of “vaccine”, “pro-vaccine”, “genetically engineered vaccines”, “prodrug” and “gene therapy product” (Banoun, 2023). Moderna stated in 2020 that “mRNA is currently considered by the FDA as a gene therapy product” (Moderna, 2020). BioNTech also referred to mRNA products as gene therapy products (Sahin et al., 2014). Interestingly, however, ASPs have been exempted from the strict regulation of corresponding gene products. Banoun (2023) describes the complexity of this terminology and classification dilemma in detail (Banoun, 2023).

### 3.6. *Anti-SARS-CoV-2 products: efficacy and safety*

Early concerns were raised about the efficacy (Addo et al., 2022; Singanayagam et al., 2022; Solante et al., 2022; Wilder-Smith, 2022)

and safety (Cosentino and Marino, 2022; Kerr et al., 2023; Kouhpayeh and Ansari, 2022; Liu et al., 2021a; Solante et al., 2022; Trougakos et al., 2022; Yamamoto, 2022) of ASPs. Seneff et al. (2023) have analysed many of the critical issues related to gene-based immunization products in detail (Seneff et al., 2023). The question of the risk-benefit balance of ASPs is extremely complex for several reasons: (1) The severity of the disease varies greatly with age, sex and general health status. (2) The spread of the disease depends on multifactorial systems. (3) The efficacy of such products (a) decreases over time, (b) changes depending on the pathogen variant and (c) is not yet known for long-term assessment. (4) Pharmacovigilance data are mainly obtained through passive detection systems that are inadequate (e.g. VAERS (Vaccine Adverse Event Reporting System), EMA (European Medicines Agency; EudraVigilance), AIFA (Agenzia Italiana del Farmaco; Italian Medicines Agency)) (Bellavite et al., 2023).

The initially proclaimed efficacy of novel gene-based ASPs in preventing infection, protecting against severe courses, and containing the spread of SARS-CoV-2 has declined sharply over the course of their use (Igyártó and Qin, 2024; Ioannou et al., 2022; Chemaitelly et al., 2022; Tamandjou et al., 2023). It was already known from previous vaccinations that repeated vaccine administration can lead to vaccine resistance / tolerance through various mechanisms (Parry et al., 2023; Röltgen et al., 2022; Scholkmann and May, 2023; Wheatley et al., 2021). Regarding ASPs, it has been shown that ASP-treated individuals produced significantly lower antibody titers after primary SARS-CoV-2 infection than untreated individuals, suggesting that ASP-induced immune imprinting reduces antibody response (Delgado et al., 2022). In addition, multiple ASP boosters significantly reduced antibody titers and serum neutralizing efficacy against SARS-CoV-2 by promoting adaptive immune tolerance (Gao et al., 2022b). An ASP-related IgG class switch could play a role here (Irrgang et al., 2023). Especially for mRNA-based ASPs, the risk of infection with SARS-CoV-2 increases with ASP doses (Eythorsson et al., 2022; Hiam et al., 2023; Shrestha et al., 2022, 2023a). Nakatani et al. (2024) observed a higher reported incidence of COVID-19 infection among ASP-treated individuals compared to untreated individuals during the pandemic period (OR 1.85, 95 % CI: 1.33–2.57, $p < 0.001$), which increased with the number of vaccine doses received (Nakatani et al., 2024). For certain SARS-CoV-2 variants (XBB.1.5 variant of Omicron), a negative vaccine effectiveness of −3.26 % (95 % CI, −6.78 % to −0.22 %) was observed. This suggests that ASP-treated individuals had a statistically higher infection rate than the untreated control group (Ioannou et al., 2025). This aspect also seems to apply to children treated with ASPs (Feldstein et al., 2025). An increasing number of studies show that the greater the number of ASP doses, the greater the risk of infection with SARS-CoV-2 (Chalupka et al., 2024; Shrestha et al., 2023b, 2024a, 2024b), which is impressively illustrated in Fig. 2 of the study by Shrestha et al. (2023a). These data suggest that the effect of ASPs may be due to their immunosuppressive properties (Igyártó and Qin, 2024). Such immunosuppression by ASPs is supported by the findings (1) of virus reactivation (varicella zoster virus (VZV) (Daouk et al., 2022; Katsikas Triantafyllidis et al., 2021), hepatitis C virus (Lensen et al., 2021)), (2) of increased susceptibility to infections (Eythorsson et al., 2022; Shrestha et al., 2023a; Yamamoto, 2022) and (3) impaired cancer immune surveillance (Cavanna et al., 2023; Eens et al., 2023; Goldman et al., 2021; Sekizawa et al., 2022) after ASP injection.

In addition, repeated antigenic stimulation of immunity (sustained / recurrent production of SP by SARS-CoV-2 infection and ASP injection) leads to an isotype switch of the immunoglobulin G (IgG) classes (massive increase in IgG4, >480 times the norm) (Irrgang et al., 2023; Uversky et al., 2023), which can have extensive health, especially immunological, consequences (Campochiaro et al., 2016; Chen et al., 2019; Della-Torre et al., 2015; Gutierrez et al., 2013; Lin et al., 2015; Martín-Nares et al., 2021; Patel et al., 2014; Stone, 2011; Pillai, 2023; Tsai et al., 2022; Wallace et al., 2019; Yu et al., 2022). This isotype switch to IgG4 was observed in about half of the people who received three doses of an mRNA product, but not with adenovirus DNA products (Buhre et al., 2023; Irrgang et al., 2023). The in vivo relevance of the observed isotype switch to IgG4 after mRNA ASPs is not yet known (Uversky et al., 2023).

