

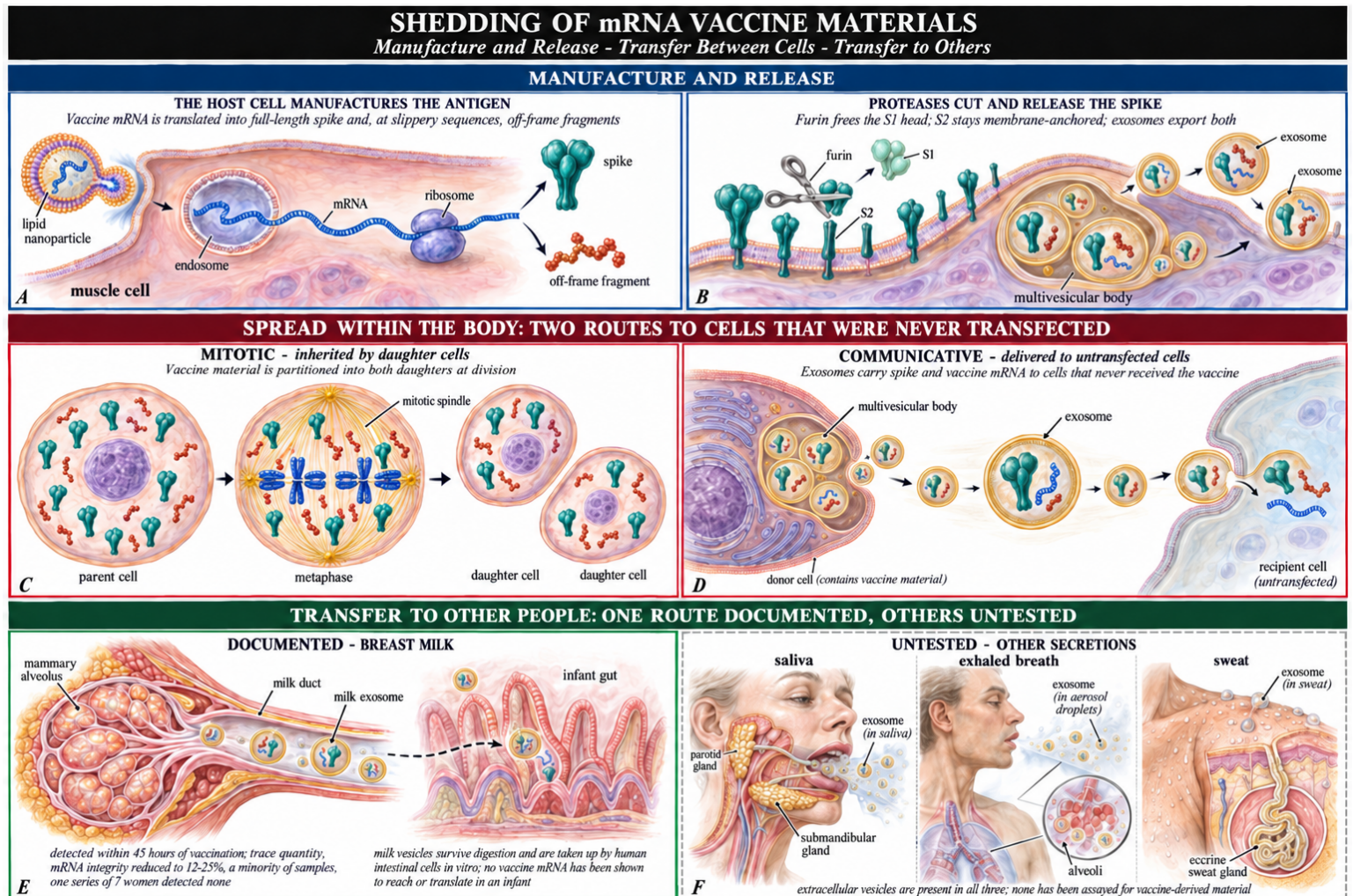
mRNA Vaccine Shedding: Internal Transcriptional Dissemination and Potential Human-to-Human Transfer

John A. Catanzaro, NMD, PhD¹, Nicolas Hulscher, MPH^{2*}, Peter A. McCullough, MD, MPH²

¹Neo7Bioscience, Inc., Dallas-Fort Worth, Texas, USA

²McCullough Foundation, Dallas, Texas, USA

*Corresponding author: nichulscher@gmail.com



Abstract

COVID-19 mRNA vaccines direct host cells to manufacture prefusion-stabilized SARS-CoV-2 spike protein that retains its furin cleavage site and carries two proline substitutions (K986P/V987P) in S2 that are not present in wild-type SARS-CoV-2 spike protein. This review examines two distinct forms of mRNA vaccine shedding: (i) molecular transcriptional shedding, involving the production, proteolytic fragmentation, persistence, and dissemination of vaccine-derived molecular products within vaccinated individuals through cellular division, extracellular release, and vesicular transport; and (ii) human-to-human shedding, involving the potential transfer of these products from vaccinated individuals to other individuals through biological secretions. Evidence supporting internal molecular dissemination includes circulating spike protein, proteolytically released fragments, vaccine-derived mRNA, and spike-bearing extracellular vesicles capable of transporting molecular cargo beyond its original cellular source. Human studies document circulating S1 within 24 hours, spike-bearing exosomes by day 14, vaccine mRNA in plasma for up to 28 days, vaccine-derived spike peptides at 69–187 days, spike protein in monocytes at 852 days, circulating spike at 1,173 days, exosomal vaccine mRNA at 1,284 days, and spike protein alongside plasmid-associated DNA sequences in skin at 1,364 days. N1-methylpseudouridine-associated +1 ribosomal frameshifting generates unintended translation products, expanding the repertoire of molecules potentially available for extracellular release. The proposed internal dissemination model incorporates two additional pathways: mitotic inheritance, whereby daughter cells may inherit an altered proteome following cellular division, and exosome-mediated communication, whereby molecular cargo may affect cells that never directly received vaccine mRNA. Experimental studies demonstrate spike-mediated interference with five interconnected molecular systems—coagulation, receptor–renin–angiotensin signaling, innate immune sensing, tumor-suppressor transcription, and vesicular interferon signaling. Together, these findings identify multiple pathways through which persistent vaccine-derived molecular products could disrupt cellular regulation, propagate abnormal signaling between cells, and potentially sustain downstream biological disturbances. Regarding human-to-human shedding, vaccine-derived mRNA has been detected in trace, fragmented form within breast-milk extracellular vesicles, establishing its presence in a biological secretion transferred between individuals. Extracellular vesicles are also present in saliva, exhaled breath, sweat, semen, and other bodily secretions. Their capacity to protect molecular cargo, survive biological barriers, enter recipient cells, and deliver functional mRNA provides a biologically plausible pathway for wider interpersonal transfer. An observational study further reported associations between proximity to vaccinated individuals and menstrual irregularities among unvaccinated women. However, no published study has directly demonstrated transfer of vaccine-derived spike protein, mRNA, or plasmid-associated DNA between individuals through respiratory emissions, saliva, sweat, or other non-milk secretions, leaving a critical evidence gap concerning the extent and biological consequences of human-to-human shedding. Collectively, these findings support intracellular and intercellular dissemination of vaccine-derived molecular products, with evidence of persistence extending over multiple years. The convergence of proteolytic fragmentation, vesicular transport, and potential mitotic inheritance suggests mechanisms through which molecular products and their downstream signaling effects could extend beyond the original cells of production. Direct experimental studies are needed to establish the functional consequences of long-term persistence, determine whether these pathways sustain molecular disturbances across cellular generations, and establish whether biologically significant human-to-human transfer occurs through additional bodily secretions and, if so, its extent.

Keywords: *mRNA vaccine shedding; transcriptional shedding; human-to-human shedding; spike protein persistence; exosomes; extracellular vesicles; cellular transmission; protein fragmentation; ribosomal frameshifting; cellular signaling disruption.*

1. Introduction

Two platform classes account for most COVID-19 vaccine antigen exposure in high-income countries: nucleoside-modified mRNA in lipid nanoparticles (BNT162b2, mRNA-1273 and later variant-updated formulations) and recombinant spike protein (NVX-CoV2373 and related constructs).^{1–7} Both instruct or supply a viral entry glycoprotein that binds angiotensin-converting enzyme 2 (ACE2) and, through a C-end rule motif, neuropilin-1 (NRP1).^{8–12} The licensed mRNA open reading frames encode full-length spike with the K986P/V987P prefusion stabilization and, unlike many protein-subunit designs, retain the polybasic furin site at the S1/S2 boundary.^{13–17}

Regulatory summaries described expression as occurring predominantly at the injection site and in the draining lymph node, with rapid mRNA degradation, while the rat biodistribution studies submitted alongside them recorded lipid-nanoparticle distribution to liver, spleen, adrenals and ovaries.^{18,19} Subsequent human measurements materially revise that model: antigen, extracellular vesicles, and fragments of vaccine mRNA are detectable in blood and lymphoid tissue for days to weeks. S1 protein has separately been reported to persist in CD16+ monocytes for up to 15 months after SARS-CoV-2 infection, a distinct exposure and different from mRNA, adenoviral DNA, or antigen-based vaccination. Case-level multi-omic reports document persistence of vaccine-derived molecular material, in one case on a multi-year horizon. These observations establish a biologically relevant persistence continuum that enlarges the time window in which transcription, translation, proteolytic processing, vesicular export, and downstream signal interference can occur.^{20–33}

Public discussion has often called this “shedding.” In vaccinology, shedding classically refers to excretion of an infectious vaccine organism.³⁴ Neither the mRNA nor the recombinant spike platforms contains a replication-competent agent, so classical shedding does not occur with these products. Two other processes carry the same name. The first is internal: host cells manufacture vaccine-encoded spike, translational diversification and proteolytic processing enlarge the product set, and vesicular export distributes those products well beyond the transfected cell within the vaccinated person. That process is molecular transcriptional shedding by proteolytic fragmentation, and the evidence for it runs from template persistence through fragment generation, extracellular release, recipient-cell signaling, and cross-cluster communication. The second is human-to-human shedding: the same molecular products leave the vaccinated person and reach a second person.

