

Preprint

Innate Immune Suppression by SARS-CoV-2 mRNA Vaccinations: The role of G-quadruplexes, exosomes and microRNAs

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Zusammenfassung

Die mRNA-Impfstoffe gegen SARS-CoV-2 wurden als Reaktion auf die weithin wahrgenommene Krise der öffentlichen Gesundheit von Covid-19 auf den Markt gebracht. Der Einsatz von mRNA-Impfstoffen im Zusammenhang mit Infektionskrankheiten war ohne Präzedenzfall, aber verzweifelte Zeiten schienen verzweifelte Maßnahmen zu erfordern. Die mRNA-Impfstoffe verwenden genetisch veränderte mRNA, die für Spike-Proteine kodiert. Diese Veränderungen verbergen die mRNA vor der zellulären Abwehr, fördern eine längere biologische Halbwertszeit der Proteine und bewirken eine höhere Gesamtproduktion von Spike-Proteinen. Sowohl experimentelle als auch beobachtete Daten zeigen jedoch eine ganz andere Immunantwort auf die Impfstoffe als auf die Infektion mit SARS-CoV-2. Wie wir zeigen werden, sind die genetischen Veränderungen, die durch den Impfstoff eingeführt werden, wahrscheinlich die Ursache für diese unterschiedlichen Reaktionen. In diesem Beitrag präsentieren wir den Nachweis, dass eine Impfung im Gegensatz zu einer natürlichen Infektion eine tief greifende Beeinträchtigung der Typ-I-Interferon-Signalisierung hervorruft, die verschiedene negative Folgen für die menschliche Gesundheit hat. Wir erklären den Mechanismus, durch den Immunzellen große Mengen von Exosomen in den Blutkreislauf freisetzen, die Spike-Proteine zusammen mit kritischen microRNAs enthalten, die eine Signalreaktion in Empfängerzellen an entfernten Stellen auslösen. Wir identifizieren auch potenziell tiefgreifende Störungen in der regulatorischen Kontrolle der Proteinsynthese und der Krebsüberwachung. Diese Störungen stehen nachweislich in direktem Zusammenhang mit neurodegenerativen Erkrankungen, Myokarditis, Immunthrombozytopenie, Bellscher Lähmung, Lebererkrankungen Lebererkrankung, beeinträchtigter adaptiver Immunität, erhöhter Tumorigenese und DNA-Schäden. Wir zeigen Beweise aus Berichten über unerwünschte Ereignisse in der VAERS-Datenbank, die unsere Hypothese unterstützen. Wir sind der Ansicht, dass eine umfassende Risiko-/Nutzenbewertung der mRNA-Impfstoffe ausschließt, dass sie einen positiven Beitrag zur öffentlichen Gesundheit leisten, selbst im Zusammenhang mit der Covid-19-Pandemie. (Übersetzt mit DeepL)

Abstract

The mRNA SARS-CoV-2 vaccines were brought to market in response to the widely perceived public health crises of Covid-19. The utilization of mRNA vaccines in the context of infectious disease had no precedent, but desperate times seemed to call for desperate measures. The mRNA vaccines utilize genetically modified mRNA encoding spike proteins. These alterations hide the mRNA from cellular defenses, promote a longer biological half-life for the proteins, and provoke higher overall spike protein production. However, both experimental and observational evidence reveals a very different immune response to the vaccines compared to the response to infection with SARS-CoV-2. As we will show, the genetic modifications introduced by the vaccine are likely the source of these differential responses. In this paper, we present the evidence that vaccination, unlike natural infection, induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health. We explain the mechanism by which immune cells release into the circulation large quantities of exosomes containing spike protein along with critical microRNAs that induce a signaling response in recipient cells at distant sites. We also identify potential profound disturbances in regulatory control of protein synthesis and cancer surveillance. These disturbances are shown to have a potentially direct causal link to neurodegenerative disease, myocarditis, immune thrombocytopenia, Bell's palsy, liver disease, impaired adaptive immunity, increased tumorigenesis, and DNA damage. We show evidence from adverse event reports in the VAERS database supporting our hypothesis. We believe a comprehensive risk/benefit assessment of the mRNA vaccines excludes them as positive contributors to public health, even in the context of the Covid-19 pandemic.

Introduction

Vaccination is an endeavor to utilize non-pathogenic material to mimic the immunological response of a natural infection, thereby conferring immunity in the event of pathogen exposure. This goal has been primarily pursued through the use of both whole organism and attenuated virus vaccines. Use of fragments of virus or their protein products, referred to as "subunit vaccines," has been more technically challenging [1]. In any event, an implicit assumption behind the deployment of any vaccination campaign is that the vaccine confers the effects of a 'benign infection,' activating the immune system against future exposure, while avoiding the health impacts of actual infection. Much of the literature on this related to COVID-19 suggests that the immune response to mRNA-based vaccination is similar to natural infection. A preprint study found "high immunogenicity of BNT162b [Pfizer]

vaccine in comparison with natural infection." The authors found there to be many qualitative similarities though quantitative differences [2]. Jhaveri (2021) suggests that mRNA vaccines do what infection with the virus does: "The protein is produced and

presented in the same way as natural infection" [3]. The U.S. Centers for Disease Control and Prevention (CDC) makes the case based upon antibody titers generated by prior infection vs. vaccination, in addition to production of memory B cells, to argue that the immune response to vaccination is analogous to the response to natural infection [4]. It is this similarity in the humoral immune response to vaccination vs natural infection, paired with both trial and observational data demonstrating reduced risk of infection following vaccination, that stands as the justification for the mass vaccination campaign. In this paper we explore the scientific literature suggesting that vaccination with an mRNA vaccine initiates a set of biological events that are not only different from that induced by vaccination but are in several ways demonstrably counterproductive to both short- and long-term immune competence and normal cellular function. These vaccinations have now been shown to downregulate critical pathways related to cancer surveillance, infection control, and cellular homeostasis. They introduce into the body highly modified genetic material. A medRxiv preprint has revealed a remarkable difference between the characteristics of the immune response to an infection with SARS-CoV-2 as compared with the immune response to an mRNA vaccine against COVID-19 [5]. Differential gene expression analysis of peripheral dendritic cells revealed a dramatic upregulation of both type I and type II interferons (IFNs) in COVID-19 patients, but not in vaccinees. One remarkable observation they made was that there was an expansion of circulating hematopoietic stem and progenitor cells (HSPCs) in COVID-19 patients, but this expansion was notably absent following vaccination. A striking expansion in circulating plasmablasts observed in COVID-19 patients was also not seen in the vaccinees. All of these observations are consistent with the idea that the vaccines actively suppress type I IFN signaling, as we will discuss below. In this paper we will be focusing extensively, though not exclusively, on vaccination-induced type I IFN suppression and the myriad downstream effects this has on the related signaling cascade. Since long-term pre-clinical and Phase I safety trials were combined with Phase II trials, then phase II and III trials were combined [6]; and since even those were terminated early and placebo arms given the injections, we look to the pharmacovigilance system and published reports for safety signals. In doing so, we find that that evidence is not encouraging. The biological response to mRNA vaccination as it is currently employed is demonstrably not like natural infection. In this paper we will illustrate those differences, and we will describe the immunological and pathological processes we expect are being initiated by mRNA vaccination. We will connect these underlying physiological effects with both realized and yet-to-be-observed morbidities. We anticipate that implementation of booster vaccinations on a wide scale will make all of these problems only more acute, and it will serve to further erode antiviral immune competence and innate cancer surveillance and protection for the global population subjected to these repeated boosters. The mRNA vaccines manufactured by Pfizer/BioNTech and Moderna have been viewed as an essential aspect of our efforts to control the spread of COVID-19. Countries around the globe have been aggressively promoting massive vaccination programs with the hope that such efforts might finally curtail the ongoing pandemic and restore normalcy. Governments seem reticent to consider the possibility that these injections might cause harm in unexpected ways, and especially that such harm might even surpass the benefits achieved in protection from severe disease. It is now clear that the antibodies induced by the vaccines fade in as little as 3 to 10 weeks after the second dose [7], such that people are being advised to seek booster shots at regular intervals [8]. It has also become apparent that rapidly emerging variants such as the Delta and now the Omicron strain are showing resistance to

the antibodies induced by the vaccines, through mutations in the spike protein [9]. Furthermore, it has become clear that the vaccines do not prevent spread of the disease, but can only be claimed to reduce symptom severity [10]. A study comparing vaccination rates with COVID-19 infection rates across 68 countries and 294 counties in the United States in early September, 2021, found no correlation between the two, suggesting that these vaccines do not protect from spread of the disease [11]. Regarding symptom severity, even this aspect is beginning to be in doubt, as demonstrated by an outbreak in an Israeli hospital that led to the death of five fully vaccinated hospital patients [12]. Similarly, Brosh-

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Nissimov et al. (2021) reported that 34/152 (22%) of fully vaccinated patients among 17 Israeli hospitals died of COVID-19 [13]. The increasing evidence that the vaccines do little to control disease spread and that their effectiveness wanes over time make it even more imperative to assess the degree to which the vaccines might cause harm. That SARS-CoV-2 modified spike protein mRNA vaccinations have biological impacts is without question. Here we attempt to distinguish those impacts from natural infection, and establish a mechanistic framework linking those unique biological impacts to pathologies now associated with vaccination. We recognize that the causal links between biological effects initiated by mRNA vaccination and adverse outcomes have not been established in the large majority of cases.