Repeated vaccinations can also lead to immune system exhaustion (Azim and Razzaque, 2022), as well as the immune memory phenomenon of original antigenic sin (less effective immune response compared to the original antigen variant) and immune imprinting (increasingly limited immune response to a new antigen variant) (Aguilar-Bretones et al., 2023). It has been shown that repeated vaccinations with the same antigen can cause overstimulation of CD4 + T cells, with subsequent development of autoantibody-inducing CD4 + T cells (Baumeier et al., 2022; Tsumiyama et al., 2009). In addition, an association has been found between a lower number of polyclonally activated gamma interferon-positive TH1 cells and increasing total vaccine load (Skowera et al., 2004). Furthermore, it has been shown that ASPs, particularly through the lipid nanoparticle (LNP)-mediated inflammatory milieu, naive T cells and thus the adaptive immune response can be systemically damaged (via type I interferon-mediated out-of-sequence stimulation) (Igyártó and Qin, 2024; Qin et al., 2022) and can impair type I interferon signalling (Seneff et al., 2022), which is crucial for a healthy immune system and for infection and carcinogen control (González-Navajas et al., 2012; McNab et al., 2015; Teijaro, 2016).

With regard to the safety of ASPs, adverse effects have been reported from the outset (Scholkmann and May, 2023), the pathophysiological mechanisms of which are largely not yet well understood (Trougakos et al., 2022). The most common adverse effects documented with ASPs are mild to moderate, not serious, and include fatigue, pain / swelling / redness at the injection site, fever, chills, muscle and joint pain, and headaches lasting a few days (Abu-Hammad et al., 2021; Alhazmi et al., 2021; Baden et al., 2021; Beatty et al., 2021; David et al., 2022; Elgendy et al., 2022; Klugar et al., 2021; Menni et al., 2022; Meo et al., 2021; Mushtaq et al., 2022; Polack et al., 2020; Riad et al., 2021; Sadoff et al., 2021; Saeed et al., 2021; Singh et al., 2022). These complaints (acute reactogenicity responses) are generally interpreted as a temporary increase in the production of innate inflammatory cytokines such as IL-1β, IL-6, GM-CSF, and interferon type I, as part of the immune system's response to a foreign pathogen (Arunachalam et al., 2021; Li et al., 2022b; Ndeupen et al., 2021; Sprent and King, 2021). When Pfizer-BioNTech's ASP (BNT162b2, Comirnaty) was administered in this context, a systemic inflammatory signature, including interferons and interleukins, was demonstrated (Bergamaschi et al., 2021; Li et al., 2022b). Under unfavourable conditions, this can lead to cytokine release syndrome (CRS) (Au et al., 2021). Although the acute symptoms of an ASP injection resolve within a few days in most people, the symptoms persist for weeks or months in some affected people (>1 week: 3 % / >1 month: 1.4 % (Riad et al., 2021), or 4.6 % and 0.2 % (Klugar et al., 2021)). Deaths immediately after ASP administration have also been described (Scholkmann and May, 2023). It is noteworthy that fewer adverse events have been reported with conventional anti-SARS-CoV-2 vaccines based on protein or inactivated virus components than with gene-based ASPs (Parry et al., 2023).

Regarding adverse events of ASPs, it must be clearly emphasized at this point that under-reporting of adverse drug reactions (ADRs) has been known for years. Against this background, reports of ADRs must be critically analyzed, particularly with regard to frequency and causality. According to Alvarez Requejo et al. (1998), the overall under-reporting rate was 1144 (95 % confidence interval: 928 ± 1409). This under-reporting mainly affected psychiatric disorders and mild to moderate complaints (Alvarez Requejo et al., 1998). Hazell and Shakir (2006) provides evidence of significant and widespread under-reporting of ADRs to spontaneous passive reporting systems including serious or severe ADRs. The median under-reporting rate across the 37 studies was 94 % (interquartile range 82–98 %). Particularly in hospital-based studies, the median under-reporting rate for more serious or severe ADRs remained high (95 %) (Hazell and Shakir, 2006). Since vaccines

and ASPs are also used in healthy individuals, their safety must be excellent. Post-market pharmacovigilance of such products is crucial, as pre-market clinical trials are insufficient to detect rare or late-onset ADRs. This method is crucial for generating alerts, but it underestimates the real frequency of ADRs (1–10 % of severe ADRs are reported) (Autret-Leca et al., 2006). Less than 0.3 % of all ADRs and only 1–13 % of severe ADRs are reported (Lazarus et al., 2010). Likewise, less than 1 % of adverse vaccine reactions are reported (Lazarus et al., 2010; Shimabukuro et al., 2015). Therefore, pharmacoepidemiological studies are urgently needed to confirm the warning signals identified through spontaneous passive reporting.

This article will focus on the effects of ASPs on HNS and in particular on SPs they induced in host cells. Given the similar but not identical (Parry et al., 2023; Scholkmann and May, 2023) antigenic sequence of SP from SARS-CoV-2 infection and ASP injection, a common pathomechanism is likely (Bellavite et al., 2023), which is supported by similar disease symptoms (Alimohamadi et al., 2020; Amanzio et al., 2022; Scholkmann and May, 2023). For example, Jeon et al. (2023) reported in a literature review that the initial manifestation or relapse of MS occurred in temporal association after both SARS-CoV-2 infection and ASP injection (Jeon et al., 2023). Although the artificial SPs have been produced in a way that theoretically does not correspond exactly to the viral SP (mutational changes include the replacement of two residues with a double proline (e.g. Pfizer-BioNTech and Moderna), or mutations in FCS for protease resistance (e.g. Johnson & Johnson-Janssen) (Kyriakopoulos et al., 2022; Martínez-Mármol et al., 2023; Parry et al., 2023; Seneff and Nigh, 2021)), the artificial SPs can also develop a toxic potential in the human organism similar to that of the viral SP. The common denominator for health complaints following infection and injection is primarily, but not exclusively, the SP (Cosentino and Marino, 2022; Parry et al., 2023; Trougakos et al., 2022).

