

REVIEW ARTICLE

Trained immunity of M1-like foamy macrophages: A key role of human endogenous retrovirus K102 particles

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Abstract

Trained immunity (TI) involves foam-cell formation in M1-like macrophages, relies on glycolysis for energy and is associated with epigenetic changes that improve accessibility to innate immunity genes. However, the mechanisms by which TI reduces all-cause mortality remain poorly defined. This review provides novel insights into the role of the protector foamy retrovirus, human endogenous retrovirus K102 (HERV-K102) located at 1q22, in generating M1-like foamy macrophages (FM) and creating TI. Remarkably, the involvement of HERV-K102 particles can help explain how TI activation can resolve or prevent infections and chronic diseases resulting in negative excess all-cause mortality. This is possible since the failed release of HERV-K102 particles from FM indicates the dysfunction of M1-like macrophages, a condition known to cause chronic diseases termed the immunosenescence of macrophages (ISM). Firstly, HERV-K102 particle production in activated macrophages causes the accumulation of high levels of these particles in vacuoles, generating the foam intrinsic to TI. These particles are then released on day 6/7 by lysis. Released protector particles launch a multi-faceted protection systemically within the host, including the all-important interferon response and the activation of innate T and B cells against the HERV-K102 envelope protein (Env). This review reveals for the first time that TI memory involves genomic modification (integration of HERV-K102) associated with protection. It also explains how HERV-K102 particles released from FM may contribute not only to sterilizing immunity and herd immunity, but also to the reversal of ISM associated with TI induction, which improves all-cause mortality.

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1. Introduction

The term “trained immunity (TI)” was first coined by Netea *et al.*¹ in 2011 to describe the enhancement of a secondary innate immune response after a primary infection or vaccination. Unlike adaptive immunity, TI lacks specificity for pathogen-specific antigens and thus invariably provides heterologous protection or cross-protection against unrelated pathogens. TI was initially invoked to explain how vaccination with the live *Bacillus Calmette–Guérin* (BCG) vaccine (attenuated *Mycobacterium bovis*) in West Africa decreased childhood mortality from several pathogens, including

that of tuberculosis. The protection furnished by the BCG vaccine was mediated by macrophages. Since macrophages in humans cannot replicate (unlike in mice) and have short half-lives, this has led to the concept of central TI in the hematopoietic stem and progenitor cells (HSPCs) in the bone marrow.²⁻⁵ Accordingly, TI involves peripheral (monocytes in the blood that differentiate into macrophages in the tissues) and central (myeloid HSPCs) compartments. Most notably, the memory aspect of TI involves metabolic and epigenetic changes. These include a switch to glycolysis enabling cholesterol synthesis, changes in histone methylation and acetylation in chromatin, and DNA methylation changes, providing improved access to macrophage lineage and inflammatory genes.⁴ Newer evidence also implicates long non-coding RNAs (lncRNAs) in epigenetic modifications.⁵ TI refers to a short-term enhancement (usually lasting 3 to 12 months) in the release of core inflammatory cytokines (such as tumor necrosis factor- α [TNF- α], interleukin [IL]-1 β , IL-6) from M1-like macrophages upon rechallenge, which is associated with enhanced heterologous anti-pathogen and anti-tumor activity *in vivo*. Epigenetic changes have also been described in other innate immune cells, including neutrophils, dendritic cells, natural killer (NK) cells, various innate lymphoid cells, and microglia, as well as non-immune cells. However, how TI in M1-like proinflammatory macrophages relates to enhanced pathogen and tumor control *in vivo* remains unclear and is yet to be fully elucidated.

This review attempts to explain key mechanisms conferring TI-mediated protection, including mechanisms that may lead to sterilizing immunity, and to examine

how TI may be critical to human survival. It also explores the possibility that immunosenescence of macrophages (ISM) induced by alpha-fetoprotein (AFP)—potentially triggered by the SARS-CoV-2 spike protein or associated with hypertension, insulin resistance, and many, if not most, age-associated chronic diseases—may impair TI induction, potentially leading to devastating outcomes for the host. A recent review proposed that TI may promote disease in an undefined, nebulous manner: “... induction of trained immunity can play a role both in maintaining health if activated at the right time and in the right place or promoting disease if inappropriately induced.”^{5(p173)} This statement highlights the current lack of a clearly defined molecular basis that can adequately explain both the protective and potentially deleterious effects of TI.

2. Implication of HERV-K102 particle production in trained immunity, foam cell formation, and heterologous protection

In an attempt to understand the molecular basis of TI in protection and dysregulated TI (ISM by AFP) in disease, a novel, potent, virus-antiviral innate defense system based on HERV-K102 particles produced in M1-like foamy macrophages (FM) has been described, helping explain how TI mediates pathogen and/or tumor clearance.⁶ HERV-K102 is a non-pathogenic foamy retrovirus encoded on chromosome 1q22 that initiates replication in proinflammatory M1-like macrophages and renders them foamy. The foam refers to high levels of HERV-K102 immature particles, about 100 nm in size, that accumulate in vacuoles, giving the cells a foamy appearance (Figure 1).⁷⁻⁸ The induction of lysis needed for the release of the

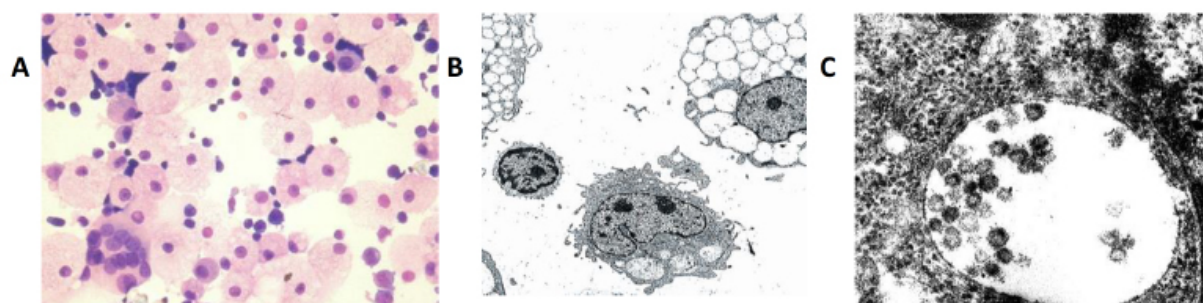


Figure 1. Morphological characterization of human endogenous retrovirus (HERV)-K102 particle production and replication *in vitro* in cord blood (CB) mononuclear cells. (A) Hematoxylin and eosin staining of day 7 CB cytopins showing highly vacuolated, foamy macrophages with diameters of 15–25 mm amongst normal small lymphocytes (magnification: 400 $\times$). Note the presence of a rare multinucleated giant macrophage. (B) Electron microscopy (EM) of vacuolating CB cells on day 11 at 1,500 $\times$. Note the lacy appearance. (C) At 100,000 $\times$, immature particles typical of foamy viruses (FV) can be seen in the vacuoles, which averaged about 100 nm $\pm$ 30 nm. Env spikes are also noted as critical for FV particle formation. No cell surface budding was observed by EM. Particle release was by lysis early on day 7. Media used was Iscove's Modified Dulbecco's Media (IMDM) with 10% fetal calf serum. In traditional Roswell Park Memorial Institute (RPMI) medium, the induction of vacuolation and HERV-K102 polymerase messenger RNA was blocked. Reprinted from Laderoute *et al.*⁸