2. Interferons: An Overview with Attention to Cancer Surveillance

Discovered in 1957, interferon (IFN) earned its name with the recognition that cells challenged by attenuated influenza A virus created a substance that “interfered with” a subsequent infection by a live virus [14]. IFN is now understood to represent a very large family of immune-modulating proteins, divided into three types, designated as type I, II, and III based upon the receptors each IFN interacts with. Type I IFN includes both IFN- α and IFN- β , and this type is the most diverse, being further divided into seventeensubtypes. IFN- α alone has thirteen subtypes currently identified, and each of those is further divided into multiple categories [15]. Type I IFNs play a powerful role in the immune response to multiple stressors. In fact, they have enjoyed clinical therapeutic value as a treatment option for a variety of diseases and conditions, including viral infections, solid tumors, myeloproliferative disorders, hematopoietic neoplasms and autoimmune diseases such as multiple sclerosis [16]. As a group, IFNs play exceedingly complicated and pleiotropic roles that are coordinated and regulated through the activity of the family of IFN regulatory factors, or IRFs [17]. IRF9 is most directly involved in anti-viral as well as anti-tumor immunity and genetic regulation [18-20]. Closely related to this are plasmacytoid dendritic cells (pDCs), a rare type of immune cell that circulate in the blood but migrate to peripheral lymphoid organs during a viral infection. They respond to a viral infection by sharply upregulating production of type I IFNs. The IFN- α released in the lymph nodes induces B cells to differentiate into plasmablasts. Subsequently, interleukin-6 (IL-6) induces plasmablasts to evolve into antibody-secreting plasma cells [21]. Thus, IFNs play a critical role in both controlling viral proliferation and inducing antibody production.

Central to both antiviral and anticancer immunity, IFN- γ is produced by macrophages and lymphocytes when either is challenged with viral or bacterial infection or encounter tumor cells [22]. Its role as a potent antiviral therapy has been recognized in the treatment of hepatitis C complications [23], Cytomegalovirus infection [24], chronic active ebola virus infection [25], inflammatory bowel disease associated with herpes virus infection [26], and others. Impaired type I IFN signaling is linked to many disease risks, most notably cancer, as type I IFN signaling suppresses proliferation of both viruses and cancer cells by arresting the cell cycle, in part through upregulation of p53, a tumor suppressor gene, and various cyclin-dependent kinase inhibitors [27,28]. IFN- γ also induces major histocompatibility (MHC) class I antigen presentation by tumor cells, causing them to be more readily recognized by the cancer surveillance system [29,30]. The range of anticancer effects initiated by IFN- γ production is astounding and occurs through both direct and indirect mechanisms. Direct effects include cell cycle arrest, induction of cell differentiation, initiation of apoptosis, activation of natural killer and CD8+ T cells, and others [31]. The indirect anticancer effects are predominantly carried out through gene transcription activation of the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway. IFN- γ binding on the cell surface initiates JAK, a tyrosine kinase, to phosphorylate STAT1 and STAT2 [32]. Once phosphorylated, these STATs form a complex with IRF9, one of a family of IRFs that play a wide range of roles in oncogene regulation and other cell functions [33]. It is this complex, named IFN-stimulated gene factor 3 (ISGF3), that translocates to the cell nucleus to enhance the expression of at least 150 genes [31]. IRF9 has been suggested to be the primary member of the IRF family of proteins responsible for activation of the IFN-

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antiproliferative effects, and that appears to be through its binding to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor 1 and 2 (TRAIL-R1/2) [34]. IRF7 is another crucial member of the IRF family of proteins involved early in the response to a viral infection. It is normally expressed in low amounts but is strongly induced by ISGF3. IRF7 also undergoes serine phosphorylation and nuclear translocation to further activate the immune response. IRF7 has a very short half-life, so its gene-induction process is transient, perhaps to avoid overexpression of IFNs [35]. Once TRAIL is bound by IRF9, it is then able to act as a ligand for Death Receptor 4 (DR4) or DR5, initiating a cascade of events involving production of caspase 8 and caspase 3, and ultimately triggering apoptosis [36]. Dysregulation of this pathway, through suppression of either IFN- γ or IRF9 and the resulting failure to bind TRAIL-R, has been associated with several hematologic malignancies [37], and has been shown to increase the metastatic potential in animal models of melanoma, colorectal cancer, and lymphoma [38]. IFN- γ both initiates and orchestrates a wide range of cancer suppressing roles. Dunn et al. (2005) showed that IFN- γ plays an active role in cancer immunoeediting, its locus of action being hematopoietic cells that are "programmed" via IFN- γ binding for tumor surveillance [39]. It is via the exceedingly complex interactions between type I IFNs and IRF7 and IRF9 in particular that a great deal of antiproliferative effects are carried out. This is evidenced by the large number of studies showing increased tumor growth and/or metastases associated with a wide number of cancer types. For example, Bidwell et al. (2012) found that, among over 800 breast cancer patients, those with high expression of IRF7-regulated genes had significantly fewer bone metastases, and they propose assessment of these IRF7-related

gene signatures as a way to predict those at greatest risk [40]. Use of microRNA to target IRF7 expression has also been shown to enhance breast cancer cell proliferation and invasion in vitro [41]. Zhao et al. (2017) found a similar role for IRF7 in relation to bone metastases in a mouse model of prostate cancer [42]. Regarding the anti-cancer mechanism behind IRF7 expression, Solis et al. (2006) found that IRF7 induces transcription of multiple genes and translation of their downstream protein products including TRAIL, IL-15, ISG-56 and CD80, with the noted therapeutic implications [43]. IRF9, too, has a central role to play in cancer surveillance and prevention. Erb et al. (2013) demonstrated that IRF9 is the mediator through which IL-6 augments the anti-proliferation effects of IFN- against prostate cancer cells [44]. Tian et al. (2018) found IRF9 to be a key negative regulator of acute myeloid leukemia cell proliferation and evasion of apoptosis [45]. It does so, at least in part, through acetylation of the master regulatory protein p53. Both IFN- and IRF9 are also apparently necessary for the cancer-preventative properties of a fully functional BRCA2 gene. In a study presented as an abstract at the First AACR International Conference on Frontiers in Basic Cancer Research, Mittal and Chaudhuri (2009) describe a set of experiments which show for the first time that BRCA2 expression leads to increased IFN- production and augments the signal transduction pathway resulting in the complexing of IRF9, STAT1 and STAT2 described previously [46]. Two years prior, Buckley et al. (2007) had established that BRCA1 in combination with IFN- promotes type I IFNs and subsequent production of IRF7, STAT1, and STAT2 [47]. Thus, the exceedingly important cancer regulatory genes BRCA1 and BRCA2 rely on IRF7 and IRF9, respectively, to carry out their protective effects. In a preprint, Mamoor (2020) used gene expression analysis to determine that infection with either SARS-CoV-1 (in mice) or MERS-CoV (in vitro) leads to increased production of IRF7 and IRF9, and the author speculates that "IRF7 and IRF9 may be important for SARS-CoV-2 immune defense in humans." [48] This speculation is somewhat confirmed by Rasmussen et al. (2021), who reviewed the compelling evidence that deficiencies of either IRF7 or IRF9 lead to significantly greater risk of severe COVID-19 illness [49]. Importantly, they also note that evidence suggests type I IFNs play a singularly important role in protective immunity against COVID-19 illness, a role that is shared by multiple cytokines in most other viral illnesses including influenza. As will be discussed in more detail below, the SARS-CoV-2 spike protein modifies host cell exosome pro-

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duction. Transfection of cells with the spike gene and subsequent spike protein production results in those cells generating exosomes containing microRNAs that suppress IRF9 production while activating a range of pro-inflammatory gene transcripts [50]. Since these vaccines are specifically designed to induce high and ongoing production of spike proteins, the implications are ominous. As described above, inhibition of IRF9 will suppress TRAIL and all its regulatory and downstream apoptosis-inducing effects. IRF9 suppression via exosomal microRNA should also be expected to impair the cancer-protective effects of BRCA2 gene activity, which depends on that molecule for its activity as described above. BRCA2-associated cancers include breast, fallopian tube, and ovarian cancer for women, prostate and breast cancer for men, acute myeloid leukemia in children, and others [51]. Vaccination has also been demonstrated to suppress both IRF7 and STAT2 [52]. This can be expected to interfere with the cancer-protective effects of BRCA1 as described above. Cancers associated with impaired BRCA1 activity include

breast, uterine, and ovarian cancer in women; prostate and breast cancer in men; and a modest increase in pancreatic cancer for both men and women [53]. Reduced BRCA1 expression is linked to both cancer and neurodegeneration. BRCA1 is a well-known breast cancer susceptibility gene. BRCA1 inhibits breast cancer cell proliferation through activation of SIRT1 and subsequent suppression of the androgen receptor [54]. In a study conducted by Suberbielle et al. (2015), reduced levels of BRCA1 were found in the brains of Alzheimer's patients [55]. Furthermore, experiments with knocking down neuronal BRCA1 in the dentate gyrus of mice showed that DNA double-strand breaks were increased, along with neuronal shrinkage and impairments in synaptic plasticity, learning and memory. Analysis detailed in a recent case study on a patient diagnosed with a rare form of lymphoma called angioimmunoblastic T cell lymphoma provided strong evidence for unexpected rapid progression of lymphomatous lesions after administration of the BNT162b2 mRNA booster shot [56]. Comparisons of detailed metrics for hypermetabolic lesions conducted immediately before and 21 days after the vaccine booster revealed a five-fold increase after the vaccine, with the post-booster test revealing a 2-fold higher activity level in the right armpit compared to the left one. The vaccine had been injected on the right side. It is worth pointing out in this regard that lymphoid malignancies have been associated with suppression of TRAIL R1 [57]. Given the universally recognized importance of optimally functioning BRCA1/2 for cancer prevention and given the central role of the TRAIL signal transduction pathway for additional cancer surveillance, the suppression of IRF7 and IRF9 through vaccination and subsequent spike protein production is extremely concerning for long-term cancer control in injected populations.