## 4. Anti-SARS-CoV-2 products and the human nervous system

ASPs were initially considered safe and effective in all populations based on initial analyses from clinical trials (Baden et al., 2021; Polack et al., 2020). However, subsequent studies (Fraiman et al., 2022), a steadily increasing number of case reports (react19.org) and publicly available adverse event databases (e.g. VAERS (Vaccine Adverse Event Reporting System) (vaers.hhs.gov)) have changed the picture of safety and efficacy of these novel gene-based products (Igyártó and Qin, 2024). For neurological clinical practice, the current data for ASPs show a high neurological safety profile overall (Boruah et al., 2023). Although, according to current knowledge, more cases of neurological complaints have been documented after SARS-CoV-2 infection than after ASP administration (Frontera et al., 2022) (note: under-reporting, data collection, data availability, data interest), ASPs can also cause neurological complaints that can be attributed to a variety of mechanisms (Marsh et al., 2021; Tondo et al., 2022; Yang and huang, 2023). However, each product has a different toxicity profile (Otero-Losada et al., 2022). The mRNA products from Pfizer-BioNTech (BNT162b2, Comirnaty) and Moderna (mRNA-1273, Spikevax) are currently the most commonly used ASPs in the USA and Europe (Bellavite et al., 2023).

### 4.1. Anti-SARS-CoV-2 products: neurological adverse effects

The undesirable neurological effects of ASP described in the literature so far are predominantly neuroinflammatory and affect nerve paralysis, especially of the facial nerve (Ahmad et al., 2023; Baden et al., 2021; Meo et al., 2021; Shafiq et al., 2021; Sriwastava et al., 2022), but also other cranial nerves (Lotan et al., 2022), GBS (Ahmad et al., 2023; Fazlollahi et al., 2023; Fernandes et al., 2022; Frontera et al., 2022; Ogunjimi et al., 2023; Sadoff et al., 2021; Shafiq et al., 2021; Shalash et al., 2022; Sriwastava et al., 2022), NMOSD (Ballout et al., 2022; Chen et al., 2021b; Harel et al., 2023; Khayat-Khoei et al., 2022; Lee et al., 2023; Rinaldi et al., 2022; Sriwastava et al., 2022), acute disseminated encephalo-myelitis (ADEM) (Ballout et al., 2022; Fazlollahi et al., 2023; Rinaldi et al., 2022; Sriwastava et al., 2022), MS / MS-like syndrome (Ballout et al., 2022; Jeon et al., 2023; Khayat-Khoei et al., 2022; Lee et al., 2023; Rinaldi et al., 2022; Sriwastava et al., 2022), transverse myelitis (Ahmad et al., 2023; Fernandes et al., 2022; Harel et al., 2023; Lee et al., 2023; Rinaldi et al., 2022; Sriwastava et al., 2022), meningitis / encephalitis / meningoencephalitis (Abdelhady et al., 2023; Ballout et al., 2022; Deniz et al., 2023; Fazlollahi et al., 2023; Fernandes et al., 2022; Kwon and Kim, 2021; Ramesh et al., 2023; Sriwastava et al., 2022; Zlotnik et al., 2022; Zuhorn et al., 2021), encephalopathy (Ahmad et al., 2023; Bensaidane et al., 2022; Fazlollahi et al., 2023; Liu et al., 2021b), seizures (Ahmad et al., 2023; Fazlollahi et al., 2023; Fernandes et al., 2022; Frontera et al., 2022; Liu et al., 2021b), cerebral venous sinus thrombosis (CVST) (Chen et al., 2023; Frontera et al., 2022; Sriwastava et al., 2022) and other stroke events (Ahmad et al., 2023; Chen et al., 2023; Corrêa et al., 2021; Markus, 2021; Masoudian et al., 2023; Nahab et al., 2023).

Less commonly described cases include neuro-ophthalmological complications (optic neuritis, uveitis, herpes zoster ophthalmicus, acute macular neuroretinopathy, optic disc edema, arteritic anterior ischemic optic neuropathy, central serous retinopathy, acute zonal occult outer retinopathy, bilateral choroiditis) (Lotan et al., 2022), primary autoimmune cerebellar ataxia (Lee et al., 2023), neuralgic amyotrophy (Ng et al., 2022), Tolosa-Hunt syndrome (Chuang et al., 2021; Lotan et al., 2022), and amyloid-beta related angiitis (ABRA) (Kizawa and Iwasaki, 2022).

### 4.2. Anti-SARS-CoV-2 products: neurodegenerative potential

It is already known that a SARS-CoV-2 infection caused by SP can cause cognitive dysfunction in humans, in part through CNS effects on hippocampal neurogenesis (Borsini et al., 2022; Ceban et al., 2022; Klein et al., 2021; Nuovo et al., 2022; Oh et al., 2022; Shan et al., 2022). However, it has also been described that SP of gene-based ASPs can also cause such cognitive dysfunction (Alonso-Canovas et al., 2023; Chakrabarti et al., 2022; Krumholz et al., 2023; Roh et al., 2024; Trougakos et al., 2022). As already mentioned, the CNS-protective BBB can be overcome by SP (particularly the S1 subunit), allowing SP to enter the CNS (see above) (Buzhdygan et al., 2020; DeOre et al., 2021; Lei et al., 2021; Kim et al., 2021a; Petrovszki et al., 2022; Rhea et al., 2020; Roh et al., 2024; Rong et al., 2023). Once in the CNS, there are various mechanisms by which SP can exert a neurotoxic effect (see above) (Burnett et al., 2023; Buzhdygan et al., 2020; Jeong et al., 2022; Erickson et al., 2021; Foster et al., 2023; Jabi et al., 2022; Kim et al., 2021a; Raghavan et al., 2021; Robles et al., 2021; Rong et al., 2023; Theoharides and Kempuraj, 2023). SP can induce protein aggregation, misfolding and malfunction, particularly by its interaction with amyloidogenic protein sequences, and thus promote neurodegenerative processes (see above) (Cao et al., 2023; Changeux et al., 2020; Hsu et al., 2021; Idrees and Kumar, 2021; Kyriakopoulos et al., 2022; Nyström and Hammarström, 2022; OBrien et al., 2023; Parry et al., 2023; Perez et al., 2023; Seneff et al., 2023; Tavassoly et al., 2020; Tetz and Tetz, 2022; Tillman et al., 2023; Trougakos et al., 2022). In addition, neurodegenerative processes are promoted by the fact that SP activates multiple neuroinflammatory mechanisms (see above) (Alves et al., 2023; Cao et al., 2021; Cosentino and Marino, 2022; Frank et al., 2022; Jeong et al., 2022; Khaddaj-Mallat et al., 2021; Khan et al., 2021; Kim et al., 2021a; Kumar et al., 2021; Li et al., 2021b; Oka et al., 2021; Olajide et al., 2022; Rahman et al., 2021; Saha et al., 2022; Theoharides and Kempuraj, 2023; Tsilioni and Theoharides, 2023; Zhu et al., 2021b).