protective foamy particles appears to be mediated by a novel lysosomal DNase2 released into the cytoplasm, associated with the disappearance of lysosomal-associated membrane protein 1 (LAMP1), as described by Fischer *et al.*⁹ in murine sebocytes. Although generally underappreciated, sebocytes are highly specialized M1-like FMs in the sebaceous glands that line the mucosa.⁶ Here, for example, in the upper respiratory tract (URT), HERV-K102 particles are released into the external environment via sebum. Sebum coats the mucosa and acts as a first line of defense. It is thought that this natural shedding of HERV-K102 particles from sebocytes in the URT may contribute to herd immunity, for example, by exhalation (see Section 2.9 for more discussion and evidence).

2.1. HERV-K102 is a non-pathogenic foamy retrovirus located at chromosome 1q22 and is considered uniquely replication competent

The HERV-K102 is a human protective foamy retrovirus and the only known HERV-K human mouse mammary tumor virus-like 2 (HML-2) group member to demonstrate natural replication competence both *in vitro* and *in vivo*.^{7,8} The claim that only HERV-K102 is naturally replication competent is corroborated by the finding that there are two entries for the amino acid sequence of the HERV-K102 envelope protein (Env). One sequence is produced when the full-length proviral sequence is transcribed (P63135 polymerase-envelope region [*pol-env*]), which is related to HERV-K102 replication, and another represents the protein produced from the spliced envelope messenger RNA (mRNA; P61567), which is related to HERV-K102 envelope expression in tumors and/or on virally infected cells.⁶ None of the other HML-2 group members showed this distinction.

2.1.1. HERV-K102 HML-2 envelope expression and significance to trained immunity

As assessed in peripheral blood mononuclear cells (PBMCs, which represent immune cells that circulate in the blood), three dominant HML-2 envelope transcripts were all type 1 HML-2 sequences that have a deletion in *pol-env*,¹⁰ and all contained the long terminal repeats (LTRs), referred to as human-specific LTR5 (LTR5Hs).¹¹

The 292-nucleotide deletion in *pol-env* for type 1 HERV-K HML-2 group members, which distinguishes them from type 2, results in the presence of an alternative transcript NP9, which is smaller than the Rec transcript.¹¹ The Rec protein is an accessory protein thought to be analogous to the orthoretroviral proteins Rev (from human immunodeficiency virus type 1 [HIV-1]) and Rex (from human T-cell leukemia virus type 1 [HTLV-1]), which facilitates the nuclear export of viral mRNAs

to the cytoplasm. This finding has led to the false assumption that type 1 HERV-K HML-2 elements are not replication-competent or capable of producing particles. However, non-pathogenic foamy retroviruses have unique properties that distinguish them from the pathogenic orthoretroviruses, as established for the well-characterized prototype foamy virus (PFV). PFV, although derived from a human nasal carcinoma from Africa and mistakenly called the human foamy virus, was later discovered to originate in chimpanzees and was renamed. PFV does not use a Rec-like domain; instead, it uses a cellular protein, human antigen R (HuR), that binds to foamy virus RNA to export mRNA to the cytoplasm for translation.¹² Subramanian *et al.*¹¹ also suggested that no HERV-K HML-2 particles (that bear RNA genomes) could be isolated from HIV-1 patients. However, from another study,¹³ there were about 8,300 DNA-bearing HERV-K HML-2 particles on average presented in 73% of HIV-1 patients. This finding was nearly identical to the post-hoc calculation of 8,200 complementary DNA (cDNA)-bearing HERV-K102 particles found in 72% of HIV-1 patients.¹⁴ From these analyses, it appears that the type 1 HERV-K HML-2 may be more closely aligned with the functions and replication mechanisms of non-pathogenic foamy retroviruses in host protection. Importantly, this includes the fact that the genomes in HERV-K102 particles are almost invariably in cDNA form.^{7,14}

The three RNA envelope transcripts (*env*) detected in PBMCs by Brinzevich *et al.*,¹⁰ in descending order of frequency, referred to HERV-KII (3q12.3), HERV-K102 (1q22), and HERV-K18 (1q23.3), of which the first and last are shared with gorillas and thus existed for a longer time. HERV-K102 is unique to humans, having been acquired in the past 2 million years^{6,11} and perhaps as recently as 700,000 to 800,000 years ago.⁶ The older sequences had multiple deletions, stop codons, and insertions, while HERV-K102 displayed a single stop codon in the *gag* region.¹¹ Phylogenetically, a potential source of HERV-K102 may have been chimpanzees, when the common ancestor of humans and other hominins was still living in Africa, and a lentivirus challenged the *Homo species*.⁶ Brinzevich *et al.*¹⁰ determined that only two HML-2 envelope RNA nucleotide sequences were translated into Env, namely HERV-K102 and HERV-K18. Interestingly, both of these type 1 HERV-K HML-2 proviruses are located on Chromosome 1, the largest chromosome in the human genome, that encode genes involved in human development and cellular maintenance. It was determined that only HERV-K18 could pseudotype HIV-1 virions, but, interestingly, not simian immunodeficiency virus,¹⁰ potentially implying co-evolution of HERV-K HML-2 elements in defense against lentiviruses of the host species.

Pseudotyping means that the HERV-K18 Env could become part of the HIV-1 virion and alter its targeting, perhaps away from macrophages and/or CD4-positive T cells. If so, it would be consistent with a role of HERV-K18 envelope expression in helping to protect the host against HIV-1 and other orthoretroviruses more generally.