3. Considerations in the Design of mRNA Vaccines

The primary goal of the developers of the SARS-CoV-2 mRNA vaccines was to design a vaccine that could induce a robust antibody response to the spike protein. Preexisting antibodies to spike protein should cause the invading viruses to be quickly cleared before they could invade host cells, thus arresting the disease process early on. As stated succinctly by Kaczmarek et al. (2021) [58]: "The rationale behind vaccination is to provide every vaccinated person with protection against the SARS-CoV-2 virus. This protection is achieved by stimulating the immune system to produce antibodies against the virus and to develop lymphocytes that will retain memory and the ability to fight off the virus for a long time." Vaccines generally depend upon adjuvants such as aluminum and squalene to provoke immune cells to migrate to the injection site immediately after vaccination. In the history of mRNA vaccine development, it was initially hoped that the mRNA itself could serve as its own adjuvant. This is because human cells recognize viral RNA as foreign, and this leads to upregulation of type I IFNs, mediated via toll like receptors such as TLR3, TLR7 and TLR8 [59]. However, with time it became clear that there were problems with this approach, both because the intense reaction could cause flu-like symptoms and because IFN- could launch a cascade response that would lead to the breakdown of the messenger RNA before it could produce adequate amounts of spike protein to

induce an immune response [60]. A breakthrough came when it was discovered experimentally that the mRNA coding for the spike protein could be modified in specific ways that would essentially fool the human cells into recognizing it as harmless human RNA. A seminal paper by Karikó et al. (2005) demonstrated through a series of in vitro experiments that a simple modification to the mRNA such that all uridines were replaced with pseudouridine could dramatically reduce innate immune activation against exogenous mRNA [59]. Andries et al. (2015) later discovered that 1-methylpseudouridine as a replacement for uridine was even more effective than pseudouridine and could essentially abolish the TLR response to the mRNA, preventing the activation of blood-derived dendritic cells [61]. This modification is applied in both the mRNA vaccines on the market [62]. For successful mRNA vaccine design, the mRNA needs to be encapsulated in carefully constructed particles that can protect the RNA from degradation by RNA depolymerases. The mRNA vaccines are formulated as lipid nanoparticles containing cholesterol and phospholipids, with the modified mRNA complexed with a highly modified polyethylene glycol (PEG) lipid backbone to promote its early release from the endosome and to further protect it from degradation [63]. The host cell's existing biological machinery is co-opted to facilitate the natural production of protein from the mRNA through endosomal uptake of a lipid particle [63]. A synthetic cationic lipid is added as well, since it has been shown experimentally to work as an adjuvant to draw immune cells to the injection site and to facilitate endosomal escape. De Beuckelaer et al. (2016) observed that "condensing mRNA into cationic lipoplexes increases the potency of the mRNA vaccine evoked T cell response by several orders of magnitude." [60] Another important modification is that they replaced the code for two adjacent amino acids in the genome with codes for proline, which causes the spike protein to stay in a prefusion stabilized form [64]. The spike protein mRNA is further "humanized" with the addition of a guanine-methylated cap, 3' and 5' untranslated regions (UTRs) copied from those of human proteins, and finally a long poly(A) tail to further stabilize the RNA [65]. In particular, researchers have cleverly selected the 3' UTR taken from globins which are produced in large quantities by erythrocytes, because it is very effective at protecting the mRNA from degradation and maintaining sustained protein production [66]. This is to be expected, since erythrocytes have no nucleus, so they are unable to replace the mRNAs once they are destroyed. Both the Moderna and the Pfizer vaccines adopted a 3' UTR from globins, and the Pfizer vaccine also uses a slightly modified globin 5' UTR [67]. De Beuckelaer et al. (2016) aptly summed up the consequences of such modifications as follows: "Over the past years, technical improvements in the way IVT [in vitro transcribed] mRNAs are prepared (5' Cap modifications, optimized GC content, improved polyA tails, stabilizing UTRs) have increased the stability of IVT mRNAs to such extent protein expression can now be achieved for days after direct in vivo administration of the mRNA." [60] However, the optimized analogue cap formation of synthetic mRNAs inevitably forces the recipient cells to undergo a cap-dependent prolonged translation, ignoring homeostatic demands of cellular physiology [65]. The cap 2' O methylation carried out by cap 2' O methyltransferase (CMTR1) serves as a motif that marks the mRNA as "self," to prevent recognition by IFN-induced RNA binding proteins [68]. Thus, the mRNA in the vaccines, equipped with the cap 2' O methylation motif, evades detection as a viral invasion. Furthermore, the overwhelming impetus for cells to perform a single and artificial approach to translation according to the robust capping and synthetic methylations of mRNAs in vaccines is fundamentally associated with disease progression due to differential

rather than normal signaling of pattern recognition receptors (PRRs) [69]. The regulatory process controlling mRNA translation is extremely complex, and it is highly disturbed in the context of mRNA vaccines [65,69]. Briefly, the idea is for mRNA vaccines to achieve the intended goal (i.e., production of the modified spike protein) through a stealth strategy that bypasses the natural immunological response to RNA-type viral infection. Injected lipid nanoparticles containing mRNA are brought to the cell interior via endocytosis. The mRNA escapes its lipid carrier and migrates to the ribosome, where it is abundantly translated into its final protein product, following an optimized program for producing large quantities of a specific protein over an extended period of time. These modified spike proteins then follow one of three primary pathways. Some are proteolytically degraded and fragments are bound by MHC class

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I molecules for surface presentation to cytotoxic T-cells. A second pathway has those same spike fragments bind MHC class II molecules, move to the cell surface, and activate T-helper cells. A final pathway has soluble spike proteins extruded from the cell in exosomes, where they can be recognized by B-cell-activated spike-specific antibodies [70]. In the end, it is through utilization of nanolipids and sophisticated mRNA technology that the normal immune response to exogenous RNA is evaded in order to produce a strong antibody response against an exogenous RNA virus.

4. GC enrichment and potential G4 (pG4) structures in vaccine mRNAs

Recently, members of our team investigated possible alterations in secondary structure of mRNAs in SARS-CoV-2 vaccines due to codon optimization of synthetic mRNA transcripts [71]. This study has shown that there is a significant enrichment of GC content in mRNAs in vaccines (53% in Pfizer BNT 162b2 and 61% in Moderna mRNA-1273) as compared to the native SARS-CoV-2 mRNA (36%). The enriched GC content of mRNAs is the result of codon optimization performed during the development of the mRNAs used in SARS-CoV-2 vaccines, apparently without determining the effect on secondary structures, particularly the G quadruplex formation [71]. Codon optimization describes the production of synthetic, codon-optimized polypeptides and proteins used in biotechnology therapeutics (such as the synthetic mRNAs used for SARS-CoV-2 vaccination). The altered codon assignments within the mRNA template dramatically increase the quantity of polypeptides and/or proteins produced [72]. Synonymous codon replacement also results in a change in the multifunctional regulatory and structural roles of resulting proteins [73]. For this reason, codon optimization has been cautioned against due to its consequent changes causing perturbation in the secondary conformation of protein products with potentially devastating effects on their resulting immunogenicity, efficacy and function [74,75]. Notably, various human diseases are the result of synonymous nucleotide polymorphisms [76]. In an experiment where GC-rich and GC-poor versions of mRNA transcripts for heat shock protein 70 were configured in the context of identical promoters and UTR sequences, it was found that GC-rich genes were expressed several-fold to over a hundred-fold more efficiently than their GC-poor counterparts [77]. This is partly because all of the preferred mammalian codons have G or C nucleotides in the third position. It is also well documented that AU-rich elements in the 3' UTRs can destabilize mRNA [78].

What may be of particular concern is the fact that GC enrichment content in vaccine mRNAs results in an enhanced ability for potential G quadruplex (pG4) formations in these structures, and this could cause onset of neurological disease [79]. Remarkably, the human prion protein (PrP) genetic sequence contains multiple G4 forming motifs, and their presence may form the missing link in the initial conversion of PrP to the misfolded form, PrP^{Sc} [80]. PrP binding to its own mRNA may be the seed that causes the protein to misfold. This observation is particularly concerning in light of the fact that the spike protein has prion-like characteristics [81]. On the one hand, the GC content has a key role in the modulation of translation efficiency and control of mRNA expression in mammals [82]. Especially during translation initiation, the GC content operating as cis-acting mRNA element orchestrates the 43S ribosomal pre-initiation complex attachment and thereafter the assembly of the eukaryotic translation initiation factor 4E (eIF4E) complex. One representative example of this system in action is the regulation of α and β globin mRNA expression through their 5' untranslated regions (5'UTRs) [82]. On the other hand, the presence of pG4s in RNAs is implicated in cancer biology as key determinants of the regulation of G4 RNA binding proteins such as helicase [83]. Generally, the G quadruplexes in RNAs have essential roles in a) the regulation of gene expression, b) the localization of ribonuclear proteins, c) the mRNA localization and d) the regulation of proto-oncogene expression [84]. Regarding SARS-CoV-2, relevant studies reveal overwhelming similarities between SARS-CoV-2 pG4s, including in RNA coding for spike protein, and those sequenced in the human transcriptome [85]. Thus, it