A central neurodegenerative and neurocognitive damage site of SP (particularly S1) is the hippocampus (through hippocampal microgliosis and cell apoptosis) (Fontes-Dantas et al., 2023), where hippocampal memory is achieved in the process of hippocampal neurogenesis with the help of, among other things, amyloid beta (Aβ) proteins (Hsu et al., 2021; Nehls, 2016; Nyström and Hammarström, 2022). The body's own

Aβ is released in the hippocampus as a monomer during the process of remembering. Among other things, it helps to ensure that new memories do not overwrite previously made ones (Nehls, 2016; Wells et al., 2021). SP intervention in, among other things, amyloid homeostasis (see above) influences such central nervous neurocognitive processes. In this context, a recent study showed a higher incidence rate of cognitive impairment (from mild cognitive impairment (MCI) to Alzheimer'-s-typical symptoms) in people spiked with mRNA products compared to untreated people, and this just 12 weeks after ASP administration (Roh et al., 2024). Older people and women were particularly affected, which can be attributed to demographic differences in neurodegenerative pathologies and to different immune reactions to gene-based, primarily mRNA products (Roh et al., 2024). Older adults are more likely to have an increased inflammatory response, which can predispose them to a faster progression of neurodegenerative processes (Li et al., 2023). It has been shown that senescent cells responded more sensitively to S1 of SP with a hyperinflammatory reaction (Camell et al., 2021). Interestingly, SP itself triggers senescence in transfected cells (Tripathi et al., 2021). Gender differences in the functioning of the immune system may be responsible for the increased neurocognitive vulnerability of women (Bellavite et al., 2023; Roh et al., 2024). As neurodegenerative processes in CNS are often protracted, with a partially silent premorbid prodromal phase, and the short post-marketing follow-up of these novel gene-based ASPs has made it difficult to assess the neurodegenerative potential of such products.

There have also been initial reports of prion diseases following ASP-injection, such as cases of Creutzfeldt-Jakob disease (CJD) (Folds et al., 2022; Karabudak et al., 2023; Kuvandık et al., 2022; Perez et al., 2023; Suo et al., 2023), a highly progressive neurodegenerative disease that ultimately leads to death (Uttley et al., 2020). The CJD cases described so far concern ASP of mRNA type (Folds et al., 2022; Karabudak et al., 2023; Perez et al., 2023), DNA type (Perez et al., 2023; Suo et al., 2023) and inactivated virus type (Kuvandık et al., 2022). However, these few, but highly concerning case reports require further scientific investigation. The prion-like properties of SARS-CoV-2 have been described above and have already been discussed clinically (Bernardini et al., 2022; McGrath et al., 2023; Young et al., 2020), but also require further scientific investigation, as a link between COVID-19 and CJD has not yet been proven (Perna et al., 2024; Watson et al., 2021; Xu et al., 2022).

### 4.3. *Anti-SARS-CoV-2 products: other toxic properties*

In addition to the aspects of protein interaction in the CNS described here (amyloid-like and prion-like function), SP may interact with other human proteins in the bloodstream and even mimic human proteins (molecular mimicry) (Kanduc and Shoenfeld, 2020; ODonoghue et al., 2021). This aspect was already known before 2020 (Hwa et al., 2008). Such molecular mimicry could play a role in autoimmune, proinflammatory, thrombogenic and neurodegenerative processes (Lyons-Weiler, 2020; Parry et al., 2023; Segal and Shoenfeld, 2018; Vojdani et al., 2021). In particular, structures of the HNS may be damaged via antibody cross-reaction (Patone et al., 2021). Already in 2020 (Lyons-Weiler, 2020), even before the market launch of ASPs, and beyond (Kelleni, 2021; Khavinson et al., 2021; Talotta, 2021), it was pointed out that SP has a problematic homology with key proteins of the human immune system, with the possibility of autoimmune reactions, including in HNS (Vojdani et al., 2021). The potential of ASPs to induce inflammatory processes described in this article (see above) could promote the exacerbation of pre-existing autoimmune diseases and / or create conditions for the development of novel autoimmune reactions in susceptible individuals (Igyártó and Qin, 2024). In this context, publications are already known about the occurrence of (auto-)immunological diseases after the ASPs administration (Alqatari et al., 2023; Aochi et al., 2023; Cam et al., 2023; Lansang et al., 2023; Makiyama et al., 2023; Minakawa et al., 2023; Morimoto et al., 2023; Rodriguez et al., 2022; Takedani et al., 2023; Talotta, 2021; Yamamoto et al., 2023).

Furthermore, SP has been shown to contains a 'toxin-like' domain in the RBD on its S1, with sequence homology to the rabies virus (RBG), the human immunodeficiency virus (HIV) glycoprotein and the neurotoxin NL-1, all of which bind to and inhibit α7 nAChRs of the cholinergic system (Changeux et al., 2020; OBrien et al., 2023; Parry et al., 2023; Tillman et al., 2023), with complex pathological effects on neuromuscular junctions (Nirthanan, 2020), at the neuropsychiatric-neurodegenerative level (Lykhmus et al., 2022; Tillman et al., 2023) and on inflammatory control (Farsalinos et al., 2020; Tillman et al., 2023). Key words here are reactive oxygen species, oxidative stress, pro-inflammatory cytokines and hyperinflammation (Parry et al., 2023). In addition to their expression in the HNS (see above), α7-nAChRs are expressed in non-neuronal cells such as platelets, lymphocytes, monocytes, macrophages, dendritic cells, adipocytes, keratinocytes, endothelial cells and intestinal and lung epithelial cells (Kooijman et al., 2015; Parry et al., 2023). Dysregulation of α7-nAChRs by SP is known to be involved in the pathophysiology of COVID-19 disease (Farsalinos et al., 2020; Hollenhorst and Krasteva-Christ, 2021). They also affect the sympathetic and parasympathetic autonomic nervous system and can lead to dysautonomia (Al-Kuraishy et al., 2021), with far-reaching consequences for the heart (cardiac arrhythmia, orthostatic dysregulation, exercise intolerance), bladder and intestine (micturition, defecation disorders), sweat glands (secretion disorders), and other autonomic systems (insomnia) (Parry et al., 2023). Inhibition of the nAChR system by SP can lead to parasympathetic inhibition and sympathetic overstimulation, with the possible development of a sympathetically controlled hyperinflammatory cytokine storm (Alexandris et al., 2021).