The two processes rest on different amounts of evidence. The internal process is documented end to end in humans: a persistent template, off-frame translation products, proteolytic cleavage, vesicular export, and altered signaling in cells that never received the vaccine. Human-to-human transfer is documented for one route. Vaccine mRNA is present in human milk, and milk is delivered to a second person;^{27,28} no other secretion has been assayed for vaccine-derived material. Sections 2 through 7 follow the internal process from template to recipient cell. Section 8 sets out the distribution pathway that process creates, Section 8A the evidence bearing on transfer between individuals, and Section 9 the extent to which the account applies to the recombinant-protein and adenoviral-vector platforms.

2. Operational definition: shedding as proteolytic release

We define proteolytic release as the export, from a cell that has translated vaccine mRNA or taken up recombinant spike, of full-length spike, S1, S2, frameshifted polypeptides, or peptide fragments, by one or more of the following routes:

(i) Furin cleavage in the trans-Golgi at the S1/S2 site (681-PRRAR-685 in the ancestral sequence), which dissociates the S1 receptor-binding subunit from membrane-anchored S2.^{8,35–37} (ii) Further processing near the S2' site by TMPRSS2 at the cell surface or by cathepsins after endocytosis, generating the fusion-primed fragment.^{9,38–40} (iii) Ectodomain release by cell-surface metalloproteinases. ADAM17 is the established sheddase for ACE2; SARS-CoV spike–ACE2 engagement increases ACE2 shedding in experimental systems, and the equivalent experiment with SARS-CoV-2 spike alone, in the absence of infection, has not been reported in those systems.^{41–43} Direct

cleavage of spike itself by these sheddases is established rather than hypothetical: recombinant SARS-CoV-2 spike is cleaved in vitro by ADAM10 and ADAM17 to yield an S2' fragment, with a spike–ADAM17 proximity-ligation signal detected in infected cells.⁴⁴ (iv) Packing into exosomes and other extracellular vesicles during multivesicular-body biogenesis, with surface or luminal spike.^{21,45} (v) Cell injury or cytotoxic-lymphocyte killing of antigen-positive cells, releasing cytosolic products into interstitial fluid.

Routes (i) and (iv) are directly supported for vaccine-encoded spike in humans or in primary human samples. Route (ii) is established for virus-derived spike in human airway cells and is inferred for the vaccine-encoded antigen. Route (iii) is established for ACE2. For spike itself, sheddase cleavage is demonstrated directly on recombinant protein and the enzyme is positioned at spike in infected cells; the product is an S2'-sized fragment, and release of the ectodomain from an intact cell surface has not been measured. None of these routes requires viral replication. Each mechanism describes export across the membrane of a single cell into the surrounding tissue and circulation. Passage out of the body, into a fluid that reaches another person, is a separate step with its own evidence and is treated in Section 8A. These routes, and the downstream steps they feed, are shown in **Figure 1**.

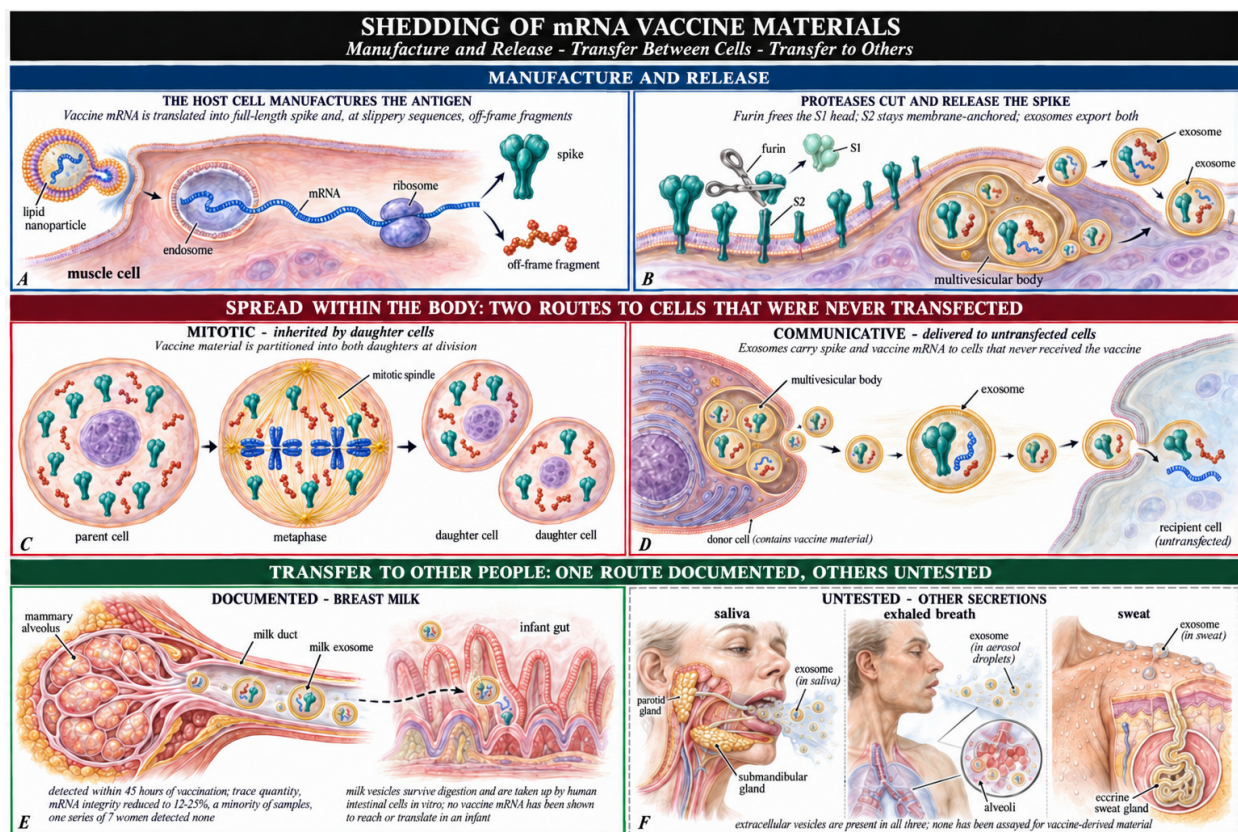


Figure 1. Manufacture, release, and transfer of vaccine-derived materials after COVID-19 vaccination. (A) Lipid-nanoparticle entry, endosomal escape, and cytosolic release of m1Ψ-modified mRNA, followed by translation of full-length spike and, at slippery sequences, off-frame products generated by +1 ribosomal frameshifting.⁴⁶ (B) Furin cleavage separating S1 from membrane-anchored S2, with additional ADAM10 and ADAM17 cleavage of spike near the S2' site shown on recombinant protein, and export of both fragments on exosomes released from multivesicular bodies.^{8–11,21,35,36,38,41–44} (C) The mitotic route: a cell that has translated vaccine mRNA partitions the altered proteome into both daughters at division. This route is inferred from the cell-cycle programs engaged after these vaccines and from spike-mediated suppression of p53 target protein induction, which removes a restraint on proliferation of the manufacturing population; it has not been directly imaged.^{47–51} (D) The communicative route: exosomes released by spike-expressing cells are taken up by cells that never received the lipid nanoparticle, where the cargo alters transcription in the recipient; vaccine mRNA has separately been recovered from circulating exosomes in a vaccinated person, although uptake of vaccine-derived exosomes has not been tested directly.^{21,32,45} (E) The one documented route out of the body: vaccine mRNA is present in human milk extracellular vesicles in trace, fragmented form and in a minority of samples,^{27,28} with an independent series detecting none;⁵² milk vesicles survive digestion and are internalized by human intestinal cells in vitro,^{53,54} although no vaccine mRNA has been shown to reach or translate in an infant. (F) Untested routes: extracellular vesicles are established in saliva and exhaled breath and have been recovered from sweat,^{55–60} but no published study has assayed any of these compartments for vaccine-derived mRNA, spike protein, or plasmid-derived DNA.⁶¹

3. Transcription and translation: how the host is made the manufacturer

3.1 Codon optimization and the modified nucleoside

Vaccine mRNA is produced by in vitro transcription, capped, polyadenylated, and substituted with N1-methylpseudouridine (m1Ψ) in place of uridine at 100% of the residues.^{62–65} The synthetic mRNA is rendered resistant to endogenous human ribonucleases.⁶⁶ Codon optimization raises GC content and removes motifs that would otherwise limit expression.⁶⁷ m1Ψ reduces Toll-like receptor 7/8 recognition, which contributes to the tolerability of the constructs at the administered dose, but it also changes ribosome processivity.^{46,62,68}

3.2 +1 ribosomal frameshifting and truncated products

Mulroney and colleagues showed that m1Ψ-containing mRNA undergoes +1 ribosomal frameshifting in vitro, attributed to ribosome stalling at slippery sequences, and that mice and humans vaccinated with BNT162b2 develop T-cell responses to the predicted +1 frame products.⁴⁶ The intended spike is still the dominant product. The off-frame polypeptides are truncated or sequence-divergent relative to spike, elicit T-cell responses consistent with MHC presentation, and are a documented form of truncated product arising from the molecular upset at the ribosome. Synonymous recoding of slippery sites reduced frameshifting in their system, which is a design correction rather than evidence that clinical lots were free of the event.⁴⁶ The off-frame products have been characterized directly. Liquid chromatography tandem mass spectrometry of the translation products of an m1Ψ-substituted reporter mRNA identified a library of six in-frame peptides and nine peptides derived from the +1 frame; the in-frame peptides mapped to the N-terminal region of the construct while the +1 frameshifted peptides mapped downstream, demonstrating a chimeric polypeptide of in-frame N-terminal and off-frame C-terminal residues. The equivalent proteomic mapping has not been performed for vaccine-encoded spike.⁴⁶ Mass spectrometry of human blood has separately recovered a tryptic peptide unique to the proline-stabilized vaccine spike from dried blood spots in half of the samples from 20 vaccinated subjects, between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ The frameshift arm therefore rests on two complementary experiments within a single study: a proteomically mapped chimeric product in a reporter system, and T-cell responses in BNT162b2-vaccinated humans to the corresponding off-frame spike peptides, consistent with translation and presentation of those products in vivo. The mechanism is demonstrated at the peptide level and its spike-specific products leave an immunological footprint in vaccinated people.³³

A separate, earlier study in a reconstituted cell-free system and in cultured cells did not find a large decoding-fidelity penalty from m1Ψ.⁶⁹ The two results are compatible: processivity errors at slippery runs need not equal random misincorporation. Frameshifting should be described as a low-frequency, sequence-dependent event with immunological correlates, not as wholesale mistranslation.