Another important aspect of the expression of HML-2 envelope was the finding by Morozov *et al.*¹⁵ that the transmembrane region of the HML-2 envelope (shared by both type 1 and type 2 HML-2) suppressed the adaptive immune response while polarizing macrophages toward the M1 pro-inflammatory phenotype, thereby promoting TI. In other words, the HML-2 transmembrane Env drives TI over adaptive immunity. This is quite significant, given that the HERV-K102 envelope is strongly upregulated in virally infected cells⁶ and in various cancers.^{6,16} HERV-K102 Env expression on the surface of these abnormal cells acts as a surrogate marker for cells that need to be eliminated from the host; i.e., allowing innate T cells and immunoglobulin G (IgG) to HERV-K102 Env to trigger apoptosis and mediate cell killing. For example, in 2012, Wang-Johanning *et al.*¹⁷ demonstrated that a monoclonal antibody specific to HERV-K102 Env could trigger apoptosis *in vitro* and *in vivo* in human breast cancer cells. However, in 2017, this same research group showed various lines of evidence that the expression of HERV-K102 Env or very similar HML-2 Env sequences appeared to mediate the malignant phenotype, largely by affecting the RAS-ERK-RSK pathway during pancreatic tumor progression. They also reported detecting HERV-K HML-2 particles produced by some pancreatic cell lines.¹⁸ As discussed below, the malignancy-conferring pathway, epidermal growth factor receptor (EGFR)/ERBB2/phosphoinositide 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway, is used to generate HERV-K102 particles in macrophages, leading to the formation of foamy M1-like macrophages. In this regard, it is essential to understand that human macrophages do not replicate, unlike those in rodent models. AFP, a tumor progression factor that confers the malignant state, is also required to generate the foam/glycolysis needed to establish TI, as discussed in Section 2.6. Accordingly, the correlation between HERV-K HML-2 Env expression and malignant potential indicates that the more malignant the tumor, the greater the need for HERV-K102 envelope expression and/or the production of HERV-K102 particles to prolong survival.¹⁹

Nevertheless, Nguyen *et al.*²⁰ provided evidence that HERV-K HML-2 Env expression reverses chemoresistance in ovarian tissues and cultured cells and may correlate with CD8+ T cell cytotoxicity. Others reported that HERV-K102 transmembrane Env upregulated the immune

checkpoint markers programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) in the alpha-beta T cell receptor-bearing (adaptive immunity) Jurkat T cells.²¹ They suggested this would lead to immune escape from adaptive immune mechanisms. However, they did not consider that this immunosuppression of adaptive immunity may favor innate immunity. Additionally, the transmembrane region of the HERV-K Env bound to the immunoreceptor tyrosine-based activation motif (ITAM) of CD3e, thereby inhibiting adaptive T cell signaling.²²

However, the claim that shed HERV-K102 Env serum levels correlated with tumor progression in cancer patients and with carbohydrate antigen 19-9 (CA19-9) and AFP levels²¹ suggests that certain malignant tumors may cleave HERV-K102 Env from the surface of tumor cells, thereby limiting the ability of innate T cells and IgG antibody to bind to HERV-K102 Env to clear tumors. Soluble circulating HERV-K102 Env would also tend to neutralize any circulating antibody specific to HERV-K102 Env, again defeating innate TI. However, for the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) results for the levels of HERV-K102 Env detected in serum in cancer patients, the variance greatly exceeded the means. This exceptional variance could have been due to the detection of variable levels of HERV-K102 particles in the blood along with shedding of envelope from HERV-K18 cross-reactive envelope which also known to be found in blood.¹⁰ Thus, further research is needed to resolve this discrepancy.

It is important to realize that, unlike HIV-1, in which virus-like particles can form in the absence of envelope expression, in non-pathogenic foamy retroviruses, envelope expression is an absolute requirement for particle production and cannot be pseudotyped by orthoretroviruses (the disease-causing retroviruses).²³ In [Figure 1](#), electron micrographs show spikes of HERV-K102 Env on immature particles, consistent with the known replication competence of HERV-K102.^{7,8}

2.1.2. The concept that HERV-K102 integration is needed for replication, and that HERV-K102 can replicate to very high levels

For retroviral replication, including that of foamy retroviruses, integration into genomic DNA is an obligate requirement,^{23,24} which can be monitored by proviral copy number. PFV, a foamy virus of chimpanzees, displayed up to 20 integrated copies in individual erythroid leukemia cells.²⁴ Similarly, HERV-K102 was identified to exhibit increased copy number (an average five-fold increase *in vivo* compared to healthy controls)⁸ in a famous cohort resistant to HIV-1 acquisition reported by Fowke *et al.*,²⁵ but not in patients with HIV-1 acquisition ([Figure 2](#)).