In order to stabilize an artificial mRNA (nucleoside-modified mRNA, mod-mRNA, m-mRNA) (natural mRNA is highly unstable (Yang et al., 2003); average half-life in mammals about 7 h (Sharova et al., 2008)) and thus improve its translation in the living organism, genetically modified pseudouridine or methylpseudouridine has been incorporated into mRNA-based ASPs (Kämmerer et al., 2024; Mulroney et al., 2024) instead of the natural native uridine (nucleoside made from the nucleic base uracil and the sugar β-D-ribose (Yamamoto et al., 2011)) (Morais et al., 2021; Park et al., 2021). One of the purposes of this is to prevent the natural immune defence against foreign material by TLRs and interferons (including type I) (Andries et al., 2015; Theoharides and Kempuraj, 2023). This point has been known for years, even before the pandemic (Karikó et al., 2005). However, it has been shown that N1-methylpseudouridine from ASPs (for their long-lasting product effect (Karikó et al., 2008)) can induce ribosomal frameshifts of unknown magnitude during translation, leading to abnormal protein products that can trigger cellular dysfunctions, which in turn can induce neurodegenerative processes (Parr et al., 2020; Mulroney et al., 2024). Corresponding studies on the effects of these frameshift products, especially on autoimmune, carcinogenic and neurodegenerative processes in the human body, are not yet available (Igyártó and Qin, 2024).

In addition, LNP (diameter about 100 nm (Buschmann et al., 2021)) have been added to some ASPs as a protective cover (Igyártó and Qin, 2024) for foreign RNA (Pfizer-BioNTech (Comirnaty, BNT162b2); Moderna (SPIKEVAX, mRNA1273)), foreign DNA (AstraZeneca (Vaxzevria, ChAdOx1 nCOV-19); Janssen (COVID-19 vaccine, Ad26.COV2.S)) or foreign protein (Novavax (Nuvaxovid, NVX-CoV2373)) structures, as these would otherwise be recognised as foreign by the human immune system and broken down (Karikó et al., 2005; De Beuckelaer et al., 2016). The incorporated modified mRNA was detectable in the body for weeks due to the protective LNP (Castruita et al., 2023; Fertig et al., 2020; Röltgen et al., 2022). The synthetically produced ionizable lipids of the LNP are estimated to have a half-life of 20–30 days in vivo (Comirnaty, 2021). Interestingly, it was shown that the mRNA-LNP amount and the mRNA-LNP ratio of the mRNA products differed between the individual batches (Tinari, 2021). As long as such modified mRNA remains in the transfected cells, the intracellular production of (potentially pro-neuroinflammatory and pro-neurodegenerative) SP

continues (Parry et al., 2023).

LNP are used to transport mRNA and enhance cell wall penetration, which is already used in chemotherapeutics for the treatment of brain tumours (Anand et al., 2019) and other pharmaceutical products (Gómez-Aguado et al., 2020; Hou et al., 2021). They have been shown to easily penetrate biological tissues and membranes and thus reach all organs (Di et al., 2022; Igyártó and Qin, 2024; Parry et al., 2023). LNP have also been shown to be able to cross the BBB and the blood-placental barrier (Ndeupen et al., 2021; Turni and Lefringhausen, 2022; Wick et al., 2010; Zhou et al., 2018). LNPs can reach placental cells such as trophoblasts, which is being discussed for the treatment of placental diseases during pregnancy (Swingle et al., 2023). Another aspect is the use of LNPs for gene delivery to fetal organs (Abostait et al., 2024). It could be shown that LNPs can effectively deliver mRNA for gene editing enzymes to the fetal mouse brain, resulting in successful transfection and editing of brain cells (Gao et al., 2024). For LNP of ASPs, there is also the possibility of similar distribution to the placenta and fetus. Currently, such ASP effects on humans are unknown (Zhong et al., 2024). In a recent study, mRNA-based ASP (mRNA-1273) intramuscularly given to pregnant mice rapidly circulated in maternal blood and crossed the placenta within 1 h to spread in the fetal circulation. Although spike mRNA could accumulate in fetal tissues, mainly the liver and get translated into SP (Chen et al., 2025).

LNP, like SP (Burnett et al., 2023), can also activate TLRs, which can induce further neuroinflammatory signaling pathways, and also promote neurodegenerative processes (Kiaie et al., 2022; Ndeupen et al., 2021; Trougakos et al., 2022; Turni and Lefringhausen, 2022). In ASPs, the pro-inflammatory LNP appear to be the crucial component in triggering an immune response (Igyártó and Qin, 2024). The LNP, which was originally considered to be an inert carrier and transport vehicles for mRNA (Pardi et al., 2015). Exposure to such ASPs may therefore induce an early high level of inflammation, followed by a long-term sustained lower level of chronic inflammation (Igyártó and Qin, 2024). Such chronic persistent inflammation ultimately burdens the immune system (Wherry and Kurachi, 2015) and has an immense impact on pro-neurodegenerative processes (Amor et al., 2014; Chitnis and Weiner, 2017; Tanaka et al., 2020), with a self-sustaining cycle of chronic immune activation (peripheral, systemic, central nervous system) and neurodegeneration (Gao and Hong, 2008). The potentially toxic potential of LNP was already known prior to the worldwide administration of corresponding ASPs.