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can be inferred that synthetic mRNAs in vaccines carrying more pG4 structures in their coding sequence for spike protein will amplify and compound the potential post-transcriptional disorganization due to G4-enriched RNA during natural SARS-CoV-2 infection. Moreover, the cellular nucleic acid binding protein (CNBP), which is the main cellular protein that binds to the SARS-CoV-2 RNA genome in human-infected cells [86], binds to and promotes the unfolding of SARS-CoV-2 G4s formed by both positive and negative sense template strands of the SARS-CoV-2 RNA genome. A similar modulation of CNBP on vaccine mRNA G4s and promotion of G4 equilibrium towards unfolded conformations create favorable conditions for miRNA binding, and this will have a direct impact on miRNA-dependent regulation of gene expression [87]. The negative-sense RNAs are intermediate molecules produced by the replicase transcriptase complex (RTC) formed by the nonstructural proteins of coronaviruses (including SARS-CoV-2) to provide efficiency in replication and transcription [88,89]. This, however, introduces another potentially serious complication associated with vaccination. Co-infection with other negative sense RNA viruses such as hepatitis C [90] or infection by other coronaviruses contemporaneous with vaccination periods would provide the necessary machinery of RTC to reproduce negative sense intermediates from synthetic mRNAs and therefore amplify the presence of pG4s by negative sense templates. This would result in further epitranscriptomic dysregulation [91]. Summarizing the topic to this point, the enrichment of GC content in vaccine mRNA will inevitably lead to an increase in the pG4 content of the vaccines. This, in turn, will lead to dysregulation of the G4-RNA-protein binding system and a wide range of potential disease-associated cellular pathologies including suppression of innate immunity, neurodegeneration, and malignant transformation [83]. Concerning the post translational deregulation due to emergence of

new G4 structures introduced by vaccination, one other important issue related to miRNA regulation and pG4s arises. In miRNA structures, hundreds of pG4 sequences are identified [92]. In their unfolded conformation, as during binding to their respective targets in 3' to 5' sequences of mRNAs, miRNAs switch off the translation of their respective target mRNA. Alternatively, when in the presence of a G4 ligand, the translation of their target mRNAs is promoted [93]. Moreover, a vast number of putative miRNA binding sites overlap with G4s in 3' UTRs of mRNAs as there are at least 521 specific miRNAs that are predicted to bind to at least one of these G4s. Overall, 44,294 G4-miRNA potential binding sites have been traced to possess putative overlapping G4s in humans [87]. As described elsewhere, during the cellular translation of vaccine mRNAs, an increased assembly of a number of RNA binding protein helicases, such as eIF4A bound to eIF4G, will occur [65]. The presence of increased pG4s in synthetic mRNAs can potentially amplify binding of RNA binding proteins and miRNAs. This form of molecular crowding of protein components (helicases) with great affinity for G4 binding [87] will decrease the number of RNA binding proteins binding G4s normally available for miRNA regulation. This loss of RNA binding proteins as well as miRNA availability for regulation by binding to G4s can dramatically alter the translational regulation of miRNAs present in cells and thereby disrupt essential regulation of oncogene expression. An example is the p16-dependent regulation of the p53 tumour suppressor protein [87,94]. This process is exceedingly complicated yet tantamount to cellular homeostasis. So, again, it merits summarizing. If pG4s accumulate, as would be expected with an increased amount of GC content in the vaccine mRNA, this would have an effect of increasing potential G4 structures available during translation events and this can affect miRNA post-transcriptional regulation. This, in turn, would either favor greater expression of the oncogenes related to a range of cancers or drive cells to apoptosis and cell death [95]. The case study described earlier in this paper strongly supports the hypothesis that these injections induce accelerated lymphoma progression in follicular B cells [56]. miRNA binding recognition patterns are imperfectly complementary to their target regions, and for this reason they are referred to as "master regulators," since one miRNA affects a plethora of different targets [92]. The multitude of pG4s in the mRNA of the vaccine would predictably act as decoys, distracting miRNAs from their normal function in regulating human protein expression. The increase in G4 targets due to the

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vaccine would decrease the availability of miRNAs to target human-expressed G4s for regulation of gene expression. This can result in downregulation of miRNA expression which is implicated in cardiovascular pathology [96], onset of neurodegeneration [97], and/or cancer progression [98]. In most respects within eukaryotic machinery, miRNAs are involved in translation repression. One example, vital for cellular normal housekeeping is that of Mouse double minute 2 homolog (MDM2), a physical negative regulatory protein of p53. P53 itself is considered the master regulator of the cellular tumor suppression network of genes. P16 controls the expression of many miRNAs, and, via miR-141 and miR-146b-5p binding to MDM2 mRNA, it induces the negative regulation of MDM2, thus enabling p53 ubiquitination and promotion of cell survival upon DNA damage events [94]. Deregulation of miRNAs that control MDM2 suppression of p53 would predictably lead to an increased risk to cancer [99].

5. Type I IFNs and COVID-19

Type I IFNs play an essential role in fighting viral infections, and deficiencies in type I IFN signaling have been associated with poor outcomes from COVID-19 in multiple studies. These cases are often associated with autoantibodies to type I IFNs. As reviewed below, type I IFNs have been used with some success in treating severe COVID-19, particularly if administered very early in the disease process. If, as argued above, the mRNA vaccines interfere with type I signaling, this could lead to increased susceptibility to COVID-19 in the two weeks following the first vaccine, before an antibody response has been initiated. Cells infected with a virus detect the presence of virus replication through a number of pattern recognition receptors (PPRs), which serve as sentinels sensing aberrant RNA structures that often form during viral replication. These receptors respond by oligomerizing and subsequently inducing type I IFNs, ultimately upregulating a large number of proteins involved in suppressing viral proliferation [100]. A multi-author study by researchers in Paris, France, involving a cohort of 50 COVID-19 patients with varying degrees of disease severity, revealed that patients with severe disease were characterized by a highly impaired type I IFN response [101]. These patients had essentially no IFN- and low IFN- production and activity. This was associated with a persistent blood viral load and an exacerbated inflammatory response, characterized by high levels of tumor necrosis factor (TNF-) and Il-6. The authors proposed type I IFN therapy as a potential treatment option. A paper by several researchers in the United States also identified a unique and inappropriate inflammatory response in severe COVID-19 patients, characterized by low levels of both type I and type III IFNs along with elevated chemokines and elevated expression of Il-6 [102]. Type I IFNs have even been proposed as a treatment option for severe COVID-19. In a hamster model, researchers exposed hamsters to SARS-CoV-2 and induced an inflammatory response in the lungs and systemic inflammation in distal tissues. They found that intranasal administration of recombinant IFN- resulted in a reduced viral load and alleviation of symptoms [103]. A retrospective cohort study of 446 COVID-19 patients determined that early administration of IFN- 2b was associated with reduced in-hospital mortality. However, late IFN therapy increased mortality and delayed recovery, revealing that early administration of interferon therapy is essential for a favorable response [104]. A surprising number of people have neutralizing autoantibodies against type I IFNs, although the underlying etiology of this phenomenon is not understood. A study using longitudinal profiling of over 600,000 peripheral blood mononuclear cells and transcriptome sequencing from 54 patients with COVID-19 and 26 controls found a notable lack of type I IFN-stimulated gene responses in myeloid cells from patients with critical disease [105]. Neutralizing autoantibodies against type I IFNs were found in 19% of patients with critical disease, 6% of patients with severe disease, and 0% of patients with moderate disease. Another study based in Madrid, Spain revealed that 10% of patients with severe COVID-19 disease had autoimmune antibodies to type I IFNs [106]. Finally, Stertz and Hale (2021) note that, whether due to autoantibodies or perhaps loss-of-function polymorphisms associated with interferon system genes, deficiencies in interferon production are associated with as many as 15% of all life-threatening COVID-19 cases [107].

6. Are the methylation strategies for cellular housekeeping generally omitted by vaccine

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mRNAs Methylation of mRNAs has been evolutionarily devised to control translation of transcripts and therefore expression of genes by a complex cascade of methylator (writers) and de-methylator (eraser) and reader proteins. A key methylation of adenosine “N6-methyladenosine (m6A)” in the 5’ UTR of mRNAs regulates normal cell physiology, the inflammatory response and cancer progression. The role and mechanisms of m6A in human disease is extensive and excellently covered in other comprehensive reviews [108,109]. Foremost among these, the SARS-CoV-2 molecular vaccination induces cell stress conditions, as is described by the elevated NF- κ B signaling after vaccination [52,110]. Under conditions of cellular stress which can be induced by a viral infection or disease states such as cancer, m6A mediates mRNAs to undergo translation preferentially in a cap-independent way [111]. As discussed previously, this is opposite to the impact of mRNA SARS-CoV-2 vaccination, which drives cells toward a cap-dependent translation. Furthermore, under diversified conditions of cellular stress, there is an overwhelming induction of transcriptome-wide addition of m6A that causes an increased number of mRNAs to possess 5’UTRs enriched with m6A [111]. Eukaryotic translation initiation factor 4E (eIF4E) is the initial mRNA cap binding protein that directs ribosomes to the cap structure of mRNAs, in order to initiate translation into protein. The dependence on cap-dependent translation of vaccine mRNAs will consume a surplus of eIF4E availability needed to translate an unnaturally high number of synthetic mRNAs. However, the cap-independent translation takes place without requiring eIF4E to be bound to eIF4F. The competition for ribosomes will shift towards the cap-independent translation of transcripts, since the mRNAs undergoing cap-independent translation are equipped, apart from internal ribosome entry sites (IRES), with special binding motifs that bind to factors that actively recruit mRNAs to the ribosome cap-independent translational enhancers (CITEs) [112]. Furthermore, this also means that eIF4E, which is a powerful oncogene regulator and cell proliferation modulator, will sustain its activities by this competition, for an unnaturally prolonged period of time, trying to counterbalance the competition between robustly-capped mRNAs in vaccines and IRES-containing mRNAs [113,65]. This type of condition results in dysregulation of co-transcriptional m6A mRNA modifications and seriously links to molecular progressions of various cancers [114], as well as creating predisposing conditions for subsequent viral infections [113]. We next consider the impact of mRNA-vaccination-derived spike protein on the cellular IFN system via massive exosome production.