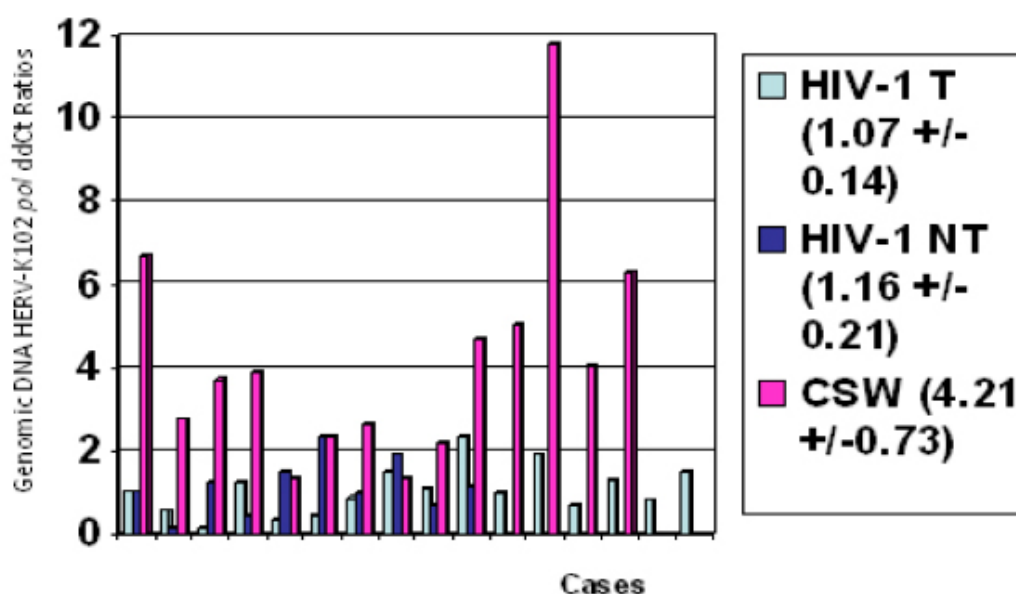


Figure 2. Increased proviral copies of human endogenous retrovirus (HERV)-K102 *pol* may be associated with resistance to HIV-1 acquisition. DNA was extracted from plasma, and the HERV-K102 *pol* delta-delta cycle threshold (ddCt) ratio was performed relative to 18S RNA as previously described^{7,8} using a uracil N-glycosylase (UNG)-containing polymerase chain reaction (PCR) buffer to digest any complementary DNA (cDNA) from particles, ensuring genomic DNA rather than particle-associated cDNA was assessed. Individual ddCt ratios were plotted: Light blue = 16 Canadian HIV-1 patients on antiretroviral therapy (HIV-1 T) with a mean genomic copy ratio of 1.07 ± 0.14 . Dark blue = 10 Canadian HIV-1 patients not on antiretroviral therapy (HIV-1 NT) with a mean of 1.16 ± 0.21 . Note there was no statistical difference in the genomic copy ratios of HERV-K102 *pol* between the Canadian HIV-1 infected patients, whether or not they were on therapy, and neither group alone or together was statistically different from normal. Pink = Commercial Sex Workers (CSW) who had shown at least three years of HIV-1 resistance to transmission despite daily exposures to HIV-1²⁵ with a mean genomic copy ratio of 4.21 ± 0.73 . This was significantly elevated above normal (0.88 ± 0.37 ; $p < 0.0005$) and above the two-standard-error cutoff of 1.62 ($n = 30$). Reprinted from Laderoute *et al.*⁸

This exceptional finding not only validated the replicative activity of HERV-K102 *in vivo* but also strongly implied its high replication in generating sterilizing immunity against RNA pandemic viruses. It also validated that HERV-K102 may naturally replicate to exceptionally high levels *in vivo* in response to viruses.

The 10^9 quantitative polymerase chain reaction (PCR) real-time delta-delta cycle threshold (ddCt) ratios commonly obtained in viremic patients (excluding HIV-1, which antagonizes HERV-K102)^{7,14} corresponded to an estimated 10^{12} HERV-K102 particles per mL of plasma. If we consider that there are about 5 L of blood in an adult (and about 60% is plasma), this means when HERV-K102 is fully induced, in the circulation, there would be about 3×10^{15} particles induced, representing an 83-fold higher level of particles than the number of cells in an adult (about 3.6×10^{13} cells per adult). Thus, the levels of HERV-K102 particles, which may be readily detectable in blood, may be at least 10-fold higher than the total number of cells in the body. When one also considers the number of HERV-K102 particles constitutively produced in sebocytes, which coat

the mucosa,²⁶ the HERV-K102 replicative response in the body is more than enough to protect most, if not all, cells.

2.1.3. A potential role of HERV-K102 in human survival warrants fast memory responses

It has been argued that HERV-K102 activation may have played a role in human survival over other hominin species that went extinct. The other hominins, Neanderthals and Denisovans, lost HERV-K102 at 1q22.⁶ Furthermore, we know that progeny from admixtures of Neanderthal and human only produced viable offspring when the female was human. This might be taken as an argument that humans had better host defenses than other hominins due to the maintenance of HERV-K102 at 1q22. If HERV-K102 activation with particle release represents the quintessential mechanisms for launching potent TI-mediated protection against emerging pathogens, it would be imperative that HERV-K102 induction and particle release occur rapidly. The question is, how fast is fast?

A patient with chronic fatigue syndrome (CFS; considered a post-viral syndrome) voluntarily interrupted

her St. John's wort therapy (in the name of science) for 84 h, during which she developed severe insomnia, post-exertional malaise, debilitating fatigue, and extensive brain fog by 24 h (and which persisted for as long as she did not take St. John's wort). At 84 h, the number of HERV-K102 particles induced from a baseline of 0 particles per mL of plasma (i.e., when she was on St. John's wort therapy) was 2.55×10^{11} particles per mL of plasma.^{7,14} Particles were isolated from plasma, and only DNA, but not RNA, could be detected in these particles using regular PCR and reverse transcription PCR. Through a special quantitative ddCt PCR (a qPCR that controls for genomic equivalents) performed in the presence versus absence of the enzyme AmpErase™ uracil N-glycosylase in the PCR buffer (which digests cDNA but not genomic DNA), it was confirmed that 100% of the HERV-K102 particles induced by 84 h in the CFS patient were all cDNA, as expected for a foamy retrovirus.^{7,23} It should be appreciated that this induction of high levels of HERV-K102 particles would be considered a memory response.

Not surprisingly, the strong short-term induction of HERV-K102, which would greatly increase plasma viscosity, was associated with a high erythrocyte sedimentation rate of about 22 mm/h and an elevated CD4/CD8 ratio of 2.1 (laboratory results), indicating an absolute loss of CD8+ T cells in the blood. Notably, these values matched the median values obtained by Diaz-Mitoma *et al.*²⁷ for CFS patients undergoing a clinical trial. The erythrocyte sedimentation rate, which is a measure of inflammation and correlates with fatigue, can be elevated in a wide variety of other diseases, including viral infections and malignancies, autoimmune diseases, metabolic disorders, and neurodegenerative diseases.²⁸ It is tempting to speculate that the fatigue associated with strong HERV-K102 activation naturally promotes bed rest, ensuring sufficient energy can be devoted to HERV-K102 particle production and, thus, to the survival of the host when needed.

2.2. HERV-K102 is a member of the HERV-K HML-2 group: Guardians of the human genome

The HERV-K HML group of endogenous retroviruses comprises about 91 almost full-length proviruses across the human genome, which are generally inactivated by mutations, some including loss of one or more LTRs.¹¹ Nevertheless, various mRNAs and/or proteins corresponding to these other HML members are variably expressed. The HML-2 group of HERV-K members represents the most biologically active endogenous retroviruses in the human genome and is the most recently

acquired. This group has coevolved with humans over the past 10 million years, and since their arrival, the invasion of the human genome by orthoretroviruses has been greatly diminished.²⁹ This phylogenetic evidence directly implicates HERV-K102 and the HERV-K HML-2 group in host defense against viruses.