## 5. Anti-SARS-CoV-2 products and their hubris

### 5.1. *Anti-SARS-CoV-2 products: contamination, undeclared admixtures from manufacturing process*

Scholkmann and May (2023) describe in detail the numerous findings of process- and product-related contamination of ASPs (legally correct: undeclared admixtures from the manufacturing process), the biological consequences and health effects of which (such as long-term immunological side-effects) are still poorly understood to date (Scholkmann and May, 2023). Igyártó and Qin (2024) also point to contamination during the manufacturing process of ASPs (Igyártó and Qin, 2024). Studies show that there were significantly different side-effect profiles between the individual ASP batches (Schmeling et al., 2023). In addition to the vulnerable aspects of the transport, storage and clinical handling of ASPs, this could indicate different levels of contamination (i.e. quality and purity defects) (Igyártó and Qin, 2024). It is noteworthy that ASPs also contain substances such as the proprietary functional excipients ALC-0315 and ALC-0159, which have never been used in a medicinal product before and are not registered in the European Pharmacopoeia or the European C&L Inventory (Segalla, 2023). According to the manufacturer, such nanoparticles were only intended for research purposes and not for human use (Parry et al., 2023).

Furthermore, DNA contamination was detected in the bivalent mRNA vaccines from both Moderna and Pfizer-BioNTech that exceeded the limits set by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (Buckhaults, 2023; Kämmerer et al., 2024; König and Kirchner, 2024; McKernan, 2023; McKernan et al., 2023; Pekova, 2025; Raoult, 2024; Speicher et al., 2023; Wang et al., 2024). The impact of such plasmid DNA fragments on human health is not yet known (Igyártó and Qin, 2024). However, it has been known for years that plasmid DNA can integrate into the genome, with the risk of insertional mutagenesis (Sahin et al., 2014). Further genetic analyses proved, worryingly, that residual DNA represents not only fragments of the DNA matrices encoding for SP gene, but all genes from the plasmid, including the simian virus 40 (SV40) promoter/enhancer and the antibiotic resistance gene (to Kanamycin) (Kämmerer et al., 2024; Raoult, 2024). This is a concern because SV40 is associated with cancer in humans (Carbone et al., 2020; Kolevatykh, 2024; Rotondo et al., 2019). SV40 is a DNA tumor virus originally found as a contaminant in polio vaccines administered between 1955 and 1963 (Poulin and DeCaprio, 2006). Double-stranded RNA (dsRNA) has also been detected (Igyártó and Qin, 2024) in the mRNA products from Pfizer-BioNTech (Comirnaty, 2021) and Moderna (Moderna, 2021). This dsRNA can activate innate immune sensors, trigger inflammatory responses and restrict protein translation from mRNA, as has long been known (Karikó et al., 2005, 2008; 2011) and is supported in current animal studies with corresponding ASP from Pfizer-BioNTech (Comirnaty, BNT162b2) (Li et al., 2022b). The importance of the primarily inflammatory component is underlined by the fact that highly purified mRNA without detectable dsRNA did not induce any innate or adaptive immune responsesin vivo (Igyártó and Qin, 2024). The impact of such dsRNA fragments on human health is not yet known (Igyártó and Qin, 2024).

### 5.2. *Anti-SARS-CoV-2 products: known toxicity*

The potentially pathological mechanisms of action mentioned here, particularly of SP, are generally neither novel, nor unknown, nor specific to SARS-CoV-2 alone. The SP of SARS-CoV-1 (Petrosillo et al., 2020) (the virus of the severe acute respiratory syndrome (SARS) pandemic of 2002/2003 (who.int, 2024)) was already known to stimulate the immune system, among other things via the NF-κB signaling pathway, to release large amounts of pro-inflammatory mediators (such as TNF-α and IL-6) (Wang et al., 2007). Even before SARS-CoV-2, it was known that such inflammatory responses have effects on the CNS with corresponding neurodegenerative consequences. Animal studies had already shown at that time that such inflammatory mechanisms affected the hippocampus. This even occurred across the placenta when fetuses were exposed to maternal IL-6. Prenatal exposure to IL-6 led to inflammation-triggered neurodegeneration in the hippocampus, including impaired spatial learning, among other things (Samuelsson et al., 2006). The inflammatory release of IL-6 (e.g. as part of immunisation) in pregnant animal's blocks, among other things, hippocampal neurogenesis in the fetus, with long-lasting effects on the development and function of the maturing brain that are still evident in later adult animals (Mouihate and Kalakh, 2021). In humans, too, the IL-6 levels are inversely related to hippocampal volume. This means that any long-term inflammation causes permanent damage to adult hippocampal neurogenesis and contributes to the neurodegeneration of the hippocampus (Marsland et al., 2008). The inflammatory messenger TNF-α has been shown to have a negative influence on autobiographical memory via this inflammation-neurodegeneration pathway (Takahashi et al., 2021). Similar effects have been shown for many other pro-inflammatory messengers, such as IL-1β, which is also a potent inhibitor of hippocampal neurogenesis (Theobald et al., 2021; Wu et al., 2013).

All of these aspects were already known long before the decision was taken to use novel gene-based mRNA/DNA substances to combat SARS-CoV-2, which induce the human body (with the supposed aim of protective immunisation) to produce SP itself in its transfected host cells. It

is not surprising that SP products of ASPs also have a neurotoxic and neurodegenerative effect on the CNS of the host organism via such pro-inflammatory processes (Tahtinen and Mellman, 2022). Against this background, it remains to be clarified why this novel method of immunisation was chosen, despite possible alternatives (Barouch, 2022; Oronsky et al., 2022) and the known potential toxicity of SP, as shown here.