7. Exosomes and MicroRNAs

An important communication network among cells consists of extracellular vesicles (EVs) that are constantly released by one cell and later taken up by another cell, which could be in a distant organ. Small vesicles known as exosomes, formed inside endosomes, are

similar in size to viruses, and are released through exocytosis into the extracellular space to subsequently circulate throughout the body [115]. Exosomes can deliver a diverse collection of biologically active molecules, including mRNA, microRNAs, proteins, and lipids [116]. During a viral infection, infected cells secrete large quantities of exosomes that act as a communication network among the cells to orchestrate the response to the infection [117]. In a collaborative effort by a team of researchers from Arizona and Connecticut, it was found that people who were vaccinated with the mRNA vaccines acquired circulating exosomes containing the spike protein by day 14 following vaccination [118]. They also found that there were no circulating antibodies to the spike protein fourteen days after the first vaccine. After the second vaccine, however, the number of circulating spike-containing exosomes increased by up to a factor of 12. Furthermore, antibodies to spike first appeared on day 14. The exosomes presented spike protein on their surface, which, the authors argued, facilitated antibody production. When mice were exposed to exosomes derived from vaccinated people, they developed antibodies to the spike protein. Interestingly, following peak expression, the number of circulating spike-containing exosomes decreased over time, in step with the decrease in the level of antibodies to the spike

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protein. Exosomes exist as a part of the mRNA decay mechanism in close association under stress conditions with stress granules (SGs) and P-bodies (PBs) [119,120]. Under conditions of vaccine-mRNA-induced translation, which could be called “excessive dependence on cap-dependent translation,” there is an obvious resistance to promotion and assembly of the large decapping complex [65], and therefore resistance against physiological mRNA decay processes [119]. This would mean that the fate of particular synthetic mRNAs that otherwise would be determined by the common cellular strategy for mRNA turnover involving messenger ribonucleoproteins (mRNPs) is being omitted [121]. Furthermore, under conditions of over-reliance on cap-dependent translation by the synthetic mRNAs in SARS-CoV-2 vaccines [65], many native mRNAs holding considerable IRES and specific methylations (m⁶A) in their structure will favorably choose cap-independent translation, which is strongly linked to mRNA decay quality control mechanisms [114]. In this sense, considerable deadenylated mRNA products as well as products derived from mRNA metabolism (decay) are directly linked to exosome cargoes [121]. A fine example of dependence on cap-dependent translation is described in T-cell acute lymphoblastic leukaemia (T-ALL). Due to mechanistic target of rapamycin C (mTORC)-1 over-functioning in T-ALL, the cells are driven completely towards cap-dependent translation [122]. An analogous condition is described by Kyriakopoulos and McCullough (2021) [65]. Even in this highly aggressive cancerous state, during inhibition of cap-dependent translation in T-ALL cells, there is a rapid reversion to cap-independent translation [122]. Similarly, a picornavirus infection [123] drives cells towards cap-independent translation due to inhibition of components of eIF4F complex and pluralism of IRES in viral RNA. In humans, there is an abundance of mostly asymptomatic picornavirus infections like the Safford Virus with an over 90% seroprevalence in young children and adults [124]. In either case, whether an apoptotic event due to a stress-like condition [125] or an mRNA-cap-driven-like carcinomatous effect [126], the miRNA levels will be increased due to the increased epitranscriptomic functioning and enhanced mRNA decay. Because of the high demand for gene expression, high levels of certain

miRNAs will be expected to be contained in exosomes via P bodies [127]. Also, under conditions of overwhelming production of spike protein due to SARS-CoV-2 molecular vaccination, it would of course be expected that a significant proportion of over-abundant intra-cellular spike proteins would also be exported via exosome cargoes [128]. A seminal paper by a research team in India investigated the role of exosomes in the cellular response to internally synthesized SARS-CoV-2 spike protein [50]. They wrote in the abstract: "We propose that SARS-CoV-2 gene product, Spike, is able to modify the host exosomal cargo, which gets transported to distant uninfected tissues and organs and can initiate a catastrophic immune cascade within Central Nervous System (CNS)." Their experiments involved growing human HEK293T cells in culture and exposing them to SARS-CoV-2 spike gene plasmids, which induced synthesis of spike protein within the cells. They found experimentally that these cells released abundant exosomes housing spike protein along with specific microRNAs. They then harvested the exosomes and transferred them to a cell culture of human microglia (the immune cells that are resident in the brain). They showed that the microglia readily took up the exosomes and responded to the microRNAs by initiating an acute inflammatory response. The role of microglia in causing neuroinflammation in various viral diseases, such as Human Immunodeficiency Virus (HIV), Japanese Encephalitis Virus (JEV), and Dengue, is well established. They proposed that long-distance cell-cell communication via exosomes could be the mechanism by which neurological symptoms become manifest in severe cases of COVID-19. In further exploration, the authors identified two microRNAs that were present in high concentrations in the exosomes: miR-148a and miR-590. They proposed a specific mechanism by which these two microRNAs would specifically disrupt type I interferon signaling, through suppression of two critical proteins that control the pathway: ubiquitin specific peptidase 33 (USP33) and IRF9. Phosphorylated STAT1 and STAT2

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heterodimers require IRF9 in order to bind IFN-stimulated response elements, and therefore IRF9 plays an essential role in the signaling response. The authors showed experimentally that microglia exposed to the exosomes extracted from the HEK293 culture had a 50% decrease in cellular expression of USP33 and a 60% decrease in IRF9. They further found that miR-148a specifically blocks USP33 and miR-590 specifically blocks IRF9. USP33 removes ubiquitin from IRF9, and in so doing it protects it from degradation. Thus, the two microRNAs together conspire to interfere with IRF9, thus blocking receptor response to type I interferons. A study by de Gonzalo-Calvo et. al. (2021) looked at the microRNA profile in the blood of COVID-19 patients and their quantitative variance based upon disease severity [129]. Multiple miRNAs were found to be up- and down-regulated. Among these was miR-148a-3p, the guide strand precursor to miR-148a. However, miR-148a itself was not among the microRNAs catalogued as excessive or deficient in their study, nor was miR-590. It appears from these findings that miR-148a and miR-590 and their inflammatory effects are unique to vaccination-induced spike protein production. Tracer studies have shown that, following injection into the arm muscle, the mRNA in mRNA vaccines is carried into the lymph system by immune cells and ultimately accumulates in the spleen in high concentrations [130]. Other studies have shown that stressed immune cells in the spleen release large quantities of exosomes that travel to the brain stem nuclei along the vagus nerve (as reviewed in Seneff and Nigh (2021) [81]). The vagus nerve is the 10th cranial nerve and it enters the brain stem near the larynx. The

superior and recurrent laryngeal nerves are branches of the vagus that innervate structures involved in swallowing and speaking. Lesions in these nerves cause vocal cord paralysis associated with difficulty swallowing (dysphagia) difficulty speaking (dysphonia) and/or shortness of breath (dyspnea) [131,132]. We will return to these specific pathologies in our review of VAERS data below. HEK293 cells were originally derived from cultures taken from the kidney of a human fetus several decades ago and immortalized through infection with adenovirus DNA. While they were extracted from the kidney, the cells show through their protein expression profile that they are likely to be of neuronal origin [133]. This suggests that neurons in the vagus nerve would respond similarly to the spike protein. Thus, the available evidence strongly suggests that endogenously produced spike protein creates a different microRNA profile than does natural infection with SARS-CoV-2, and those differences entail a potentially wide range of deleterious effects. A central point of our analysis below is the important distinction between the impact of vaccination versus natural infection on type I IFN. While vaccination actively suppresses its production, natural infection promotes type I IFN production very early in the disease cycle. Those with preexisting conditions often exhibit impaired type I IFN signaling, which leads to more severe, critical, and even fatal COVID-19. If the impairment induced by the vaccine is maintained as antibody levels wane over time, this could lead to a situation where the vaccine causes a more severe disease expression than would have been the case in the absence of the vaccine. Another expected consequence of suppressing type I IFN would be reactivation of preexisting, chronic viral infections, as described in the next section.

8. Reactivation of Varicella-zoster

Type I IFN receptor signaling in CD8+ T cells is critical for the generation of effector and memory cells in response to a viral infection [134]. CD8+ T cells can block reactivation of latent herpes infection in sensory neurons [135]. If type I IFN signaling is impaired, as happens following vaccination but not following natural infection with SARS-CoV-2, CD8+ T cells' ability to keep herpes in check would also be impaired. Might this be the mechanism at work in response to the vaccines? Shingles is an increasingly common condition caused by reactivation of latent herpes zoster viruses (HZV), which also causes chicken pox in childhood. In a systematic review, Katsikas et al., (2021) identified 91 cases of herpes zoster occurring an average of 5.8 days following mRNA vaccination [136]. While acknowledging

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that causality is not yet confirmed, "Herpes zoster is possibly a condition physicians and other healthcare professionals may expect to see in patients receiving COVID-19 vaccines" [136]. In a letter to the editor published in September 2020, Fathy et al. (2021) reported on 672 cases of skin reactions that were presumably vaccine-related, including 40 cases of herpes zoster and/or herpes simplex reactivation [137]. These cases had been reported to the American Academy of Dermatology and the International League of Dermatological Societies' COVID-19 Dermatology Registry, established specifically to track dermatological sequelae from the vaccines. There are multiple additional case reports of

herpes zoster reactivation following COVID-19 vaccination in the literature [138,139]. Lladó et al. (2021) noted that 51 of 52 reports of reactivated herpes zoster infections happened following mRNA vaccination [140]. Herpes zoster itself also interferes with IFN- signaling in infected cells both through interfering with STAT2 phosphorylation and through facilitating IRF9 degradation [141]. An additional case of viral reactivation is noteworthy as well. It involved an 82-year-old woman who had acquired a hepatitis C viral (HCV) infection in 2007. A strong increase in HCV load occurred a few days after vaccination with an mRNA Pfizer/BioNTech vaccine, along with an appearance of jaundice. She died three weeks after vaccination from liver failure [142].