2.3. HERV-K102 is potentially the elusive (protector) foamy retrovirus of humans and undergoes clinically significant proviral amplification

Where examined, most mammalian species carry foamy retroviruses that have coevolved with the host over millions of years. While the human foamy retrovirus has not been truly identified, accumulating evidence implies that HERV-K102, although encoded within the human genome, may be the elusive foamy retrovirus of humans. Notably, HERV-K102 has all the hallmarks of (non-pathogenic) foamy retroviruses and shares many, if not most, properties with PFV of chimpanzees (see the extensive list in the supplemental materials in Laderoute *et al.*⁸). This includes certain unique properties of foamy retroviruses,^{23,30} such as the telltale sign of induction of foam in cells when they replicate *in vitro* (Figure 1), genomes in immature particles being primarily cDNA relating to a reversed lifecycle to orthoretroviruses, and certain genetic attributes such as integration of proviruses starting with "tgtg." Since foamy retroviruses are considered nonpathogenic and are transmitted via saliva, it has been observed that upon transmission to a new host, integration can be detected in all organs and tissues, but expression is detected only in the oral mucosa, as studied for simian foamy retroviruses.³⁰ In this regard, HERV-K102 RNA expression has been detected in human sebocytes (which have identical morphology and the same differentially expressed genes [DEGs] common to foamy M1-like macrophages),^{6,26} suggesting that HERV-K102 is likely spread by saliva and/or exhalation, as expected for foamy retroviruses. Therefore, a role in establishing "herd immunity," especially to emerging pathogens, is plausible and will be discussed in Section 2.9.

Despite being nonpathogenic, PFV paradoxically induces apoptosis in some but not other fibroblast cell lines.²³ Similarly, a strong induction of apoptosis at 24 h was observed with HERV-K102 particles when added to MRC-5 cells, but not to human fetal lung fibroblast (HFL-1) cells.⁶ It was subsequently discovered that PFV is oncolytic, inducing apoptosis upon entry into tumor cells,³¹ and virolytic, inducing apoptosis in virally infected cells.³² Accordingly, it is extremely important to address whether HERV-K102 also shares oncolytic and virolytic properties with PFV, as this would help explain its potency

for clearing cells infected with intracellular pathogens and/or tumors.

On the other hand, upon entry into healthy cells, HERV-K102 likely integrates into open chromatin, and these extra copies would create more accessible targets, enhancing TI memory for HERV-K102 full-length RNA and spliced envelope expression upon host rechallenge. This would help explain the significance of the finding of increased HERV-K102 copy number in host resistance to HIV-1 acquisition (Figure 2)⁸ and the reported association with improved overall survival in patients with lung adenocarcinomas (LUADs).¹⁹

2.3.1. Upregulated HERV-K102 integration in pandemics and cancers

In 2015, we were the first to report the detection of significantly increased HERV-K102 proviral copies in genomic DNA in an HIV-1-exposed seronegative (HESN) cohort that was resistant to HIV-1 acquisition while not observed in HIV-1 patients whether or not on anti-retroviral therapy.⁸ Both HIV-1 and SARS-CoV-2 viruses caused pandemics and both are “enveloped” RNA viruses that bud from the cell surface. This means these pandemic viruses are amenable to tight control by the HERV-K102 defense system, which involves an antibody to the HERV-K102 Env expressed on the cell surface of virally or tumor-transformed cells. Accordingly, upon budding from the cell surface, these “enveloped viruses” retain HERV-K102 Env, meaning the corresponding antibody can destroy and remove the virions and not just the infected cells (Figure 3). This HESN cohort was the first of its kind discovered by Fowke *et al.*²⁵

It was more recently reported that the HERV-K102 region around 1q22 at 1q21 often undergoes amplification in LUAD tissues.³³ Indeed, the study by Ng *et al.*¹⁹ was very informative about the important roles of HERV-K102 envelope expression in LUAD patients, which is associated with increased HERV-K102 proviral integration. First, HERV-K102 envelope mRNA is the most highly expressed HML-2 member or HERV in LUAD. Second, the HERV-K102 envelope is expressed at higher levels in LUAD than in adjacent normal tissues. Third, HERV-K102 envelope mRNA expression is correlated with the levels of IgG antibodies to HERV-K102 Env. Fourth, the envelope mRNA in LUAD is also correlated most strongly with the transcriptional signatures of cytotoxic T cells, including CD8⁺ T cells. Fifth, both the HERV-K102 envelope mRNA in the tumor and HERV-K102 envelope-specific IgG levels are correlated with ploidy-adjusted HERV-K102 copy number in LUAD. These findings documented that increased integration of HERV-K102 in tumor tissues

(a measure of HERV-K102 replication) was, associated with enhanced T and B cell activation to HERV-K102 envelope. This would be consistent with HERV-K102 particles directly stimulating their activation, although this needs to be directly tested. In a small LUAD sample ($n = 7$), pre-treatment levels of antibodies specific to the HERV-K102 envelope predicted responses to immune checkpoint blockade, and these antibody levels correlated more with overall survival than with progression-free survival. The levels of these antibodies are also correlated with NK cell-mediated antibody-dependent cytotoxicity. In a larger sampling of 68 LUAD patients, it was shown that LUAD tissues with higher levels of HERV-K102 envelope mRNA before immune checkpoint blockade treatment were correlated with favorable responses and overall survival.¹⁹ Thus, HERV-K102 replicative activity (increased integration) was correlated with the activation of T and B cell responses linked to HERV-K102 Env expression and promoted overall survival in LUAD patients. These findings,¹⁹ along with those reported earlier for the HESN cohort in 2015,⁸ may be among the first to confirm that TI memory involves genetic recombination, putatively to amplify HERV-K102 particle production to enhance protection.