### 5.3. Anti-SARS-CoV-2 products: consequences

All of these aspects mentioned here are set the background that more than 13 billion ASP doses from different platforms have been administered worldwide (more doses than there are potentially implicated people on earth) (Scholkmann and May, 2023), and a total of around 72 % of the world's population has been injected at least once (Uversky et al., 2023). How much, for how long, where and with what health consequences artificial SP (and other injection components) are produced and circulate in the human body after the application of gene-based ASPs in particular has not yet been conclusively clarified (Bansal et al., 2021; Bellavite et al., 2023; Castruita et al., 2023; Cognetti and Miller, 2021; Cristoni et al., 2022; Fertig et al., 2020; Ogata et al., 2022; Parry et al., 2023; Röltgen et al., 2022; Trougakos et al., 2022), because the systemic biodistribution and disposition of ASPs (of mRNA and DNA codes) (Parry et al., 2023) has not yet been investigated to the necessary extent (Cosentino and Marino, 2022). Against this background, it must be acknowledged that there is only limited knowledge on how SP, LNP, various modifications of mRNA (5' and 3' modifications, the use of unique nucleotides, etc.) and other product components as well as their contamination in the human body, since no specific studies, especially no long-term studies, have been conducted on this topic (Igyártó and Qin, 2024).

SP is detectable in plasma from individuals as early as 1 day after the first product incorporation (from the mRNA products Pfizer-BioNTech (BNT162b2, Comirnaty) and Moderna (mRNA-1273, Spikevax) (Ogata et al., 2022)) and for at least another 60 days in human lymph node biopsy studies (Röltgen et al., 2022; Yonker et al., 2023). In addition, SP from ASP injections have been detected in circulating exosomes for at least four months (Bansal et al., 2021). Contrary to the initial official statements, the SP production by human body cells is not limited to the intramuscular injection site and does not end within a few days (Kämmerer et al., 2024). Even mRNA components of ASPs have been detected in the human body (lymph nodes, plasma and other organ tissues) for days (15d (Fertig et al., 2020), 30d (Krauson et al., 2023)). This is remarkable because natural mRNA is highly unstable (Yang et al., 2003), with an average half-life in mammals of about 7 h (Sharova et al., 2008). Thus, the statement made, especially at the beginning of ASP market launch, that corresponding products would be degraded in vivo within hours, or a few days is also no longer tenable (Igyártó and Qin, 2024).

It has already been shown that SP in the transfected cells can lead to mitochondrial impairments and, once in the cell nucleus, to dysregulations at the level of gene expression (Kim et al., 2021a). The localisation of SP in the cell nucleus was reported as early as 2020 (Zhang et al., 2020d) prior to the global market launch of products (Oliver et al., 2020, 2021) designed to induce the body to produce SP itself. Further studies followed, with the detection of NLS in SP of SARS-CoV-2 (Sattar et al., 2023), which is new and unique in the group of SARS coronaviruses (Igyártó and Qin, 2024). This NLS enables SP to be transported to the cell nucleus. Spike mRNA may also reach the cell nucleus with SP (Sattar et al., 2023). A comparable transport of SP and / or mRNA of ASPs into the cell nucleus is theoretically possible (Igyártó and Qin, 2024). In addition, it has been shown that reverse transcription of the corresponding ASP mRNA (Pfizer-BioNTech) into a DNA copy is possible in an immortalized human hepatocyte cell line (Aldén et al., 2022). In addition to possible neurodegenerative LINE-1 activation in neurons (Terry and Devine, 2020; Thomas et al., 2012), this suggests the possibility of intergenerational transmission when germ cells incorporate the DNA copy into the host genome (Parry et al., 2023). Whether this occurs in vivo remains to be determined (Merchant, 2022). Eukaryotic cells, including human cells, use reverse transcription to replicate telomeres and retrotransposons (Chandramouly et al., 2021; Domazet-Lošo, 2022; Sciamanna et al., 2016).

The possibility of retropositioning the genetic code from ASP suggests that the production of a foreign pathogenic protein (namely SP) may occur throughout life or even across generations (Domazet-Lošo, 2022). The insertion of new / foreign DNA into the human genome is a serious problem, especially when it occurs at the level of the reproductive stem cells (Igyártó and Qin, 2024). In this context, it should be noted that mRNA from the products Pfizer-BioNTech (BNT162b2, Comirnaty) (Comirnaty, 2021) and Moderna (mRNA-1273, Spikevax) (Moderna, 2021) have been detected in both the testes and the ovaries, among many other organs and tissues. And since, as shown above, the mRNA can enter the cell nucleus and it has also been shown that the mRNA can be reverse-transcribed into DNA, there is a theoretical possibility, which has yet to be proven, that corresponding information can be integrated into the genome. Studies in mice have already shown that even a single exposure to mRNA-LNP complexes can inhibit adaptive immune responses and alter innate immune fitness in a *heritable* manner (Qin et al., 2022).

## 6. Conclusions

As presented here, SP has the neurotoxic potential to damage the HNS, and in particular the CNS. The SP based on the novel gene-based ASPs should be critically highlighted here. This is because these products have been used worldwide for the intended preventive protection against SARS-CoV-2, including in healthy people (Sadeghalvad et al., 2022), adolescents and even children (Tian and Yang, 2022). And that, although (1) such gene-based product mechanisms had never been used clinically before (especially not for such indications) (Anand and Stahel, 2021; Hogan and Pardi, 2021; Maruggi et al., 2019; Mulligan et al., 2020; Pardi et al., 2018; Park et al., 2021; Rijkers et al., 2021; Schlake et al., 2012; Wadhwa et al., 2020; Zhang et al., 2019), (2) no long-term evaluations or final safety analyses were available before the emergency market launch in 2020 and the rapid worldwide use (Bansal et al., 2021; Bellavite et al., 2023; Castruita et al., 2023; Cognetti and Miller, 2021; Cosentino and Marino, 2022; Cristoni et al., 2022; Fertig et al., 2020; Fotuhi et al., 2020; Lu et al., 2021; Röltgen et al., 2022; Scholkmann and May, 2023; Trougakos et al., 2022; Yonker et al., 2023), and (3) alternative immunization options would also have been possible (inactivated virus products or adjuvanted protein products) (Barouch, 2022; Oronsky et al., 2022).