9. Impaired DNA Repair and Adaptive Immunity

The immune system and the DNA repair system are the two primary systems that higher organisms rely on for defense against diverse threats, and they share common elements. Loss of function of key DNA repair proteins leads to defects in repair that inhibit the production of functional B and T cells, resulting in immunodeficiency. Non-homologous end joining (NHEJ) repair plays a critical role in lymphocyte-specific V(D)J recombination, which is essential for producing the highly diverse repertoire of B-cell antibodies in response to antigen exposure [143]. Impaired DNA repair is also a direct pathway towards cancer. A seminal study conducted by researchers in Shanghai, China monitored several parameters associated with immune function in a cohort of patients by conducting single-cell mRNA sequencing of peripheral blood mononuclear cells (PBMCs) harvested from the patients before and 28 days after the first inoculation of a COVID-19 vaccine based on a weakened version of the virus [52]. While these vaccines are different from mRNA vaccines, they also work by injecting the contents of the vaccine into the deltoid muscle, bypassing the mucosal and vascular barriers. The authors found consistent alteration of gene expression following vaccination in many different immune cell types. Observed increases in NF- κ B signaling and reduced type I IFN responses were further confirmed by biological assays. Consistent with other studies, they found that STAT2 and IRF7 were significantly downregulated 28 days after vaccination, indicative of impaired type I IFN responses. They wrote: "Together, these data suggested that after vaccination, at least by day 28, other than generation of neutralizing antibodies, people's immune systems, including those of lymphocytes and monocytes, were perhaps in a more vulnerable state." [52]. These authors also identified disturbing changes in gene expression that would imply impaired ability to repair DNA. Up to 60% of the total transcriptional activity in growing cells involves the transcription of ribosomal DNA (rDNA) to produce ribosomal RNA (rRNA). The enzyme that transcribes ribosomal DNA into RNA is RNA polymerase I (Pol I). Pol I also monitors rDNA integrity and influences cell survival [144]. During transcription, RNA polymerases (RNAPs) actively scan DNA to find bulky lesions (double-strand breaks) and trigger their repair. In growing eukaryotic cells, most transcription involves synthesis of ribosomal RNA by Pol I. Thus, Pol I promotes survival following DNA damage [144]. Many of the downregulated genes identified by Liu et al. (2021) were linked to the cell cycle, telomere maintenance, and both promoter opening and transcription of POL I, indicative of impaired DNA repair processes [52]. One of the gene sets that were suppressed was due to "deposition of new CENPA [centromere protein A] containing nucleosomes at the centromere." Newly synthesized CENPA is

deposited in nucleosomes at the centromere during late telophase/early G1 phase of the cell cycle. This points to arrest of the cell cycle in G1 phase as a characteristic feature of the response to the inactivated SARS-CoV-2 vaccine. Arrest of pluripotent embryonic stem cells in the G1 phase (prior to replication initiation) would result in impaired

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self-renewal and maintenance of pluripotency [145]. Two checkpoint proteins crucially involved in DNA repair and adaptive immunity are BRCA1 and 53BP1, which facilitate both homologous recombination (HR) and NHEJ, the two primary repair processes [146,147]. In an in vitro experiment on human cells, the SARS-CoV-2 full-length spike protein was specifically shown to enter the nucleus and hinder the recruitment of these two repair proteins to the site of a double-strand break [143]. The authors summarized their findings by saying, "Mechanistically, we found that the spike protein localizes in the nucleus and inhibits DNA damage repair by impeding key DNA repair protein BRCA1 and 53BP1 recruitment to the damage site." Another mechanism by which the mRNA vaccines could interfere with DNA repair is through miR-148. This microRNA has been shown to downregulate HR in the G1 phase of the cell cycle [148]. As was mentioned earlier in this paper, this was one of the two microRNAs found in exosomes released by human cells following spike protein synthesis in the experiments by Mishra and Banerjee (2021) [50].

10. Immune Thrombocytopenia

Immune thrombocytopenia is an autoimmune disorder, where the immune system attacks circulating platelets. Immune thrombocytopenic purpura (ITP) has been associated with several vaccinations, including measles, mumps, rubella (MMR), hepatitis A, varicella, diphtheria, tetanus, pertussis (DPT), oral polio and influenza [149]. While there is broad awareness that the adenovirus DNA-based vaccines can cause vaccine-induced immune thrombotic thrombocytopenia (VITT) [150], the mRNA vaccines are not without risk to VITT, as case studies have been published documenting such occurrences, including life threatening and fatal cerebral venous sinus thrombosis [151-153]. The mechanism is believed to involve VITT antibodies binding to platelet factor 4 (PF4) and forming immune complexes that induce platelet activation. Subsequent clotting cascades cause the formation of diffuse microclots in the brain, lungs, liver, legs and elsewhere, associated with a dramatic drop in platelet count (Kelton et al., 2021). The reaction to the vaccine has been described as being very similar to heparin-induced thrombocytopenia (HIT), except that heparin administration is notably not involved [154]. It has been shown that the mRNA vaccines elicit primarily an immunoglobulin G (IgG) immune response, with lesser amounts of IgA induced [155], and even less IgM production [156]. The amount of IgG antibodies produced is comparable to the response seen in severe cases of COVID-19. It is IgG antibodies in complex with heparin that induce HIT. One can hypothesize that IgG complexed with the spike protein and PF4 is the complex that induces VITT in response to mRNA vaccines. It has in fact been shown experimentally that the receptor binding domain (RBD) of the spike protein binds to PF4 [157]. The underlying mechanism behind HIT has been well studied, including through the use of

humanized mouse models. Interestingly, human platelets, but not mouse platelets, express the Fc RIIA receptor, which responds to PF4/heparin/IgG complexes through a tyrosine phosphorylation cascade to induce platelet activation. Upon activation, platelets release granules and generate procoagulant microparticles. They also take up calcium, activate protein kinase C, clump together into microthrombi, and launch a cell death cascade via calpain activation. These activated platelets release PF4 into the extracellular space, supporting a vicious cycle, as this additional PF4 also binds to heparin and IgG antibody to further promote platelet activation. Thus, Fc RIIA is central to the disease process [158]. Studies on mice engineered to express the human Fc RIIA receptor have shown that these transgenic mice are far more susceptible to thrombocytopenia than their wild type counterparts [159]. It has been proposed that platelets may serve an important role in the clearance of antibody-antigen complexes by trapping the antigen in thrombi and/or carrying them into the spleen for removal by immune cells. Platelets are obviously rapidly consumed in the process, which then results in low platelet counts (thrombocytopenia). Platelets normally circulate with an average lifespan of only five to nine days, so they are constantly synthesized in the bone marrow and cleared in the spleen. Antibody-bound platelets, subsequent to platelet activation via Fc receptors, migrate to the spleen where they are trapped and removed through phagocytosis

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by macrophages [160]. Fully one third of the body's total platelets are found in the spleen. Since mRNA vaccines are carried into the spleen by immune cells initially attracted to the injection site in the arm muscle, there is tremendous opportunity for the release of spike-protein-containing exosomes by vaccine-infected macrophages in the spleen. One can speculate that platelet activation following the formation of a PF4/IgG/spike protein complex in the spleen is part of the mechanism that attempts to clear the toxic spike protein. We mentioned earlier that one of the two microRNAs highly expressed in exosomes released by human cells exposed to the spike protein was miR-148a. miR-148a has been shown experimentally to suppress expression of a protein that plays a central role in regulating Fc RIIA expression on platelets. This protein, called T-cell ubiquitin ligand-2 (TULA-2), specifically inhibits activity of the platelet Fc receptor. miR-148a targets TULA-2 mRNA and downregulates its expression. Thus, miR-148a, present in exosomes released by macrophages that are compelled by the vaccine to synthesize spike protein, acts to increase the risk of thrombocytopenia in response to immune complexes formed by spike antigen and IgG antibodies produced against spike.

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As we have already stated, an experiment by Mishra and Banerjee (2021) demonstrated that the spike protein induces the release of exosomes containing microRNAs that specifically interfere with IRF9 synthesis [50]. In this section we will show that one of the consequences of suppression of IRF9 would be reduced synthesis of sulfatide in the liver, mediated by the nuclear receptor peroxisome proliferator-activated receptor (PPAR- α). Sulfatides are major mammalian serum sphingoglycolipids which are synthesized and secreted mainly from the liver [161]. They are the only sulfonated lipids in the body.

Sulfatides are formed by a two-step process involving the conversion of ceramide to galactocerebroside and its subsequent sulfation. Sulfatide is expressed on the surface of platelets, erythrocytes and lymphocytes. Serum sulfatides exert both anti-coagulative and anti-platelet-activation functions. The enzyme in the liver that synthesizes sulfatide, cerebroside sulfotransferase, has specifically been found to be induced by activation of PPAR- in mice [162]. Therefore, reduced expression of PPAR- leads to sulfatide deficiency. PPAR- ligands exhibit anti-inflammatory and anti-fibrotic effects, whereas PPAR- deficiency leads to hepatic steatosis, steatohepatitis, steatofibrosis, and liver cancer [163]. In 2019, a seminal experiment was conducted by a team of researchers in Japan on mice with a defective gene for PPAR- [161]. These mice, when fed a high cholesterol diet, were susceptible to excess triglyceride accumulation and exacerbated inflammation and oxidative stress in the liver, along with increased levels of coagulation factors. The mice also manifested with decreased levels of sulfatides in both the liver and the serum. The authors hypothesized that cholesterol overload exerts its toxic effects in part by enhancing thrombosis, following abnormal hepatic lipid metabolism and oxidative stress. They showed that PPAR- can attenuate these toxic effects through transcriptional regulation of coagulation factors and upregulation of sulfatide synthesis, in addition to its effects in ameliorating liver disease. They proposed that therapies such as fibrates aimed at activating PPAR- might prevent high-cholesterol-diet-induced cardiovascular disease. Tracer studies have shown that the mRNA from mRNA vaccines migrates preferentially to the liver and spleen, reaching higher concentration there than in any other organs [130]. Thus, there is potential for suppression of IRF9 in the liver by the vaccine. IRF9 is highly expressed in hepatocytes, where it interacts with PPAR- , activating PPAR- target genes. A study on IRF9 knockout mice showed that these mice developed steatosis and hepatic insulin resistance when exposed to a high-fat diet. In contrast, adenoviral-mediated hepatic IRF9 overexpression in obese mice improved insulin sensitivity and ameliorated steatosis and inflammation [164]. Multiple case reports in the research literature describe liver damage following mRNA vaccines [165-167]. A plausible factor leading to these outcomes is the suppression of PPAR- through downregulation of IRF9, and subsequently decreased sulfatide synthesis in the liver.