3.3 Duration of the mRNA template

Vaccine mRNA remained quantifiable in plasma out to 14 to 28 days after a Moderna Spikevax booster, weakly detectable at day 28 in about half of subjects; the intact species decayed with a half-life of 1.1 days, matching the ionizable lipid and consistent with recirculating lipid nanoparticles.²⁵ RNA-seq has recovered spike-matched vaccine sequences in plasma up to 28 days.²⁴ Fertig and colleagues detected vaccine mRNA in plasma and in the white-blood-cell fraction for at least two weeks.²³ Autopsy PCR found vaccine mRNA in axillary lymph node and myocardium in a subset of persons who died within 30 days of vaccination.²⁶ These intervals exceed the early expectation of hours-long persistence. None of these studies sampled to the point of non-detection — vaccine mRNA remained weakly detectable at the last timepoint — so the end of the persistence window is unknown. They do not, by themselves, prove continued translation at late time points.

3.4 Reverse transcription: a plausible enzymatic route from cell-line data

Aldén and colleagues reported intracellular reverse transcription of BNT162b2 mRNA into DNA (444 base pair DNA fragment) in the Huh7 hepatoma line, accompanied by increased LINE-1 expression and nuclear ORF1p; dependence on LINE-1 was inferred rather than tested.⁷⁰ Reverse-transcribed SARS-CoV-2 RNA has been shown to partially integrate into the genome of cultured human cells and to be expressed in patient-derived tissues after infection.⁷¹ Those experiments alone do not prove routine genomic integration of the entire mRNA code for spike. They do define a plausible mechanism for partial reverse transcription and potential genotoxicity. The patient-level observations presented in Section 3A imply that rapid clearance of vaccine mRNA and spike does not occur.^{32,72}

3A. Long-standing tissue persistence and insertional risk

The persistence claim in this review rests on work already published by the authors, not on a new dataset. In a nucleocapsid-negative longitudinal case, the authors and colleagues reported S1 protein in classical and non-classical monocytes at 852 days, free Wuhan spike in plasma and in circulating exosomes at 1,173 days, and vaccine-derived spike mRNA inside circulating exosomes at 1,284 days, with PBMC RNA negative after DNase treatment.³² Serial truncal skin biopsies at 1,160, 1,249, and 1,364 days showed spike in endothelium and macrophages, and at 1,364 days in nerve fibers. The same 1,364-day biopsy contained spike-gene amplicons, ori1/ori2, and the SV40 enhancer, confirmed by PCR and Sanger sequencing.³² That is multi-year persistence of spike protein and plasmid DNA in somatic tissue, and of vaccine mRNA in circulating exosomes, in a peer-reviewed case report.³²

Insertional risk is addressed in a second case reported by the authors. In a case report, they described a 31-year-old woman who developed stage IV bladder cancer within 12 months of a three-dose Moderna series.⁷² Multi-omic profiling showed dysregulation of KRAS, ATM, MAPK1, NRAS, CHD4, PIK3CA, SF3B1, and DNA-repair genes including MSH2. A host–vector chimeric read in circulating tumor DNA mapped to chr19:55,482,637–55,482,674 (GRCh38), cytoband 19q13.42, and aligned over 20 of 20 base pairs to a segment of the spike open reading frame of the BNT162b2 plasmid reference (GenBank OR134577.1); the plasmid sequence of the administered product is not deposited in GenBank, and the matched segment lies in spike sequence common to both platforms.⁷² The site is outside the AAVS1 safe harbor, in a gene-dense region. The authors judged random matching unlikely. This is a single chimeric read in one patient, not a population integration rate. It is nonetheless direct sequence evidence that a spike-related fragment can be found joined to host DNA after mRNA vaccination: a demonstrated insertional event in one patient, pending replication, rather than a dismissed in vitro artifact.⁷²

A third case adds tissue-level evidence, from a different compartment, that vaccine-manufacturing genetic material can be recovered from malignant tissue. In a case report, in a 35-year-old man with primary left-atrial intimal sarcoma diagnosed 170 days after the first and 146 days after the second BNT162b2 dose, the authors and colleagues analyzed archived tumor tissue and detected, by PCR of total tissue DNA, three codon-optimized vaccine spike (S) coding fragments distinguishable from wild-type SARS-CoV-2 together with the plasmid-backbone origin-of-replication (ORI) sequence; the SV40 enhancer was not detected.⁷³ A separate analysis of the same material found neither viral spike protein nor SARS-CoV-2 nucleocapsid protein.⁷³ Molecular profiling demonstrated MDM2 and KDR amplification, consistent with cardiac intimal sarcoma.⁷³ This observation does not by itself demonstrate transcription, translation, genomic integration, or proteolytic shedding from the recovered DNA fragments, and it does not establish that vaccination caused the malignancy. It does, however, extend the persistence/distribution evidence by demonstrating vaccine-derived coding and plasmid-backbone sequences within archived human tumor tissue. That finding strengthens the upstream substrate component of the transcriptional-shedding pathway: vaccine-derived genetic material can reach and persist in a tissue compartment in which transcriptional and proteolytic consequences can be tested directly.⁷³

The authors and colleagues have also tied persistence to transcriptional injury. They reported widespread transcriptomic dysregulation in peripheral blood from 3 patients with new-onset post-vaccination adverse events

and 7 with new cancer diagnoses, against 803 unvaccinated reference individuals from the GTEx dataset, sampled before COVID-19 vaccines existed, including mitochondrial dysfunction, proteasome stress, nonsense-mediated decay, ribosomal stress, MYC activation, and proliferative signaling with suppressed tumor control, and, in the cancer group, genomic instability and epigenetic reprogramming.⁷⁴ That paper explicitly connects m1Ψ-related frameshifting, LINE-1 reverse transcription, residual plasmid DNA including the SV40 enhancer, and prolonged spike protein to the observed programs.⁷⁴ The authors reviewed the same multi-omic pattern as gene-expression alteration by the platform itself, not as nonspecific LNP inflammation alone.⁷⁵ The authors and colleagues had already argued that the designed stability of the modified mRNA, its distribution, and continued spike production require a deactivation strategy, including siRNA and RIBOTACs, precisely because clearance cannot be assumed.⁷⁶

Taken together, the persistence, chimeric-sequence, tumor-tissue, transcriptomic, and translational-fidelity findings materially strengthen the truncated-fragment pathway. Frameshifted polypeptides are not merely predicted off-target immunogens: the spike-specific products have immunologic correlates after BNT162b2 in mice and in vaccinated humans, and tandem mass spectrometry in a reporter system has identified nine distinct +1-frame peptides and mapped them to the C-terminal portion of a chimeric polypeptide.⁴⁶ When vaccine-derived mRNA, spike protein, plasmid-associated sequences, and extracellular-vesicle cargo persist beyond the early post-exposure interval, the substrate for repeated translation, proteolytic fragmentation, and vesicular dissemination remains biologically available. The recovery of codon-optimized spike-coding fragments and ORI plasmid sequence from archived cardiac intimal-sarcoma tissue further documents tissue distribution of vaccine-derived genetic material, while the spike-aligned host–vector chimera demonstrates an insertional class of event in human tumor-associated DNA. Read together, these findings support transcriptional shedding as a durable molecular process capable of extending beyond the initially modeled expression window and of coupling persistence to downstream cross-cluster signaling.^{32,33,46,72–77}

4. Proteolytic processing of the manufactured spike

The ancestral spike furin site is a four-residue insertion, 681-PRRA-684, completing the polybasic motif 681-PRRAR-685, which SARS-CoV lacks. Furin cleavage in the producer cell primes spike, loosens the S1–S2 interaction, and is a determinant of pathogenicity in animal models of the virus.^{8,35,37,78,79} Licensed mRNA vaccines kept this site. Prefusion prolines (2P) stabilize the trimer but do not remove furin sensitivity.^{13–17} Protein-subunit vaccines have often deleted or mutated the site (GSAS or equivalent) precisely to keep the antigen intact; those constructs are a partial mechanistic control.^{5,17}

Cleavage has two consequences for release. S1, once cut, is non-covalently associated and can dissociate into fluid phase. That is the most parsimonious explanation for early circulating S1 after mRNA-1273, detected by ultrasensitive single-molecule array in 11 of 13 recipients from day 1 and clearing as IgG and IgA rise; full-length spike was additionally detected in 3 of the 13 recipients, on average about 15 days after the first dose.²⁰ S2 remains largely membrane-anchored unless the cell exports it in vesicles or dies. A second cut at S2' by TMPRSS2 liberates the fusion peptide in the viral life cycle; on a vaccinated cell the same proteases can generate additional membrane stubs and soluble pieces.^{9,38,40}

Proteomic evidence bears directly on what is available for release. Mass-spectrometric examination of human blood detected a vaccine-spike tryptic peptide in half of the samples from 20 vaccinated subjects between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ Separately, tandem mass spectrometry of the translation products of an m1Ψ-substituted reporter mRNA identified nine peptides derived from the +1 frame alongside six in-frame peptides.⁴⁶ Boros and colleagues have reviewed this evidence in arguing for persistence of modified mRNA and its translation products in human tissues and circulation. Both the intended antigen and its off-frame counterparts are therefore characterized molecular species available for proteolytic processing, extracellular-vesicle packaging, and downstream signaling.^{30,33}