2.3.2. Mechanisms by which antibodies specific to HERV-K102 Env may neutralize viruses

As detailed previously,⁶ in addition to defense against HIV-1, a pandemic RNA virus, HERV-K102 activation was associated with recovery from COVID-19, caused by another pandemic RNA virus, SARS-CoV-2. No less significantly, HERV-K102 may have contributed to human survival over other hominins. Neanderthal and the Denisovans lost HERV-K102 at 1q22 and went extinct.⁶ RNA epidemics are postulated to at least partially explain these extinctions. One manner in which the HERV-K102 protection system may be particularly valuable to the host against emerging pathogens, and RNA viruses in particular, is that the HERV-K102 envelope is expressed on virally infected cells. Accordingly, for enveloped viruses, such as HIV-1 and SARS-CoV-2, that bud from the cell surface membrane, the released virions would incorporate HERV-K102 Env from the plasma membrane. This means IgG antibodies specific to HERV-K102 Env could clear and/or neutralize the viral particles, preventing infection, host acquisition, and transmission to third parties (Figure 3). In patients with mild COVID-19 disease, both IgA and IgG antibodies specific to HERV-K102/HERV-K18 envelope are universally detected in saliva.³⁴ Thus, in mild COVID-19, innate antibodies specific to HML-2 Env can neutralize and clear SARS-CoV-2 virions in the URT before the onset of adaptive IgG antibodies specific to the spike protein.³⁵

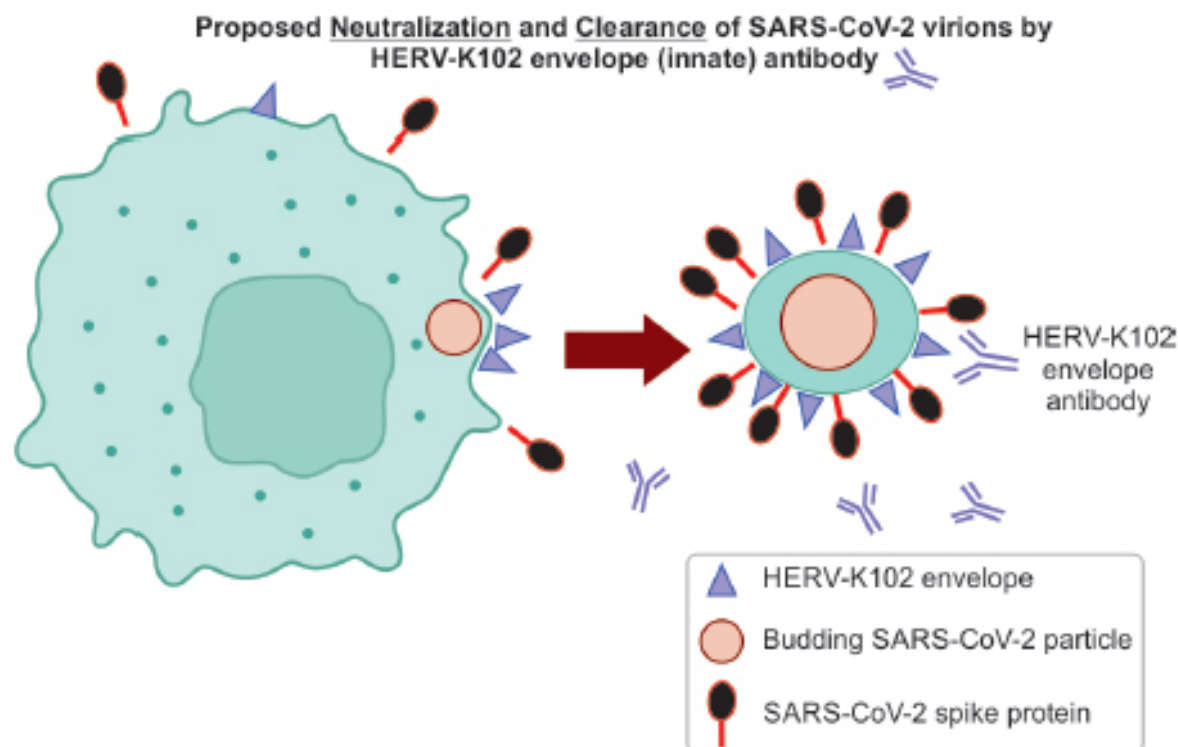


Figure 3. How trained immunity (TI) neutralizes or clears “enveloped” virions that bud from the cell surface. Virus-infected or tumor cells express the human endogenous retrovirus (HERV)-K102 envelope protein (Env) on their cell surface, which induces clearance or apoptosis by Env-specific T cells and/or antibodies. Antibodies to HERV-K102 Env have been demonstrated in patients with HIV-1 or other viral infections.⁷ Viruses such as SARS-CoV-2 and HIV-1, which bud through the cell surface (the so-called enveloped RNA viruses), likely contain the HERV-K102 envelope (or an HML-2 Env that is 95–97% identical) in their virions, which they acquire during budding. This allows the inactivation and/or clearance of these enveloped pandemic viruses through the immunoglobulin G (IgG) antibody to the HERV-K102 envelope. There is no way to select for viral variants with TI, which provides TI with a significant advantage over adaptive immunity. Reprinted with permission from Laderoute.⁶ Copyright 2024 Jaypee Brothers Medical Publishers (P) Ltd.

This may be a key mechanism explaining the sterilizing immunity associated with HERV-K102 activation and resistance to HIV-1 acquisition.^{8,14} Presumably, it also helps explain how the transmission of HERV-K102 particles from the URT may generate herd immunity in the new host, not only by spreading the type I interferon response but also by HERV-K102 activation in the new host. This would ultimately induce the activation of innate B cells that produce antibodies specific to the HERV-K102 Env, as well as innate T cell responses to the Env (*i.e.*, lacking major histocompatibility complex [MHC] restriction).

For more information on this relatively obscure yet incredibly potent innate immunity protection system involving HERV-K102 particle production in macrophages, the reader is referred to a recent comprehensive review with supporting data.⁶

2.4. The current functional definition of trained immunity is inadequate

Since TI reportedly occurs in M1-like macrophages, with or without induction of inflammatory cytokines, as revealed by single-cell sequencing,^{36,37} this poses a conundrum for the functional definition of TI, which defines training as a larger and faster recall response involving heightened proinflammatory factor release from macrophages. This could be easily reconciled, however, by proposing that it may well be the mere production and release of HERV-K102 foamy retroviral particles in and from M1-like macrophages that generate the critical TI heterologous protection associated with foam cell formation. Indeed, Li *et al.*³⁷ have indicated that transcription factors critical for training in all monocyte subsets, including those that lack induction of inflammatory cytokines, such as SPI1, CCAAT/enhancer-binding protein beta (C/EBPβ),

interferon regulatory factor 1 (IRF-1), IRF-9, signal transducer and activator of transcription 1/2 (STAT1/2), RELA/B, and nuclear factor kappa B subunit 1 (NF- κ B1/2), appear to implicate the expression of full-length HERV-K102 proviral transcripts as being necessary and sufficient for TI.^{38,39} SPI1 and C/EBP β are enhancers that induce DEGs involved in establishing TI in macrophages.