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12. Guillain Barré Syndrome and Other Neurological Conditions

GBS is an acute inflammatory demyelinating neuropathy associated with long-lasting morbidity and a significant risk of mortality [168]. The disease involves an autoimmune attack on the nerves associated with the release of pro-inflammatory cytokines. GBS is often associated with autoantibodies to sulfatide and other sphingolipids [169]. Activated T cells produce cytokines in response to antigen presentation by macrophages, and these cytokines can induce auto-antibody production through epitope spreading [170]. The antibodies, in turn, induce complement activation, which causes demyelination and axonal damage, leading to severe injury to peripheral neurons [171]. The spike protein has been shown to bind to heparan sulfate, which is a sulfated amino-sugar complex resembling the sulfated galactose in sulfatide [172]. Thus, it is conceivable that spike also binds to sulfatide, and this might trigger an immune reaction to the spike-sulfatide

complex. As described in the previous section, impaired sulfatide synthesis in the liver due to suppression of IRF9 will lead to systemic sulfatide deficiency over time. Sulfatide deficiency can have major impact in the brain and nervous system. Twenty percent of the galactolipids found in the myelin sheath are sulfatides. Sulfatide is a major component of the nervous system, found in especially high concentrations in the myelin sheath in both the peripheral and the central nervous system. Deficiencies in sulfatide can lead to muscle weakness, tremors, and ataxia [173], which are common symptoms of GBS. Chronic neuroinflammation mediated by microglia and astrocytes in the brain leads to dramatic losses of brain sulfatide, and brain deficiencies in sulfatide are a major feature of Alzheimer's disease [174]. Mice with a defect in the ability to synthesize sulfatide from ceramide show an impaired ability to maintain the health of axons as they age. Over time, they develop redundant, uncompacted and degenerating myelin sheaths as well as deteriorating structure at the nodes of Ranvier in the axons, causing the loss of a functionally competent axoglial junction [175]. Angiotensin II (Ang II), in addition to its profound effects on cardiovascular disease, also plays a role in inflammation in the brain leading to neurodegenerative disease [176]. The SARS-CoV-2 spike protein contains a unique furin cleavage site not found in SARS-CoV, which allows the extracellular enzyme furin to detach the S1 segment of the spike protein and release it into circulation [177]. S1 has been shown to cross the blood-brain barrier in mice [178]. S1 contains the receptor binding domain that binds to ACE2 receptors, disabling them. When ACE2 receptor signaling is reduced, Ang II synthesis is increased. Neurons in the brain possess ACE2 receptors that would be susceptible to disruption by S1 released from spike-containing exosomes or spike-producing cells that had taken up the nanoparticles in the vaccines. Ang II enhances TLR4-mediated signaling in microglia, inducing microglial activation and increasing the production of reactive oxygen species leading to tissue damage, within the paraventricular nucleus in the brain [179]. Overexpression of Ang II is a causal factor in neurodegeneration of the optic nerve, causing optic neuritis, which can result in severe irreversible visual loss [180]. Multiple case reports have described cases of optic neuropathy appearing shortly after mRNA vaccination for COVID-19 [181, 182]. Other debilitating neurological conditions are also appearing shortly after vaccination, where a causal relationship is suspected. A case study based in Europe tracking neurological symptoms following COVID-19 vaccination identified 21 cases developing within a median of 11 days post-vaccination. The cases had diverse diagnoses including cerebral venous sinus thrombosis, nervous system demyelinating diseases, inflammatory peripheral neuropathies, myositis, myasthenia, limbic encephalitis, and giant cell arteritis [183]. Khayat-Khoei et al. (2021) describe a case series of 7 patients, ages ranging from 24 to 64, presenting with demyelinating disease within 21 days of a first or second mRNA vaccination [184]. Four had a prior history of (controlled) MS, while three were previously healthy. Hearing loss and tinnitus are also known rare side effects of COVID-19. A case study involved a series of ten COVID-19 patients who suffered from audiovestibular symptoms such as hearing loss, vestibular dysfunction and tinnitus [185]. The authors demonstrated that human inner ear tissue expresses ACE2, furin and the transmembrane protease serine 2 (TMPRSS2), which facilitates viral entry. They also showed that SARS-CoV-2 can infect specific human inner ear cell types.

Another study evaluating the potential for the SARS-CoV-2 virus to infect the ear specifically examined expression of the receptor ACE2 and the enzymes furin and TMPRSS2 various types of cells in the middle and inner ears of mice. They found that ACE2 and furin were “diffusely present in the eustachian tube, middle ear spaces, and cochlea, suggesting that these tissues are susceptible to SARS-CoV-2 infection.” [186]. Tinnitus is positively associated with hypertension, which is induced by elevated levels of Ang II [187]. Headache is a very common adverse reaction to the COVID-19 mRNA vaccines, particularly for people who are already susceptible to headaches. In a study based on a questionnaire involving 171 participants, the incidence of headaches was found to be 20.5% after the first vaccine, rising to 45.6% after the second shot [188]. A case study described a 37-year-old woman suffering from a debilitating migraine attack lasting for 11 days following the second Pfizer/BioNTech mRNA vaccine [189]. Steroids are often used as adjunct therapy to treat migraine [190]. Dexamethasone and other steroids stimulate PPAR- receptors in the liver through the steroid receptor, thus offsetting the effects of IRF9 suppression [191]. A theory for the origins of migraine involves altered processing of sensory input in the brainstem, primarily trigeminal neurons [192]. The trigeminal nerve is in close proximity to the vagus nerve in the brain-stem, so spike-carrying exosomes could easily reach it along the vagal route. Magnetic resonance imaging has revealed that structural changes in the trigeminal nerve reflecting aberrant microstructure and demyelination are a characteristic feature of people who suffer from frequent migraine headaches [193]. A potential factor linked to either SARS-CoV-2 infection or mRNA vaccination is an excessive level of Ang II in the brainstem due to spike inhibition of ACE2 receptors. ACE inhibitors and Ang II receptor antagonists have become popular drugs to treat migraine headaches off-label [194,195]. Migraine headache could thus arise from both the spike protein’s disruption of ACE2 receptors and the destruction of the myelin sheath covering critical facial nerves through a microglial inflammatory response and loss of sulfatide. The source of that spike protein could be either exogenous or endogenous.

13. Bell’s Palsy

Bell’s palsy is a common cranial neuropathy causing unilateral facial paralysis. Even in the Phase III clinical trials, Bell’s palsy stood out, with seven cases appearing in the treatment arm as compared to only one in the placebo group [196,197]. A case study reported in the literature involved a 36-year-old man who developed weakness in the left arm one day after vaccination, progressing to numbness and tingling in the arm and subsequent symptoms of Bell’s palsy over the next few days. A common cause of Bell’s palsy is reactivation of herpes simplex virus infection centered around the geniculate ganglion [198]. This, in turn, can be caused by disruption of type I IFN signaling.

14. Myocarditis

There has been considerable media attention devoted to the fact that COVID-19 vaccines cause myocarditis and pericarditis, with an increased risk in particular for men below the age of 30 [197,200]. Myocarditis is associated with platelet activation, so this could be one

factor at play in the response to the vaccines [201]. However, another factor could be related to exosomes released by macrophages infected with the mRNA vaccines, and the specific microRNAs found in those exosomes. A study involving patients suffering from severe COVID-19 disease looked specifically at the expression of circulating microRNAs compared to patients suffering from influenza and to healthy controls. One microRNA that was consistently upregulated in association with COVID-19 was miR-155, and the authors suggested that it might be a predictor of chronic myocardial damage and inflammation. By contrast, influenza infection was not associated with increased miR-155 expression. They concluded: "Our study identified significantly altered levels of cardiac-associated miRs in COVID-19 patients indicating a strong association of COVID-19 with cardiovascular ailments and respective biomarkers" [202]. A study comparing 300 patients with cardiovascular disease to healthy controls showed a statistically significant increase in circulating levels of miR-155 in the patients compared to controls. Furthermore, those with more highly constricted arteries (according to a Gensini score) had higher levels than those with lesser

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disease [203]. Importantly, exosomes play a role in inflammation in association with heart disease. During myocardial infarction, miR-155 is sharply upregulated in macrophages in the heart muscle and released into the extra-cellular milieu within exosomes. These exosomes are delivered to fibroblasts, and miR-155 downregulates proteins in the fibroblasts that protect from inflammation and promote fibroblast proliferation. The resulting impairment leads to cardiac rupture [204]. We have already discussed how the S1 segment of the spike protein can be cleaved by furin and released into circulation. It binds to ACE2 receptors through its receptor binding domain (RBD), and this inhibits their function. Because ACE2 degrades Ang II, disabling ACE2 leads directly to overexpression of Ang II, further enhancing risk to cardiovascular disease. Ang II-induced vasoconstriction is an independent mechanism to induce permanent myocardial injury even when coronary obstruction is not present. Repeated episodes of sudden constriction of a cardiac artery due to Ang II can eventually lead to heart failure or sudden death [205]. ACE2 suppression had already been seen in studies on the original SARS-CoV virus. An autopsy study on patients succumbing to SARS-CoV revealed an important role for ACE2 inhibition in promoting heart damage. SARS-CoV viral RNA was detected in 35% of 20 autopsied human heart samples taken from patients who died. There was a marked increase in macrophage infiltration associated with myocardial damage in the patients whose hearts were infected with SARS-CoV. Importantly, the presence of SARS-CoV in the heart was associated with marked reduction in ACE2 protein expression [206].