5. Protein–protein interaction interference

Spike is a multivalent ligand. The receptor-binding domain engages ACE2.^{10–12} Prefusion stabilization does not remove that engagement: the K986P/V987P substitutions sit in S2 while the receptor-binding domain sits in S1, and the prefusion-stabilized trimer binds ACE2 with an affinity of 11.3 nM.^{13,15} In the virus, receptor engagement then drives the metastable prefusion trimer into the highly stable postfusion conformation, consuming it. The two prolines sit in the turn between the central helix and heptad repeat 1 — the turn that must refold into a continuous helix for that transition — so the vaccine antigen is restrained from the collapse that spends viral spike.^{15,16} Vaccine-encoded spike can therefore occupy ACE2 without completing the transition that resolves the interaction in the virus, and the licensed constructs retain the furin site that the soluble research antigen removes.¹⁷ The furin-cleaved C-terminus of S1 contains an RXXR C-end rule motif recognized by NRP1, which potentiates entry in the virus and can bind soluble S1.^{80,81} Spike and S1 also interact, in biochemical and cell assays, with TLR4, TLR2, and the estrogen receptor; the *in vivo* ranking of these interactions is not settled.^{82–87}

ACE2 is not only an entry receptor for the virus. It converts angiotensin II to angiotensin-(1–7). ADAM17-mediated ACE2 shedding after SARS-CoV spike engagement is reported in experimental systems,^{41–43} and SARS-CoV-2 spike itself downregulates surface ACE2 and degrades junctional proteins in endothelial models,^{88,89} together offering a route from antigen display to local renin–angiotensin imbalance. This is interference with a host protein–protein and protein–peptide network, not infection. Endothelial experiments have shown barrier and mitochondrial changes after spike exposure, and mouse studies report S1 transit across the blood–brain barrier and S1-induced endothelial injury *in vivo*;^{88–92} doses in those systems are often higher than measured plasma levels after vaccination, so extrapolation to clinical myocarditis or thrombosis requires the human antigen measurements, not the cell-culture result alone.^{22,93–96}

A second interaction cluster is coagulopathic. S1 induces fibrin(ogen) resistant to fibrinolysis *in vitro*.⁹⁷ Spike has separately been reported to interact with amyloidogenic proteins,⁹⁸ to undergo amyloidogenesis itself,⁹⁹ and to promote coagulation through binding to heparan sulfate.¹⁰⁰ Circulating microclots and hyperactivated platelets have been described after infection, and S1 activates microvascular endothelial cells and complement, leading to platelet aggregation *in vitro*.^{101–103} Causation at population scale is not established by those assays. The molecular observation still matters: a host-manufactured viral glycoprotein is being released into a compartment where it can meet fibrinogen.

Adaptive imprinting adds a further interaction layer. Repeated mRNA dosing is associated with class switching toward spike-specific IgG4, a subclass with limited Fc effector function.^{104,105} Clearance of circulating S1, which Ogata and colleagues reported to correlate with rising IgG and IgA,²⁰ may therefore change with additional doses. Yonker and colleagues found free spike only in the myocarditis cases, not in asymptomatic vaccinated controls, which is consistent with failed or delayed binding rather than with antigen production in every recipient.²²

Figure 2 places the protein–protein and cross-cluster steps on one page. The released ligand set is followed into five host clusters, with six edges marking the connections between them. Aberrancy is the replacement of normal receptor and p53 interactions by spike and by off-frame truncated fragments, and the export of that disturbance by exosomes.

COMPOUNDING PROTEIN-INTERACTION ABERRANCY

One Shared Ligand Pool - Five Host Clusters - A Circuit That Feeds Itself

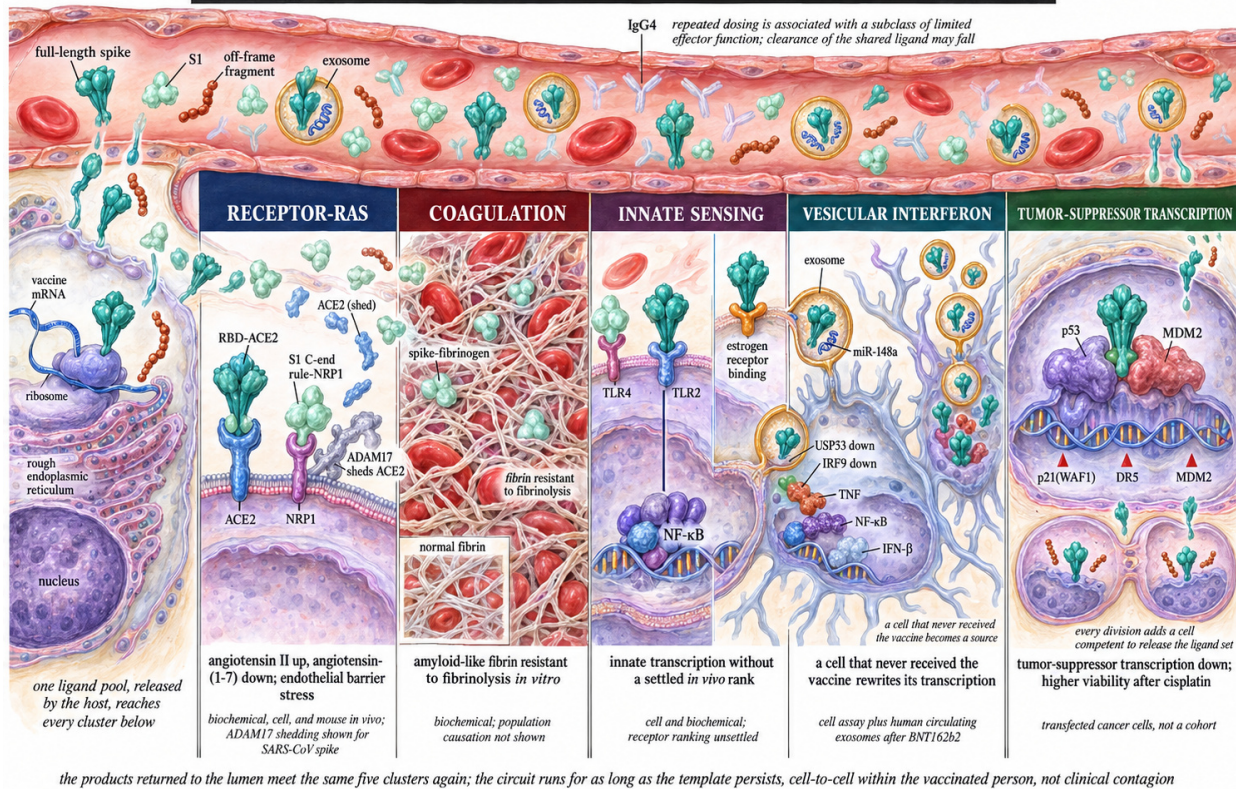


Figure 2. Compounding protein–interaction aberrancy after transcriptional shedding. Host-manufactured products — full-length spike, S1, off-frame products of +1 ribosomal frameshifting, and exosome-associated cargo — enter a shared circulating pool that reaches all five clusters. Receptor–RAS: the receptor-binding domain engages ACE2 and the furin-cleaved C-terminus of S1 engages neuropilin-1; ADAM17-mediated ACE2 shedding is established for SARS-CoV spike, and the equivalent SARS-CoV-2 experiment has not been reported.^{10,11,41–43,80,81,88,91,92} Coagulation: S1 induces fibrin(ogen) resistant to fibrinolysis in vitro.^{97,101} Innate sensing: spike and S1 interact with TLR4 and with TLR2–NF-κB in biochemical and cell assays, with estrogen-receptor binding reported separately; the in vivo ranking of these interactions is not settled.^{82,84,85} Vesicular interferon: exosomal miR-148a suppresses USP33 and IRF9 in an human microglial line CHME3, with parallel shifts in TNF, NF-κB and IFN-β promoter-reporter activity.^{21,45} Tumor-suppressor transcription: spike interrupts the p53–MDM2 interaction and suppresses induction of p21(WAF1), TRAIL death receptor DR5, and MDM2 protein.⁵¹ Six relationships connect these clusters: receptor–RAS output entering the fibrinogen compartment;^{88,89,97} local innate sensing followed by vesicle-borne IRF9 loss, as one relay;^{45,47–50,82} loss of p53 targets together with cell-cycle programs expanding the manufacturing population;^{47,48,51} IgG4 class switching altering clearance of the shared ligand;^{20,22,104,105} +1 frameshift products entering the secretory and vesicle routes;⁴⁶ and exosome uptake by a cell that never received the lipid nanoparticle.^{21,45} Three of these return product to the shared pool: division of a manufacturing cell, conversion of a recipient cell into a source of its own, and reduced clearance of circulating antigen. The ensemble meeting the five clusters is therefore replenished for as long as the template persists. Table 1 gives the evidence class for each cluster and each relationship, and distinguishes those demonstrated in the cited experiments from those inferred from the cited nodes. All transfer shown here is between cells of the vaccinated individual.

Taken one at a time, each of these interactions reads as a separate toxicity. They share a single ligand set, and the disturbance moves between them.

5A. Cross-cluster communication aberrancy

Cross-cluster communication aberrancy, as used here, means that host-made spike, soluble S1, S2 stubs, and frameshifted junk fragments do not stay inside the pathway that first binds them. The same unplanned ligand set meets the receptor–renin–angiotensin system (RAS) cluster, the innate-sensing cluster, the coagulation cluster, the tumor-suppressor cluster, and the vesicular-interferon cluster. The edges between those clusters are the aberrancy. They are what convert a local protein–protein interaction into a signal that a second cell, or a daughter cell, inherits. Figure 2 draws the map. Table 1 grades the evidence.