By examining single-cell RNA sequencing data involving the activation of human macrophages with the TEcount and Telescope software packages, Russ *et al.*⁴⁰ determined that with M1 polarization in response to lipopolysaccharide (LPS), which triggers Toll-like receptor 4 (TLR4) and interferon (IFN)- γ proinflammatory signaling, HERV-K102 activation comprised the vast majority of HML-2 transcripts in direct substantiation of our *in vitro* work.^{7,8,14} Additionally, the transcription factors STAT1 and IRF-1 are critical for HERV-K102 induction by IFN- γ , bound to a region called “LTR12E,” which resides just upstream of the 5' LTR of HERV-K102. This may help explain why the HERV-K102 locus on chromosome 1q22 was vital for the survival of *Homo sapiens*, while other similar HERV-K HML-2 elements in non-syntenic regions of the hominin genome were apparently insignificant to prevent the extinction of Neanderthals and Denisovans (as discussed by Laderoute *et al.*⁶).

Genes subsequently induced by HERV-K102 expression in M1 macrophages included: (i) via cyclic GMP-AMP synthase (cGAS; recognizing double-stranded DNA [ds DNA]): *IRF1*, *IRF8*, *SOCS3*, and *ICAM1*; (ii) via interferon sensitive response elements (ISREs; triggered by complexes of STAT1/STAT2 and IRF-9): *MX1*, *ISG15*, *IFIT1-3*, *USP18*, *OAS1-3*, *OASL*, and *ISG20*; and (iii) via cGAS and ISREs: *STAT1/2*, *IRF9*, *IFITM1*, *BST2*, *TAP1*, *SOCS1*, *IFI35*, *HLA*, *ZC3HAV1*, *AIM2*, and *TRIM69*.⁴¹ Many of these genes are type I interferon-stimulated genes that induce an antiviral state, demonstrating how IFN- γ (a product of adaptive and innate immunity) may boost innate immunity. These observations also imply HERV-K102 activation in amplifying the critical type I interferon response *in vivo*.^{40,41} Indeed, LTRs from HERV-K proviruses act as enhancers for a number of interferon response genes that play major roles in innate immunity function, coordination, and activation.³⁹⁻⁴¹ Furthermore, in a humanized mouse model of mild COVID-19, macrophages were able to amplify the type I interferon response, which is critical for recovery.⁴² Most probably, it involved HERV-K102 particles.

Russ *et al.*⁴⁰ also reported that vitamin D receptor (VDR) response elements and the glucocorticoid receptor response elements, along with response elements for NF- κ B1 and IRF-1, are contained within the 5' LTR of HERV-K102, in agreement with others.^{38,39} Notably, this

also includes estrogen response elements, substantiating an important role for HERV-K102 particles in protection during human early embryonic development.⁴³

As mentioned, the HERV-K102 particles contain double-stranded cDNA genomes,⁷ a hallmark of non-pathogenic foamy retroviruses.^{23,30} This cDNA triggers the type I interferon response by alternative means to RNA virus invasion, such as through cGAS–stimulator of interferon gene (STING) pattern recognition receptors,⁴¹ which may serve as an alternative backup system against RNA pandemic viruses.⁴⁴ HERV-K102 expression/entry activates three types of pattern recognition receptors, namely TLRs, RIG-1-like receptors (RLRs), and cGAS, to promote and enhance the antiviral state caused by the type I interferon response.^{40-42,44} This would be important for spreading herd immunity to third parties, for example, by shedding HERV-K102 particles, such as those from the URT (see Section 2.9).

Docking and entry of HERV-K102 into cells are mediated by heparan sulfate, which is expressed on most cell types in the body.^{45,46} These immature, 100 nm particles that resemble exosomes are studded with Env (Figure 1).⁶ Accordingly, these particles with spikes of Env may preferentially target the HERV-K102 particles to innate immunity cells that may have receptors for HERV-K102 Env. This may involve gamma–delta T cells ($\gamma\delta$ T cells) and/or innate B cells, and consequently play a role in their activation. For example, $\gamma\delta$ T cells are activated via the cGAS–STING pathway,⁴⁷ implying that HERV-K102 cDNA genomes are potentially involved in their activation. This is very significant, as accumulating evidence implicates $\gamma\delta$ T cells in cancer recovery.⁴⁸⁻⁵⁰ Additionally, during cancer therapy, altered DNA leaks into the cytoplasm, triggering the cGAS–STING pathway and macrophage polarization to M1 via the STING–IRF-3–STAT1 axis.⁴⁷ Both C–C motif chemokine ligand 2 (CCL2; a chemotactic factor for macrophages) and type I interferons can convert M2 macrophages to M1 macrophages, favoring TI.

2.5. Molecular mechanisms involved in generating trained immunity

Commonly used inducers of TI include microbial products such as beta-glucan, LPS (also called endotoxin), and muramyl dipeptide, as well as oxidized low-density lipoprotein (oxLDL), uric acid, the BCG vaccine, other live vaccines, and viral exposures.⁵¹⁻⁵² TI is also potentially induced by spike mRNA gene therapy products and spike cDNA adenovirus vectors.⁶ The differences in epigenetic marks by the different TI inducers have been reviewed elsewhere.⁵² As already mentioned, the myeloid-specific enhancers SPI1 and C/EBP β are specific enhancers of TI

in macrophages.^{40,41,53}

In terms of innate memory responses, LPS has dual effects: at a low dose (10 ng/mL), it induces TI in bone marrow-derived murine macrophages, whereas at a high dose (100 ng/mL), it induces tolerance.⁵⁴ However, in that paper, the authors considered “trained immunity” to be a separate entity from “tolerance,” but both are unified under the notion of innate immune memory. That they are distinct phenomena is further substantiated by the finding that the TI targets are linked via p53 (and Foxo3) related to apoptosis (presumably involving AFP expression tied to both), DNA repair, and polycomb repressive complex (PRC2), while the LPS tolerance targets form three clusters: (i) histone-modifying enzymes, (ii) cell division involving Aurora kinase (probably not applicable to humans as macrophages do not replicate in humans but do in mice), and (iii) base-excision repair. Agents of tolerance include high-dose LPS, Pam3CysSERLys4, and inflammatory cytokines, such as TNF- α . The main mechanism for innate memory (TI and/or tolerance) is through epigenetic “rewiring,” involving histone modification, DNA methylation and demethylation, and non-coding RNA expression.⁵⁴ During beta-glucan TI activation, active histone marks include acetylation of lysine 27 (H3K27ac) and monomethylation and trimethylation of lysine 4 on histone H3 at the promoters of targeted genes, which open chromatin. In contrast, active histone marks in LPS-tolerant macrophages emerged during LPS priming and were replaced by repressive epigenetic marks, such as H3K9me2 and DNA CpG methylation, after restimulation with LPS. It is also possible that LPS-induced tolerance could suppress NF- κ B activation and polarize the macrophages to M2. Beta-glucans can reverse trained tolerance. It is presently unclear how LPS tolerance relates to ISM by active AFP, but emerging evidence does implicate TI in reversing chronic diseases, including cancer.⁵⁴ For example, a study of seven integrated health care organizations in the United States of America (USA) demonstrated that heterologous protection against non-COVID-19 mortality was induced upon the administration of the first dose, which was not appreciably altered upon receiving the second dose, at least for the first 7.5 months of the vaccination campaign (basically prior to the full dominance of the Delta variant).⁵⁵