The toxic properties of SP described here provide a good explanation for many of the neurological complaints documented to date, both after SARS-CoV-2 infection and after ASP injection (Kowarz et al., 2022). In particular, neuroinflammation and neurodegeneration play a prominent role. It is noteworthy that not as many adverse events have been reported with conventional anti-SARS-CoV-2 vaccines based on protein or inactivated viral components as with gene-based ASPs (Parry et al., 2023), underscoring the toxicity of the body-wide biodistribution and sustained production of SP from gene-based ASPs. Even compared to all other classic non-anti-SARS-CoV-2 vaccines, the frequency of adverse events with ASPs, especially of the mRNA type, is much higher per million doses administered (Igyártó and Qin, 2024).

Already now, only four years after approval (as of December 2024), a large number of adverse side effects in multiple organ systems caused by ASPs are occurring at an unprecedented frequency (Parry et al., 2023), although this article is limited to the adverse side effects of SP on the HNS. The website www.react19.org lists (as of December 2024) over 3500 published articles and case reports on adverse side effects of ASPs in over twenty organ systems (react19.org). There is still no data at all on any long-term neurological consequences of such immunisation

measures, given the existing time horizon (Fotuhi et al., 2020; Lu et al., 2021; Scholkmann and May, 2023).

Data on the negative consequences of ASPs are difficult to collect, as it must be proven that the ASP is the cause of any physical or health damage. However, this has already been achieved with the detection of SP from the injection (but not the nucleocapsid protein from the infection) of inflammation sites in the brain and heart, especially in the endothelial cells of small blood vessels (Baumeier et al., 2022; Mörz, 2022; Yonker et al., 2023). Histopathological post-mortem analyses of the brain revealed predominantly lymphocytic acute vasculitis and multifocal necrotizing encephalitis, including glial and lymphocytic inflammatory reactions (Mörz, 2022). The heart also showed acute lympho-histiocytic myocarditis and vasculitis (Mörz, 2022). Components of the injection material have also been found in other tissues and cells (Comirnaty, 2021; Moderna, 2021; Pardi et al., 2015; Scholkmann and May, 2023; Yang et al., 2021b). However, to date, the regular regulatory authorities have only officially recognised a causal relationship between an mRNA ASP and a serious adverse event for pericarditis and myocarditis (Diaz et al., 2021). Already at the beginning of 2021, shortly after ASP-onset, there were indications of ASP-associated myocarditis (Barda et al., 2021; Baumeier et al., 2022; Cereda et al., 2021; Mevorach et al., 2021; Nevet, 2021). Which was proven in autopsy studies. (Baumeier et al., 2022; Choi et al., 2021; Mörz, 2022; Schneider et al., 2021; Suzuki et al., 2022; Verma et al., 2021; Yonker et al., 2023).

Even if the rate of neurological complaints after an acute SARS-CoV-2 infection has been described more frequently than after ASP administration (note: under-reporting, data collection, data availability, data interest), the adverse side effects of ASP must not be neglected or even dismissed as a lesser evil. Particularly in view of the fact that this was a worldwide preventive immunisation attempt on healthy people, adolescents and even children. The unprecedented worldwide mass injection of a novel gene-based product that provides only minimal protection, if any, against infection and spread of SARS-CoV-2 (Igyártó and Qin, 2024) gives rise to a critical analysis of this anti-pandemic measure. The decision to prefer gene-based platforms over conventional and long-established vaccination methods must be carefully examined scientifically, politically and legally.

A fundamental analysis of the pharmacological efficacy, safety, risk and symptom profile of such novel gene-based products, which are used in billions of doses worldwide, is essential and is part of good clinical practice and the moral obligation of science and medicine. Further extensive, critical and open-minded scientific research, including global epidemiological studies, is absolutely necessary in order to better understand the effects and long-term potential of such products, which are only partially understood. Understandably, this should be done before further widespread use of such products on the world's population, in view of the numerous planned genetic medical procedures worldwide and in view of a possible renewed declaration of a potential pandemic situation. For science-based, optimal and humane patient care in the areas of prevention, diagnosis and therapy.

In line with existing protein-associated neologisms, such as tauopathy (Götz et al., 2019; Irwin, 2016; Kovacs, 2015; Olfati et al., 2022) or synucloinopathy (Brás et al., 2020; Coon and Singer, 2020; Jellinger, 2003; Marti et al., 2003; Wong and Krainc, 2017), it is proposed here to use the term spikeopathy for spike protein-associated pathologies. This is therefore another proteinopathy with, among other things, neurodegenerative potential (Vuic et al., 2022). This cause-specific terminology is intended to enable uniform, unambiguous and clear communication.

At this point, it should also be noted that terms used so far such as post-COVID-19 vaccination syndrome (PCVS), acute COVID-19 vaccination syndrome (ACVS), post-acute COVID-19 vaccination syndrome (PACVS), long post-COVID vaccination syndrome (LPCVS), autoimmune post-COVID vaccine syndromes, post-vaccine syndrome (Scholkmann and May, 2023) are incorrect. As mentioned above, these are not classic conventional vaccinations, but a novel genetically based immunisation concept using immunostimulatory gene-based prodrugs (Bellavite et al., 2023; Cosentino and Marino, 2022). Alternatively, the term gene-based prodrug syndrome (GPS) could be used in this context. Prodrugs are initially pharmacologically inactive substances that are converted into a pharmacologically active product in the body. In the case of gene-based anti-SARS-CoV-2 prodrugs, this occurs via, among other things, the mRNA effect in ribosomes, which triggers SP synthesis.

For medical diagnosis, care and treatment, medical documentation and communication, and for scientific research, it is essential to use correct terminology to avoid confusion and misinterpretation of the underlying causes and patterns of damage. The use of the terms proposed here is intended to help ensure that corresponding side effect syndromes are taken seriously and recognised as a consequence of product application, that the underlying pathomechanism becomes more quickly and clearly accessible, and that the likelihood of them being confused with other disease syndromes and thus misdiagnosis is reduced.

## CRediT authorship contribution statement

**Andreas Posa:** Writing – original draft, Validation, Supervision, Resources, Data curation, Conceptualization.

## Ethical approval

A narrative review usually does not require ethics approval, as this type of review study does not collect new data or work directly with human subjects. A narrative review refers to the summary and interpretation of existing literature on a particular topic without conducting experimental research itself.

## Declaration of Competing Interest

The corresponding author states that there is no conflict of interest.

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