5A.1 Sharing by exosomes

Circulating exosomes carry a diverse range of naturally occurring signaling peptides throughout the bloodstream to direct systemic communication between distant organs. These membrane-bound vesicles package hormones, growth factors and neurotrophins that are otherwise routed through the classical secretory pathway, including vascular regulators such as VEGF-A, tissue-repair growth factors such as TGF- β 1, and neurotrophic factors such as BDNF.^{106,107} By transporting these peptide signals in a protective lipid bilayer, exosomes shield them from enzymatic degradation, allowing targeted tissue regulation, metabolic homeostasis, and immune response coordination.¹⁰⁶ Four products are released by vaccine mRNA. Full-length prefusion spike, stabilized by K986P/V987P and still carrying 681-PRRAR, is the designed antigen.^{13–17} Soluble S1 is the furin-released subunit detected in plasma from day 1 after mRNA-1273.^{8,20,35} S2 remains largely membrane-anchored until vesiculated or further cut; circulating exosomes display spike S2 by day 14 after the first BNT162b2 dose.^{9,21,38} The fourth product is not designed. m1 Ψ -dependent +1 frameshifting yields truncated off-frame polypeptides, and BNT162b2-vaccinated humans mount ELISpot responses to the predicted off-frame spike peptides, consistent with their presentation on MHC.⁴⁶ These four species are the ligand set. Downstream clusters do not each require a separate exposure. Tandem mass spectrometry of the translation products of an m1 Ψ -substituted reporter mRNA identified nine +1-frame peptides and mapped them downstream of the in-frame N-terminal residues,⁴⁶ so the fourth species is a characterized proteomic product rather than a translation-only prediction.³³

5A.2 Five clusters, cited at the node

Receptor–RAS. The receptor-binding domain engages ACE2.^{10–12} The furin-cleaved C-terminus of S1 contains an RXXR C-end rule motif recognized by neuropilin-1, so soluble S1 is not only a detached subunit; it is a ligand for NRP1.^{80,81} SARS-CoV spike–ACE2 engagement increases ADAM17-mediated shedding of ACE2 in experimental systems; the equivalent SARS-CoV-2 experiment has not been reported.^{41–43} Loss of surface ACE2 removes the enzyme that converts angiotensin II to angiotensin-(1–7).⁸⁸ Endothelial barrier and mitochondrial changes are reported after spike exposure, at doses often higher than measured plasma levels, so the human antigen measurements remain the required bridge to clinical inference.^{22,88–92}

Innate sensing. Spike and S1 interact in biochemical and cell assays with TLR4 and with TLR2, the latter feeding NF- κ B.^{82,84} Estrogen-receptor binding is reported biochemically.⁸⁵ Spike also drives inflammasome activation through long-lived macrophage reprogramming after infection.⁸⁶ The in vivo ranking of these interactions is not settled, and Figure 2 marks that limit rather than promoting any one binding to a clinical rank.

Coagulation. S1 induces fibrin(ogen) resistant to fibrinolysis in vitro.⁹⁷ Spike has separately been reported to interact with amyloidogenic proteins,⁹⁸ to undergo amyloidogenesis itself,⁹⁹ and to promote coagulation through binding to heparan sulfate.¹⁰⁰ Population causation is not established. The compartmental point is. A host-manufactured glycoprotein is released into the fluid phase where fibrinogen resides.

Tumor-suppressor transcription. Spike expression in cancer cells interrupts the p53–MDM2 interaction and suppresses p53-dependent induction of p21(WAF1), TRAIL death receptor DR5, and MDM2 protein, with higher viability after cisplatin.⁵¹ This is not an epidemiologic cancer claim. It is a direct demonstration that host-made spike blunts the protein output of the principal tumor-suppressor program.

Vesicular interferon. Exosomes released by spike-transfected cells and enriched in miR-148a are internalized by an human microglial line CHME3, where USP33 and IRF9 fall; promoter-reporter assays, run in HEK-293T rather than in the microglia, show increased TNF, NF- κ B and IFN- β promoter activity.⁴⁵ Bansal showed that BNT162b2 itself induces circulating exosomes with spike on their surface, and that those vesicles are immunogenic in mice.²¹ Immunogenicity is not toxicity. It is evidence that a cell other than the injected myocyte can receive vaccine-encoded antigen in a membrane-protected form.

5A.3 The edges are the aberrancy

Six bridges connect these clusters. They are mechanistic readings of cited nodes, not independent clinical endpoints.

Bridge 1, receptor–RAS to coagulation. ACE2 shedding and endothelial barrier stress place soluble S1 in the compartment where spike can meet fibrinogen.^{88,89,97} The two assays are usually published apart. The shared ligand makes them one circuit.

Bridge 2, innate sensing to distant interferon. TLR4 and TLR2–NF-κB are events at or near the manufacturing cell. USP33–IRF9 suppression is an event in a cell that took up the vesicle.^{45,82} The communication step is the exosome, not a second exposure. Comparative vaccinology shows a strong interferon program after BNT162b2, especially after the boost, so a uniform impairment claim does not survive every dataset.^{47–50} The edge that does survive is narrower: local innate sensing and vesicle-borne rewrite of IRF9 can run in series.

Bridge 3, p53–target loss to factory expansion. Suppression of p21 and DR5 removes a documented pressure toward cell-cycle arrest and death-receptor output.⁵¹ Cell-cycle modules are already engaged after BNT162b2 and persist beyond the first day in human data, and to day 7 in mouse systems.^{47,48} Division increases the number of cells competent to cleave spike and load vesicles. A tumor-suppressor interaction thereby becomes one that expands the carrier population: the vaccinated person, in whom manufacture and release run in the same body.

Bridge 4, IgG4 imprinting to ligand persistence. Repeated mRNA dosing is associated with class switching toward spike-specific IgG4, a subclass with limited Fc effector function.^{104,105} Ogata linked the fall in free S1 to rising antibody.²⁰ Clearance of the ligand that feeds the other clusters may therefore change with additional doses. Yonker found free spike in post-vaccination myocarditis and not in asymptomatic vaccinated controls in the same assay, consistent with failed or delayed binding rather than with antigen production in every recipient.²²

Bridge 5, junk fragment to MHC. Off-frame polypeptides are truncated relative to spike, lack the folding constraints of the intended trimer, and elicit T-cell responses in vaccinated humans consistent with presentation.⁴⁶ Mulroney and colleagues noted that no adverse outcomes attributable to these products have been reported in humans. That is an absence of reports, not a clearance of the fragments. The fragments add an unplanned ligand to the secretory and vesicle routes that carry designed spike.

Bridge 6, exosome to the next cell. A naive cell takes up exosomal miR-148a and rewrites transcription; the donor vesicles in that experiment came from plasmid-transfected cells, and uptake of vaccine-derived vesicles has not been tested directly.^{21,45} That cell never saw the lipid nanoparticle. This is the communicative generation drawn at the base of Figure 2. The mitotic generation is the daughter cell that inherits the disturbed proteome. Germinal-center spike is still detectable at 8 weeks in some individuals, so the window for both generations is measured in weeks at minimum, and in the longitudinal case literature in years.²⁹

These nodes and edges describe disturbances arising within and between the cells of the vaccinated individual. The definite risk is the molecular one mapped in Figure 2. The interactions assigned to each cluster and edge, with the evidence class supporting each, are set out in **Table 1**.

Cluster or edge	Interaction	Aberrancy	Evidence class	Refs
Receptor–RAS	RBD–ACE2; S1 C-end rule–NRP1; ADAM17 sheds ACE2 (shown for SARS-CoV spike)	Ang II up, Ang(1–7) down; endothelial barrier stress	Biochemical, cell, and mouse in vivo; human S1 is the ligand anchor	10, 11, 41–43, 80, 81, 88, 91, 92
Innate sensing	Spike/S1–TLR4; spike–TLR2–NF-κB; ER binding	Innate transcription without a settled in vivo rank	Cell and biochemical; ER rank unsettled	82, 84, 85
Coagulation	Spike–fibrinogen	Amyloid-like fibrin resistant to fibrinolysis in vitro	Biochemical; population causation not shown	97, 101
Tumor-suppressor transcription	Spike interrupts p53–MDM2	p21, DR5, and MDM2 protein down; higher viability after cisplatin	Transfected cancer cells, not a cohort	51
Vesicular interferon	Exosomal spike and miR-148a	USP33 and IRF9 down in an microglial line CHME3; TNF, NF-κB, IFN-β promoter reporters up in HEK-293T	Cell assay plus human exosomes after BNT162b2	21, 45

Cluster or edge	Interaction	Aberrancy	Evidence class	Refs
Edge 1	RAS output enters the fibrinogen compartment	Shared ligand joins two assays usually published apart	Inferred from cited nodes	88, 89, 97
Edge 2	TLR/NF- κ B then vesicle-borne IRF9 loss	Local sensing and distant rewrite are one relay	Inferred; IFN impairment is not uniform	45, 47–50, 82
Edge 3	p53-target loss plus cell-cycle modules	Division expands the manufacturing population	Cell assay joined to vaccine transcriptomics	47, 48, 51
Edge 4	IgG4 class switch and circulating S1	Clearance of the shared ligand may change	Human serology; mechanism inferred	20, 22, 104, 105
Edge 5	+1 frameshift products on MHC	Unplanned ligand in secretory and vesicle routes	Human ELISpot after BNT162b2	46
Edge 6	Exosome uptake by a naive cell	Communicative generation; no second injection required	Cell-to-cell, with donor vesicles from transfected cells; not clinical contagion	21, 45

Table 1. Protein–protein interactions and cross-cluster edges, with the evidence grade for each node and edge. “Inferred” means the bridge is a mechanistic reading of cited primary results, not a new experiment in this review. No row is a population cancer incidence or a person-to-person transmission result. Shaded edge rows are inferred bridges.

6. Transcriptional programs, cell cycle, and proliferative pressure

Single-cell and bulk transcriptomic studies of BNT162b2 show a day-1 interferon-stimulated gene program in monocytes and dendritic cells, stronger after the second dose, with persistent cell-cycle module activation in NK and T cells out to day 7 in mouse systems and a parallel human innate signature.^{47–50} The mRNA itself, sensed through MDA5 and TLR pathways, contributes; empty LNPs are inflammatory in animal models.^{48,68,108} This is a transcriptional alteration caused by the formulation and by antigen, not by viral replication.

Type I interferon ordinarily restrains proliferation through p53 and cyclin-dependent kinase inhibitors. Seneff, Nigh, Kyriakopoulos and McCullough have argued that mRNA vaccination produces a discordant state — innate sensing without the full antiviral interferon amplitude seen in infection — and that exosomes carrying spike and regulatory microRNAs could propagate that state to distant cells.^{45,109} The transcriptomic series described in Section 3A points the other way, reporting Toll-like receptor and type I interferon signaling particularly elevated in the cancer group.⁷⁴ The discordant-interferon claim is supported by comparative transcriptomics in some cohorts and disputed in others; it is a hypothesis with partial evidence, not a demonstrated oncogenic pathway. Expansion of circulating hematopoietic progenitors, reported in infection and not consistently after vaccination, is one of the observations used in that argument.¹⁰⁹

What can be said from the data is narrower and more secure on mechanism, and more serious on risk. Antigen-positive cells are under selection by cytotoxic T cells. Interferon, chemokine, and cell-cycle programs are documented in blood after these vaccines; whether the antigen-positive cells themselves carry those programs has not been resolved.^{47–50} Division does not end the disturbance. It creates the next cellular generation of the manufacturing host. Export does not end it either. It creates the next communicative generation in a cell that never saw the lipid nanoparticle. That pairing — proliferation plus proteolytic fragmentation release — is what makes the vaccinated individual both factory and vector. Bridge 3 above is the protein-interaction form of the same claim: p53-target suppression removes a restraint, and proliferation increases yield.