15. Considerations Regarding the Vaccine Adverse Event Reporting System (VAERS)

The Food and Drug Administration's Vaccine Adverse Event Reporting System (VAERS) is an imperfect but valuable resource for identifying potential adverse reactions to vaccines. Established through collaboration between the CDC and FDA, VAERS is "a national early

warning system to detect possible safety problems in U.S.-licensed vaccines." According to the CDC it is "especially useful for detecting unusual or unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine." (<https://vaers.hhs.gov/about.html>) Even the CDC recognizes that adverse events reported to VAERS represent "only a small fraction of actual adverse events [207]. A widely cited report noted that less than 1% of all vaccine-related adverse events are reported to VAERS [208]. That assertion, though, has no citation so the basis for the claim is unclear. Rose (2021) published a much more sophisticated analysis of VAERS data to offer an estimate of underreporting by a factor of 31 [209]. While it is impossible to determine underreporting with precision, the available evidence is that underreporting very strongly characterizes the VAERS data. The information presented below should be understood in that light.

15.1 VAERS Signal for Immune Suppression, Thrombocytopenia and Neurodegeneration

All of the tabulations on the number of reports for a specific condition mentioned in this subsection are based on a probe of the VAERS database online tool, <http://wonder.cdc.gov/vaers.html>, on November 29, 2021 and include all reports for any COVID-19 vaccine but restricted to the US population. Over the 31-year history of VAERS, there were a total of 9,153 deaths reported in association with any vaccine, and 7,114 (78%) of those deaths were linked to COVID-19 vaccines. Importantly, only 14% of VAERS-reported deaths as of June 2021 could have vaccination ruled out as a cause [210]. This strongly suggests that these unprecedented vaccines exhibit unusual mechanisms of toxicity that go well beyond what is seen with more traditional vaccines. A shocking 96% of all cases linking Bell's palsy to any vaccine since 1990 were linked to COVID-19 vaccines (3,197 out of 3,331 cases). There were 760 reports of Guillain Barré Syndrome (GBS) for COVID-19 vaccines. Over 100 cases of optic neuritis or optic neuropathy were listed. A total of 8,298 reports linked migraine headache to COVID-19. There were 52 cases of Herpes zoster oticus linked to COVID-19 vaccines. This is basically a case of herpes affecting the cranial nerves near the ears. Hearing loss is a characteristic symptom of Herpes zoster oticus, and it can become permanent [211,212]. As of November 19, 2021, there were 12,204

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cases where "tinnitus" was mentioned. Deafness is of course much more serious and therefore less common, and yet it also has a striking number of hits, coming in at 2,662 cases. There were 653 VAERS reports linking the COVID-19 vaccines to thrombocytopenia. This is to be compared with 774 cases reported for all the other vaccines over the 31-year period from 1990 to 2021. The VAERS database includes many terms related to liver dysfunction, and there were around 2,000 reports in VAERS for various liver-related terms linked to COVID-19 vaccines, such as hepatomegaly (73 cases), hepatic steatosis (105 cases), hepatic enzyme increased (338 cases), liver disorder (71 cases), liver injury (44 cases), hepatic pain (91 cases) and hepatitis (62 cases). There were 4,650 cases with dysphagia, 1,697 cases of dysphonia, and 37,132 cases of dyspnea

in reaction to COVID vaccines. As reviewed previously in this paper, a likely cause is vagus nerve damage due to inflammation induced by exposure to exosomes containing the spike protein and the associated microRNAs. In addition, there were 13,789 reports of syncope. Vasovagal syncope is the most common type of syncope among all age groups [213]. 67,682 cases of nausea and 26,630 cases of vomiting may reflect damage to vagal neurocircuits that play a central role in inducing nausea and vomiting in response to various insults [214].

Table 1. Number of events in the VAERS database from 1990 to December 12, 2021, where several terms indicating cancer occurred in association with COVID-19 vaccines or with all other vaccines, along with the ratio between the two counts. Counts were restricted to data from the United States. Note that counts for all the other vaccines are totals for 31 years, whereas the COVID-19 counts are for a single class of vaccines over less than one year.

Cancer Reports to VAERS	Counts COVID-19 vaccines	Counts All other vaccines	Ratio: COVID-19 vaccines/ All other vaccines
Breast	147	49	3.00
Prostate	32	13	2.46
Lung	82	46	1.78
Colorectal/Colon	30	7	5.00
Ovarian	24	7	3.43
Uterine	11	5	2.20
Uterine leiomyoma	80	12	6.67
Lymphoma (subtypes not identified)	52	47	1.11
B-cell lymphoma	19	3	6.33
Follicular lymphoma 1	3	1	13.00
Metastasis	13	7	1.86
Glioblastoma	16	3	5.33
Brain neoplasm	22	34	0.65
Neoplasm (unspecified)	71	82	0.87
Hepatic	40	8	5.00
Pancreatic	27	6	4.50
Prostate	23	13	1.77
Squamous cell carcinoma (not otherwise characterized)	33	25	1.32
Total	735	368	2.00

15.2 VAERS Signal for Cancer

Cancer is a disease generally understood to take months or, more commonly, years to progress from an initial malignant transformation in a cell to development of a clinically recognized condition. Since VAERS reports of adverse events are happening primarily within the first month or even the first few days after vaccination [209], it seems likely that the acceleration of cancer progression following vaccines would be a difficult signal to recognize. Furthermore, most people do not expect cancer to be an adverse event that could be caused by a vaccine. However, as we have outlined in our paper, if the mRNA vaccinations are leading to widespread dysregulation of oncogene controls, cell cycle regulation, and apoptosis, then VAERS reports should reflect an increase in reports of cancer, relative to the other vaccines. This is in fact what VAERS reports reflect, and dramatically so. Table 1 illustrates events involving the most common cancers reported to VAERS in the US, cancers either newly identified or stable disease newly progressing. It compares reports related to COVID-19 vaccination to reports related to all other vaccinations over the 31-year history of VAERS information collection. To obtain this table, we searched the online resource, <http://wonder.cdc.gov/vaers.html>, for search terms indicating cancer, such as "cancer," "carcinoma," "mass," "neoplasm," etc., and summed over all hits related to a particular organ, such as "lung." These data were collected on December 12, 2021. Notably, there were three times as many reports of breast cancer following a COVID-19 vaccine, and more than six times the number of reports of B-cell lymphoma. All but one of the cases of follicular lymphoma were associated with COVID-19 vaccines. Pancreatic carcinoma was more than three times as high. This cannot be explained by reference to a disproportionately large number of people receiving an mRNA vaccination in the past year compared to all other vaccinations. The total number of people receiving a non-COVID-19 vaccination is unknown, but over the 31 years history of reports VAERS contains it is unquestionably many orders of magnitude larger than the number receiving an mRNA vaccination in the past year. Overall, in the above table, twice as many cancer reports to VAERS are related to a COVID-19 vaccination compared to those related to all other vaccines. That, in our opinion, constitutes a signal in urgent need of investigation.

16. Discussion

There has been an unwavering message about the safety and efficacy of mRNA vaccinations against SARS-CoV-2 from the public health apparatus in the US and around the globe. The efficacy is increasingly in doubt, as shown in a recent letter to the Lancet Regional Health by G unter Kampf [215]. Kampf provided data showing that the vaccinated are now as likely as the unvaccinated to spread disease. He concluded: "It appears to be grossly negligent to ignore the vaccinated population as a possible and relevant source of transmission when deciding about public health control measures." In this paper we call attention to three very important aspects of the safety profile of these vaccinations. First is the extensively documented subversion of innate immunity, primarily via suppression of IFN- and its associated signaling cascade. This suppression will have a wide range of consequences, not the least of which include the reactivation of latent viral infections and the reduced ability to effectively combat future infections. Second is the dysregulation of the system for both preventing and detecting genetically driven malignant transformation within cells and the consequent potential for vaccination to promote

those transformations. Third, mRNA vaccination potentially disrupts intracellular communication carried out by exosomes, and induces cells taking up spike mRNA to produce high levels of spike-carrying exosomes, with potentially serious inflammatory consequences. Should any of these potentials be fully realized, the impact on billions of people around the world could be enormous and could contribute to both the short-term and long-term disease burden our health care system faces. Given the current rapidly expanding awareness of the multiple roles of GCs in regulation of mRNA translation and clearance through stress granules, the increase in pGCs due to enrichment of GC content as a consequence of codon optimization has unknown but likely far-reaching consequences. Specific analytical evaluation of the safety of these constructs in vaccines is urgently needed, including mass spectrometry for identification of cryptic expression and immunoprecipitation studies to evaluate the potential for disturbance of or interference

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with the essential activities of RNA and DNA binding proteins.¹⁷ Conclusions It is imperative that worldwide administration of the mRNA vaccinations be stopped immediately until further studies are conducted to determine the extent of the potential pathological consequences outlined in this paper. It is not possible for these vaccinations to be considered part of a public health campaign without a detailed analysis of the human impact of the potential collateral damage. It is also imperative that VAERS and other monitoring system be optimized to detect signals related to the health consequences of mRNA vaccination we have outlined. We believe the upgraded VAERS monitoring system described in the Harvard Pilgrim Health Care, Inc. study, but unfortunately not supported by the CDC, would be a valuable start in this regard [208]. In the end, we are not exaggerating to say that billions of lives are at stake. We call on the public health institutions to demonstrate, with evidence, why the issues discussed in this paper are not relevant to public health, or to acknowledge that they are and to act accordingly. Until our public health institutions do what is right in this regard, we encourage all individuals to make their own health care decisions with this information as a contributing factor in those decisions. Author Contributions: S.S., G.N and A.K. all contributed substantially to the writing of the original draft. P.M. participated in the process of editorial revisions. Funding: This research was funded in part by Quanta Computers, Inc., Taipei, Taiwan, under the auspices of the Qmulus project. Conflicts of Interest: The authors declare no conflict of interest.

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