6A. Post-generational failure: truncated fragments as pathogenic and oncogenic signals

Post-generational failure, as used here, has two molecular meanings and one biological implication. The first is mitotic. A cell that has translated vaccine mRNA and then divides hands its daughters a proteome already altered by full-length spike, S1, and frameshifted polypeptides. The second is communicative. A cell that never translated the vaccine mRNA takes up an exosome or a soluble fragment and rewrites its own transcription. The biological implication is that the person carrying both processes is the source: vaccine-derived products circulate in blood and vaccine mRNA leaves the body in milk.^{20–28,45} Figure 2 places both generations under the cross-cluster map rather than after it.

6A.1 Junk fragments are a documented product, not a theoretical impurity

Mulrone and colleagues demonstrated that m1Ψ-containing mRNA undergoes +1 frameshifting, and that BNT162b2-vaccinated humans and immunized mice mount IFN γ ELISpot responses to predicted +1-frame spike peptides, which places the off-frame products in vivo and is consistent with their presentation on MHC.⁴⁶ Proteomic evidence addresses the translated products directly. Tandem mass spectrometry of the translation products of an m1Ψ-substituted reporter mRNA identified six in-frame and nine +1-frame peptides, mapping the off-frame peptides downstream of the in-frame N-terminal residues,⁴⁶ and mass spectrometry of human blood has detected a vaccine-spike tryptic peptide in half of the samples from 20 vaccinated subjects between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ The sequence from modified-mRNA translation error to a mapped off-frame product is therefore established at the peptide level. In the transcriptional-shedding model, those products enlarge the secreted and vesicle-transported ligand ensemble beyond the intended spike trimer and provide additional substrates for proteolytic fragmentation and downstream protein-interaction interference.^{33,46}

6A.2 Oncogenic signal transduction from spike and from fragment-bearing vesicles

Zhang and El-Deiry transfected cancer cells with SARS-CoV-2 spike and found that spike interrupts the p53–MDM2 interaction and suppresses p53-dependent induction of p21(WAF1), TRAIL death receptor DR5, and MDM2 protein, including after nutlin and after chemotherapy. Cisplatin-treated spike-expressing tumor cells had higher viability than controls.⁵¹ This is not an epidemiologic cancer claim. It is a direct demonstration that host-made spike blunts the protein output of the principal tumor-suppressor program, including the cell-cycle arrest and death-receptor effectors downstream of it. A manufacturing cell, or a daughter cell that continues to display spike, is therefore under a documented pressure against p53-dependent restraint.⁵¹

The communicative half is exosomal. Spike-transfected cells release exosomes enriched in miR-148a and miR-590. An human microglial line CHME3 internalizes that cargo, with USP33 and IRF9 falling; TNF, NF- κ B, and IFN- β promoter-reporter activity shifts in parallel assays.⁴⁵ Bansal showed that BNT162b2 itself induces circulating exosomes with spike on their surface, and that those vesicles are immunogenic in mice.²¹ Together these observations describe a relay: the manufacturing host packages spike and regulatory RNA, the vesicle crosses to a cell that did not receive the injection, and that cell changes its transcriptional state. That is post-generational signal transduction. It does not require the recipient cell to be infected, and it does not require the fragment to be full-length.

Seneff, Nigh, Kyriakopoulos, and McCullough argued from the same exosome and interferon literature that repeated mRNA exposure can impair type I interferon cancer surveillance and propagate that impairment by vesicles.¹⁰⁹ Comparative vaccinology shows a strong interferon program after BNT162b2, especially after the boost, so the impairment claim is not uniform across datasets.^{47–50} The risk statement that survives both literatures is narrower and sufficient: cell-cycle modules are engaged, p53 target protein induction can be suppressed by spike in tumor cells, and exosomal cargo from spike-expressing cells rewrites transcription at a distance.^{45,47–51,109} Truncated frameshift products add an unplanned ligand set to that relay.⁴⁶

6A.3 Why proliferation makes the person the vector

A single transfected myocyte is a poor vector. A proliferating, antigen-bearing population is not. Germinal-center spike is still detectable at 8 weeks in some individuals.²⁹ Cell-cycle transcriptional modules rise after vaccination and persist beyond the first day in human data, and to day 7 in mouse systems.^{47,48} Each division increases the number of cells competent to cleave spike and load vesicles. Proteolytic fragmentation multiplies the species released: S1 dissociates after furin cleavage, S2 remains membrane-anchored until shed or vesiculated, and frameshifted polypeptides are presented on MHC, although their entry into the same secretory and vesicular export routes has not been measured.^{8–11,20,21,35,36,38,39,46} The individual becomes the vector because the manufacturing process

and the release process run in the same body, and proliferation increases both the yield and the duration. Vector here denotes the internal carrier of the manufactured products rather than a transmitting host; whether those products pass to another person is a separate question, taken up in Section 8A.

The definite risk argued here is the molecular one: truncated junk fragments and cleaved spike are produced by the host, released by proteolysis and vesicles, amplified by proliferative programs, and competent — on the cited cell data — to disturb p53-dependent and interferon-dependent signal transduction in the next cell.^{45,46,51}

7. Vesicular export and the compartments that receive the product

Bansal and colleagues isolated circulating exosomes after BNT162b2 and detected spike S2 on their surface by day 14 after dose 1, with a further rise after dose 2 and a decline by four months. Electron microscopy showed spike antigen on the vesicle surface. Mice immunized with those exosomes mounted humoral and cellular responses, which demonstrates that the exported material is immunogenic.²¹ Immunogenicity is not the same as toxicity, but it is direct evidence that a cell other than the injected myocyte can receive vaccine-encoded antigen in a membrane-protected form.

Breast milk is the best-studied secretion. Trace vaccine mRNA is detectable within 45 hours in two series from one group — 5 of 11 women and 7 of 131 samples, and 10 of 20 vaccine exposures among 13 women — with an independent series of 7 women negative, concentrated in milk extracellular vesicles, with integrity reduced to roughly 12–25 percent in one droplet-digital PCR study, and without detectable spike translation in the HT-29 assay used.^{27,28,110} A drug and lactation database summarizing the available reports states that infant serum has been negative for vaccine mRNA where tested.¹¹⁰ The product therefore reaches milk at trace levels in fragmented form for about two days; a translating dose in the infant has not been shown.

The lymph node is the intended productive compartment. Röltgen and colleagues found spike protein in germinal centers up to 8 weeks after mRNA vaccination in some individuals.²⁹ Prolonged germinal-center antigen is a feature of the platform. It also means the window for vesicular export from antigen-bearing cells is measured in weeks at minimum.

8. Transcriptional shedding creates a biologically active distribution pathway

Transcriptional shedding is supported by the convergence of several experimentally demonstrated steps. Following mRNA vaccination, host cells translate vaccine-encoded spike; circulating S1 has been detected in plasma, spike-bearing extracellular vesicles appear in circulation, vaccine mRNA has been recovered from plasma and extracellular vesicles, and vaccine-derived RNA has been identified within milk extracellular-vesicle fractions.^{20–28} These observations establish that vaccine-derived molecular products are not confined to the initially transfected cell. Rather, translated antigen, proteolytically released fragments, nucleic-acid cargo, and membrane-protected extracellular-vesicle cargo can leave the cellular site of production and enter extracellular and circulating compartments.

This process is strengthened by direct evidence of extracellular-vesicle-mediated biological communication. BNT162b2 vaccination induces circulating exosomes displaying spike protein, demonstrating that host-manufactured vaccine antigen can be packaged into membrane-bound vesicles and distributed beyond the cell in which translation occurred.²¹ In complementary experimental systems, spike-expressing cells release exosomes containing biologically active molecular cargo that is internalized by recipient cells and alters downstream transcriptional signaling, including the USP33–IRF9/interferon axis.⁴⁵ Extracellular release therefore represents more than passive antigen disposal: it provides a mechanism by which molecular products generated in one cell can become signaling inputs to another.

Tandem mass spectrometry of reporter translation products identified both in-frame and +1-frame peptides,⁴⁶ and a vaccine-spike tryptic peptide has been recovered from human blood in half of the samples from 20 vaccinated subjects between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ These findings further strengthen the model.³³ Modified-mRNA translation is therefore not restricted to the intended full-length antigen. The recoverable molecular ensemble can include intended spike together with unintended frameshift-derived polypeptides. When considered with furin-mediated S1/S2 processing, extracellular proteolysis, and vesicular export, these findings support a broader definition of transcriptional shedding: the release and distribution of products generated from vaccine-derived transcriptional/translation templates, including full-length antigen, proteolytic fragments, unintended translation products, extracellular-vesicle-associated cargo, and persistent nucleic-acid species.^{21,23–28,33,45,46}

The biological significance of this pathway is that release expands the field of molecular exposure beyond the original manufacturing cell. Soluble S1 can engage ACE2 and neuropilin-1; spike-related products can interact with innate-sensing and coagulation pathways; extracellular vesicles can deliver protein and regulatory cargo to recipient cells; and frameshift-derived products expand the antigenic and proteomic repertoire generated from the modified transcript.^{10,11,21,33,45,46,80–82,97–99,101} Thus, the recipient becomes not merely a site of antigen production but a distributed molecular system in which products originating from vaccine-directed translation can move between cellular compartments and propagate signaling effects.

Molecular transcriptional shedding does not require replication of an intact virus. The relevant event is the production, fragmentation, release, transport, and recipient-cell interaction of host-manufactured molecular products. Evidence for circulating S1, spike-bearing exosomes, extracellular-vesicle-associated vaccine mRNA, persistent vaccine-derived molecular material, and cellular immune responses to predicted +1-frame spike peptides in vaccinated humans establishes multiple components of this sequence.^{20–28,32,33} The mechanistic chain can therefore be expressed as: persistent template → host translation → intended and frameshift-derived products → proteolytic fragmentation → extracellular/vesicular release → systemic distribution → recipient-cell uptake or receptor engagement → secondary molecular signaling.

Transcriptional shedding is a molecular communication phenomenon rather than conventional viral shedding. Figure 2 captures this progression: the manufacturing cell generates the molecular products, proteolytic and vesicular processes release them, and subsequent receptor engagement and extracellular-vesicle transfer extend their biological reach to additional cellular compartments. The consequence is a transition from localized expression to a distributed and potentially persistent signaling network, providing the mechanistic foundation for the cross-cluster communication aberrancy developed throughout this review.

8A. Transfer of vaccine-derived products between individuals

Vaccine-derived products are not confined to the cell that manufactured them, and on present evidence they are not confined to the vaccinated individual either. Material produced in response to vaccination is already documented to reach a second person by one route, and the carrier that conveys it there is present in several other secretions that pass between people. What has not been done is the measurement that would establish whether those other secretions carry it.

8A.1 Transfer to a second individual is already documented

Breast milk is the established case. Vaccine mRNA has been detected in human milk in two reports from the same group: in 5 of 11 lactating women and 7 of 131 samples within 45 hours of vaccination, at concentrations higher in the extracellular-vesicle fraction than in whole milk,²⁸ and in 10 of 20 vaccine exposures among 13 women, again concentrated in the milk extracellular-vesicle fraction, with mRNA integrity reduced to 12 to 25 percent.²⁷ An independent study of 7 women and 13 samples collected 4 to 48 hours after vaccination detected no vaccine mRNA

in milk supernatant or fat, with cells assayed in 2 samples and no extracellular-vesicle fraction isolated,⁵² so detection is neither universal nor uniform across cohorts. Milk is by definition a fluid transferred from one individual to another, and the recipient is an infant whose gastrointestinal and immune systems are still developing. Vaccine-derived material therefore already crosses from a vaccinated person into a second person under ordinary conditions, with no experimental intervention and no unusual exposure.

Milk extracellular vesicles are not inert in the recipient. Human milk exosomes and their microRNA cargo survive simulated gastric and pancreatic digestion and are internalized by human intestinal epithelial cells,⁵³ a result that extends to milk from mothers delivering preterm.⁵⁴ Bovine milk exosomal microRNAs withstand sequential digestion with salivary, gastric, biliary and pancreatic fluids and undergo trans-epithelial transport across a Caco-2 monolayer.¹¹¹ Uptake at the intestinal epithelium is an endocytosis-mediated, saturable process.¹¹² Orally administered milk exosomes are bioavailable in mice, with distinct microRNA cargos accumulating in distant tissues.¹¹³ The strength of these links is uneven: the digestion and uptake work is *in vitro*, the distant-tissue delivery is from animal models, and the single human study reporting dose-dependent appearance of milk microRNA in plasma after oral ingestion has not been consistently replicated.¹¹⁴ Within those limits, the route from a milk vesicle to a recipient cell is characterized rather than hypothetical.

The limits on this route are real and should be stated. The quantities recovered from milk are trace, mRNA integrity is reduced to 12 to 25 percent, the milk vesicles did not express spike protein and did not induce spike expression in the HT-29 assay used,²⁷ the drug and lactation database summarizing the available reports states that infant serum has been negative where tested, and translation of vaccine mRNA in the infant has not been demonstrated.¹¹⁰ Those findings bound the magnitude of the transfer. They do not bear on whether it occurs, which is established. The question for the remainder of this section is accordingly not whether vaccine-derived material can reach another person, but whether milk is the only route by which it does.

8A.2 The carrier is general, and the association with vaccine product is durable

The vehicle in milk is the extracellular vesicle, and that vehicle is not peculiar to milk. Exosomes carrying distinct mRNA and microRNA populations have been isolated and characterized from human saliva.^{55,56} Vesicles are recoverable from exhaled breath and from exhaled breath condensate, where their microRNA cargo is of lung-tissue origin.^{57,58} Vesicles have been isolated from human sweat, although that compartment remains minimally characterized, resting on a small number of independent studies without a consensus profile.^{59,60} Exosomes have likewise been isolated and characterized from human tears,¹¹⁵ nasal lavage fluid,¹¹⁶ semen,¹¹⁷ and urine.¹¹⁸ Milk exosomes themselves were characterized as immunomodulatory particles well before the vaccine-specific milk measurements described above.¹¹⁹

Vaccine-derived material is demonstrably vesicle-associated in the donor. Spike protein is carried on the surface of circulating exosomes after BNT162b2,²¹ and vaccine mRNA in milk is concentrated in the vesicle fraction.^{27,28} The duration of that association exceeds what the original biodistribution model assumed: in the longitudinal case described in Section 3A, free spike was recovered from plasma and from circulating exosomes at 1,173 days, and vaccine-derived spike mRNA from circulating exosomes at 1,284 days.³² If vaccine material remains vesicle-associated in the circulation for years, then the interval during which it could enter any vesicle-producing secretion is measured in years rather than in the days originally modeled.

8A.3 The carrier delivers functional cargo to recipient cells

Vesicles are not inert containers. Exosomes transfer mRNA and microRNA between cells, and mRNA delivered by this route is translated into protein in the recipient cell.¹²⁰ Tumor-derived microvesicles deliver RNA that is taken up by recipient cells and alters their behavior in a human disease system.¹²¹ Exosomes released by spike-expressing cells are themselves biologically active, delivering cargo that alters transcription in cells that were never transfected.⁴⁵ Delivery across a mucosal surface is documented as well: exosomes transfer functional P-glycoprotein

between epithelial cells at the human sinonasal mucosa,¹²² and exosomes applied intranasally cross the nasal mucosa and deliver encapsulated cargo to the brain in mice.¹²³ The carrier therefore has demonstrated capacity to deliver functional nucleic acid into cells that did not produce it.

8A.4 A reported human signal beyond the milk route

One human dataset reports an outcome associated with proximity to vaccinated people, though it measures no analyte. In an online survey of 6,049 respondents recruited through a menstrual-tracking platform, 92.3 percent reported menstrual irregularities following the COVID-19 vaccine rollout; within a subgroup of 3,390 respondents who reported no vaccination, no COVID-19 symptoms, and no positive test, daily proximity to vaccinated persons outside the household was associated with higher relative risks for heavier bleeding, earlier onset of menses, and prolonged bleeding, with relative risks of approximately 1.26 to 1.34.¹²⁴

The authors state that the analysis addresses association and does not establish causation, and several design features constrain inference: recruitment was self-selected through a platform oriented to menstrual symptoms, exposure and outcome were both self-reported by the same respondent, pre-rollout cycles served as each respondent's own baseline, and no unexposed comparison group was obtainable during a period of widespread vaccination.¹²⁴ The survey cannot demonstrate transfer, and it is not treated here as having done so. What it supplies is a reported human signal in the direction the mechanism predicts, produced by the only investigators who have attempted the question at all. That is a reason to measure, not a substitute for measurement.

8A.5 The one link that has never been examined

Each component set out above is independently established: a vaccine product that is vesicle-associated in the donor and remains so for years; a carrier established in saliva and exhaled breath, recovered from sweat, and present in milk; a carrier with demonstrated capacity to deliver translatable RNA into recipient cells; and one documented route by which that carrier already passes from one person to another. One link is missing, and it is a specific one. No published study has looked for vaccine-derived mRNA, spike protein, or plasmid-derived DNA in saliva, exhaled breath, or sweat following COVID-19 vaccination. A systematic review of vaccine-derived material in human fluids and tissues searched sixteen bodily-fluid types and found reports confined to blood compartments — plasma, circulating monocytes and dried blood spots — together with lymph-node material and breast milk, with no reports for any other fluid; its tissue findings are those discussed in Section 3A.⁶¹ The most recent biodistribution study likewise maps distribution across tissues, in mice and in humans.¹²⁵ Published post-vaccination saliva studies we identified measured antibody responses, or viral RNA in breakthrough infection, rather than vaccine-derived products. The gap is therefore an absence of investigation rather than a negative finding: the measurement has not been attempted.

Were vaccine-derived material found in those compartments, transfer sufficient to produce an effect in a recipient would still require survival of the material outside the body in intact form, deposition on a mucosal or cutaneous surface, uptake into recipient cells, and delivery in biologically meaningful quantity. The vesicle literature addresses the first of these only partially. Intact exosomes can be recovered from whole human saliva stored at 4 °C for up to 20 months, with membrane integrity preserved through freeze-thaw cycles,¹²⁶ and endogenous microRNAs in raw milk resist acid and RNase treatment while synthetic microRNAs spiked into the same milk are degraded, indicating that vesicle packaging confers the protection.¹²⁷ What does not exist is any measurement of vesicle integrity or cargo persistence in saliva, sweat, or exhaled breath at ambient conditions outside the body, on a surface or in air. Extrapolation from refrigerated storage to ambient environmental persistence is unsupported and is not made here. These are empirical questions, and each is answerable with existing methods.

8A.6 The study that would settle it

Shedding assessment is an established element of the environmental risk assessment applied to gene-therapy medicinal products containing genetically modified organisms. The governing guideline recommends incorporating shedding studies in an animal model, and states that urine, feces, or mucosal nasal swabs may be analyzed for the product as part of biodistribution work.¹²⁸ The mRNA COVID-19 vaccines were not classified as genetically modified organisms; the European Medicines Agency has stated that the GMO regulation was intended for other vaccine types, such as those using attenuated or live vectors, and that it was therefore acceptable for environmental risk assessment studies not to be provided in the marketing authorization applications.¹²⁹ The secretion sampling that the gene-therapy framework contemplates was consequently never performed for these products. No shedding study was required, and none has been published.

A definitive study is feasible with existing methods. It would require serial sampling of saliva, exhaled breath condensate, and skin surface or sweat from recently vaccinated individuals, assayed by droplet digital PCR using primers specific to the codon-optimized vaccine spike sequence, which is distinguishable from wild-type SARS-CoV-2,⁷³ and to the plasmid backbone, together with targeted mass spectrometry for the proline-stabilized spike peptide. It would require parallel sampling of unvaccinated household or occupational contacts using the same assays, with prespecified detection endpoints. It would require negative controls drawn from unexposed populations or from biobanked pre-rollout specimens. Analyte detection and quantity, rather than symptom report, should be the primary endpoints, since self-reported symptoms cannot distinguish molecular transfer from expectation effects in an unblinded population.

Until that study is conducted, transfer of vaccine-derived products between individuals by routes other than milk should be described as untested rather than as demonstrated or excluded. The components of the pathway are in place; the measurement is not. Given that vaccine-derived material has already been shown to reach a second person through milk, that it remains vesicle-associated in the circulation for years, and that the carrier is present in secretions exchanged in ordinary contact, the absence of that measurement is the most consequential gap identified in this review.

9. Non-mRNA platforms: recombinant spike and adenoviral vector

NVX-CoV2373 presents prefusion spike around a polysorbate-80 nanoparticle, with the furin site modified, adjuvanted with Matrix-M.^{5,130} There is no mRNA template and no m1Ψ frameshifting. Proteolytic release can still occur: administered protein is taken up by antigen-presenting cells, processed, and can be re-exported on vesicles, and any residual uncleaved molecules remain substrates for extracellular proteases. The duration and magnitude of circulating free spike after protein-subunit vaccination are less completely described than after mRNA vaccination. Adenoviral-vector vaccines are a third case: they deliver DNA encoding spike, so host transcription is nuclear rather than cytosolic. The constructs differ at the cleavage site. ChAdOx1 encodes spike retaining the polybasic site, whereas the Ad26.COVS immunogen carries a mutated furin cleavage site, R682S and R685G, alongside the prefusion prolines, so the principal fragmentation step is not common to the two.^{131–134} The frameshift arm of Figure 2 is mRNA-specific. The receptor, coagulation, and vesicle arms are not. Proteolytic release and vesicular export are therefore platform-general, while translational diversification is specific to the modified-mRNA products, so the distribution and transfer questions raised in Sections 7 through 8A are not confined to the mRNA platforms even though the off-frame product set is.

10. Discussion

The central argument is mechanistically convergent. mRNA vaccination installs a host manufacturing process in which modified mRNA is translated into intended spike while sequence-dependent frameshifting can generate additional truncated or divergent products. Human immunologic data identify responses to +1-frame peptides, and mass-spectrometric data identify both in-frame and +1-frame peptides among reporter translation products⁴⁶

together with a vaccine-spike tryptic peptide recovered from human blood in half of the samples from 20 vaccinated subjects between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ Furin and related proteases fragment the manufactured spike ensemble, extracellular vesicles export spike-related cargo, and proliferation expands the number of cells capable of sustaining or propagating the altered signaling state. This linked sequence—template persistence, translation, off-frame product generation, proteolytic release, vesicular transport, and recipient-cell signaling—is the molecular basis of transcriptional shedding.^{8–11,20,21,29,33,35,36,38,39,46–48}

The oncogenic signaling limb is supported by convergent molecular observations. Spike expression suppresses p53-dependent induction of p21, DR5, and MDM2 protein and increases chemotherapy survival in tumor cells; exosomes from spike-expressing cells suppress USP33–IRF9 in the microglial line CHME3; and frameshifted products are immunologically recognized and have been mapped by tandem mass spectrometry among reporter translation products. These findings connect unplanned translation products, tumor-suppressor interference, and vesicle-borne transfer into a coherent mechanism by which proliferative and communicative risk can be propagated within and beyond the original manufacturing cell.^{33,45,46,51,77}

A companion paper by Catanzaro and colleagues expands this signaling framework by identifying 35 published mechanisms that converge on four linked routes: proto-oncogene activation, mutation pressure, protein–protein-interaction network interference, and cancer-stem-cell clonal acceleration. In the concurrent-hit model, persistent or repeatedly generated spike-related products, translational infidelity, residual nucleic-acid species, inflammatory signaling, and extracellular-vesicle communication can act as overlapping molecular pressures rather than isolated events. This framework aligns transcriptional shedding with oncogenic risk by providing a mechanistic basis through which persistent molecular cargo and cross-cluster signaling disturbance could contribute to accelerated malignant evolution in susceptible tissues.⁷⁷

In a case report of cardiac intimal sarcoma, codon-optimized vaccine spike-coding fragments and the plasmid ORI sequence were recovered from archived tumor DNA, while a separate analysis found no viral spike or nucleocapsid protein.⁷³ Vaccine-derived genetic material therefore reached the tissue compartment in which the malignancy developed. Read with m1Ψ-associated translational frameshifting, persistent spike-related products, circulating spike-bearing extracellular vesicles, interference with tumor-suppressor and inflammatory signaling networks, and the host–vector chimeric read reported by the same group, the case supplies direct tissue evidence within a continuum of persistence → tissue distribution → altered translation → proteolytic fragmentation → vesicular export → cross-cluster signaling disruption → oncogenic pressure.^{32,33,45,46,51,72–77} Its force is that persistent or aberrantly translated spike-derived products could supply repeated inputs to the p53/MDM2, innate-immune, inflammatory, proliferative and genomic-stability networks implicated in the companion framework.^{51,74,77} That makes vaccine-derived persistence and signaling disruption worth investigating as contributing determinants in this tumor, rather than treating the sequence recovery as an isolated finding.^{73,77}

The transfer limb rests on a different evidentiary footing from the oncogenic one. What has been measured is a single route. Vaccine mRNA is present in human milk within 45 hours of maternal vaccination, concentrated in the extracellular-vesicle fraction, in 5 of 11 women and 7 of 131 samples in one series and in 10 of 20 vaccine exposures among 13 women in a second from the same group, with an independent series of 7 women negative.^{27,28,52} Milk reaches a second person under ordinary conditions and with no experimental intervention, so molecular transfer between individuals is established rather than postulated. What has not been measured is every other route. The vehicle is general: vesicles are established in saliva and exhaled breath and have been recovered from sweat,^{55–60} tears, nasal lavage fluid, semen and urine;^{115–118} vaccine spike is vesicle-associated in the circulation, and that association persisted to 1,284 days in one longitudinal case;^{21,32} milk vesicles survive simulated gastric and pancreatic digestion and are internalized by human intestinal epithelium;^{53,54} and vesicle-borne mRNA is translated

in recipient cells in vitro.¹²⁰ Each component of a wider route is established, in humans or in vitro, and the single step that would connect them has never been attempted.

11. Conclusion

The evidence assembled in this review supports transcriptional shedding as a coherent molecular pathway arising from host manufacture of vaccine-encoded spike and associated off-frame translation products. m1Ψ-associated sequence-dependent frameshifting generates truncated or divergent polypeptides; vaccinated humans develop cellular responses to +1-frame peptides, tandem mass spectrometry has identified nine +1-frame peptides among reporter translation products,⁴⁶ and a vaccine-spike tryptic peptide has been recovered from human blood in half of the samples from 20 vaccinated subjects between 69 and 187 days after vaccination, with all 40 unvaccinated controls negative, 20 of them recovered from COVID-19.³⁰ Furin and related proteases process the manufactured spike ensemble, while extracellular vesicles transport spike-related material into blood and other compartments. Multi-year recovery of vaccine-derived mRNA, spike protein and plasmid-associated sequences in one longitudinal case, together with spike-coding fragments reported in tumor tissue 170 days after the first dose and a spike-aligned host–vector chimeric read within twelve months, expands the biologic time and tissue space in which these processes can operate. A transcriptomic study of 3 patients with new-onset post-vaccination adverse events and 7 with new cancer diagnoses further documents mitochondrial, ribosomal, proteostatic, MYC-associated, proliferative-signaling and genomic-instability programs that provide a functional context for continued signal disruption. These observations span the receptor–RAS, innate-sensing, coagulation, tumor-suppressor transcription, and vesicular-interferon clusters. The resulting model is stronger than a collection of isolated toxicities: persistent molecular substrate feeds altered translation; altered translation expands the proteomic ensemble; proteolytic fragmentation and vesicular export distribute that ensemble; and recipient and daughter cells extend the signaling disturbance across cellular generations. This is the central biological meaning of molecular transcriptional shedding by proteolytic fragmentation.^{8–11,20,21,27,32,33,35,36,38,39,45,46,51,72–76}

Whether this process extends beyond the vaccinated individual is a separate question, and it is only partly answered. What is at issue is passage of molecular material, not of a replicating organism. Transfer to a second person is already documented by one route: vaccine mRNA appears in breast milk within 45 hours of maternal vaccination, concentrated in the milk extracellular-vesicle fraction, in two series from one group and absent in an independent series of 7 women, in trace and fragmented form and without demonstrated translation in the recipient.^{27,28,110} The carrier is general. Vesicles are established in saliva and exhaled breath and have been recovered from sweat,^{55–60} vaccine spike protein is carried on circulating exosomes in vaccinated humans,²¹ in one longitudinal case that association persisted to 1,284 days,³² and vesicle-borne mRNA is translated in recipient cells in vitro.¹²⁰ Every component of a transfer pathway is therefore established, in humans or in vitro, except one. No study has assayed saliva, exhaled breath, or sweat for vaccine-derived products after COVID-19 vaccination,⁶¹ no controlled study of transfer between individuals has been conducted, and no shedding study was required for these products, although the framework governing gene-therapy products containing genetically modified organisms contemplates exactly such secretion sampling.^{128,129} A survey reporting menstrual changes associated with proximity to vaccinated individuals raises the question but cannot settle it.¹²⁴ Transfer beyond the milk route should therefore be described as untested rather than as demonstrated or excluded, and conducting that test is the clearest outstanding priority identified by this review.

Declarations

Ethics Statement: Institutional Review Board approval and informed consent were not required for this study because it is a review based exclusively on previously published literature and publicly available sources. No human participants, animals, or identifiable personal data were involved.

Conflict of Interest Statement: JAC is Chief Executive Officer of Neo7Bioscience, Inc., which develops personalized peptide and molecular-surveillance products.

Data Availability Statement: No datasets were generated or analyzed during the current study. All data supporting the findings discussed herein are available in the cited published literature.

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