The transcription factor hypoxia-inducible factor-1 alpha (HIF-1 α) plays an important role in TI. The metabolic and epigenetic changes in myeloid cells associated with TI are generally mediated via the PI3K/Akt/mTOR/HIF-1 α pathway,⁵⁶⁻⁶⁰ although in BCG-induced TI, other pathways may also be involved, including EGFR, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) signaling.⁵ There are three main aspects of metabolic reprogramming: glycolysis and

glutaminolysis; tricarboxylic acid (TCA) cycle integration, where glutamine replenishes the TCA cycle and fumarate accumulates; and cholesterol synthesis. The role of cellular metabolites, such as fumarate, as cofactors for epigenetic enzymes is a new area of interest.⁶¹ Fumarate is a key metabolite that can induce TI at least partially by creating histone modifications similar to beta-glucan, such as H3K4Me3 and H3K27Ac. It inhibits the bioactivity of lysine demethylase 5 (KDM5), while α -ketoglutarate can counteract this effect. Interestingly, fumarate also inhibits proteasomal degradation of HIF-1 α , an essential transcription factor required for TI induction by beta-glucan.

Glycolysis is necessary to drive the PI3K/Akt/mTOR/HIF-1 α pathway.⁵⁸ In M1 macrophages, activation leads to the accumulation of succinate in the Krebs cycle, stabilizing HIF-1 α . HIF-1 α induces the transcription of glycolysis genes.⁶⁰ In contrast, M2 macrophages primarily use oxidative phosphorylation.

Trained immunity involves the formation of foam cells and FM s .⁶² Most notably, the mevalonate (cholesterol) pathway is needed for TI in the monocyte/macrophage lineage, as statins, which inhibit HMG-CoA reductase (HMGCR), block TI induction.⁶³ Trained macrophages take up lipids, such as oxLDL, through the oxidized low-density lipoprotein receptor 1 (OLR1; previously called LOX-1) to form foam cells and produce high levels of TNF- α , IL-6, IL-8, and IL-18 upon secondary challenge,⁶⁴ which is associated with glycolysis.⁶⁵ Interestingly, SARS-CoV-2 infection disrupts the mevalonate pathway,⁶⁶ suggesting that it directly targets foam cell formation and thus TI and HERV-K102 activation.

The HIF-1 α protein plays a key role in initiating and promoting foam cell formation in macrophages.⁶⁷ NF- κ B1, which induces the inflammatory response in macrophages, is required for HIF-1 α transcription.⁶⁸ A critical role of HIF-1 α in foam cell formation in macrophages was demonstrated by inhibiting foam cell formation with HIF-1 α -targeting small interfering RNAs.⁶⁹ Thus, it is very clear that TI critically involves the induction of foam in proinflammatory macrophages, associated with NF- κ B1 and HIF-1 α expression, and the introduction of glycolysis.

The PI3K/Akt/mTOR pathway plays roles in autophagy, apoptosis, metabolism, and cell growth, but is commonly hyperactivated in tumors, where it contributes to malignant potential.⁷⁰ It is also hyperactivated upon SARS-CoV-2 infection, as in the hepatocellular cell line Huh7, which is associated with ERBB2 hyperactivity.⁷¹ Moreover, as might be anticipated, SARS-CoV-2 infection significantly elevated AFP mRNA and protein expression (Professor Ujjwal Neogi, personal communication,

July 22, 2020), which is known to increase malignant potential. In macrophages, this malignancy-promoting pathway is used by EGFR for foam cell formation.⁷² For example, *EGFR* deletion in macrophages in murine models limits IL-6 and TNF- α production, reduces lipid uptake by lowering CD36 expression, reduces macrophage accumulation, and inhibits atherosclerosis development, which involves FMs.⁷³ Similarly, in human macrophages, EGFR is activated by TLR4, and disrupting either TLR4 or EGFR reduces inflammation and foam cell formation.^{73,74} Triggering TLR4 activates HIF-1 α , IRF-1 (which induces HERV-K102 proviral transcription⁶), VDR, S100A9, and NR3C1 (the glucocorticoid receptor), while downregulating peroxisome proliferator-activated receptor gamma (PPAR γ) and IFN- γ receptor 1.⁷⁵ EGFR antagonists also blocked oxLDL-induced inflammation and foam cell formation in macrophages, downregulating IL-6 and TNF- α .⁷⁴ Again, this provides further proof that TI critically involves EGFR and/or TLR4-induced foam cell formation in proinflammatory macrophages.

Indicators or target genes of the transcription factor HIF-1 α include *PLAUR*, *HK2*, *NAGK*, and *CXCR4*.⁷⁶ While *PLAUR* (the plasminogen activator urokinase receptor) and these other genes strongly correlate with the progression of atherosclerosis (a disease related to dysfunctional FMs⁷⁷), *PLAUR* was expressed only in M0 macrophages. Curiously, the M1-like macrophages do not express markers associated with atherosclerosis, whereas the M2-like macrophages express *CXCR4* and *NAGK*. This aligns with the new immunosenescence paradigm for macrophages, in which dysfunctional macrophages in atherosclerosis are M2, not M1.⁷⁷⁻⁷⁸ In CD8+ T cells, NK cells, monocytes, and naïve B cells, atherosclerosis correlates with pyruvate dehydrogenase kinase 3 (PDK3) expression.⁷⁶ PDK3 is part of a mitochondrial multienzyme complex that converts pyruvate to acetyl-CoA and CO₂, providing a link between glycolysis and the TCA cycle (which regulates glucose metabolism). For example, PDK3 promotes the use of fat as an energy source when glucose is insufficient during fasting.

2.6. Alpha-fetoprotein expression is essential for foam cell formation

In hepatitis B infection, the viral X protein expressed in hepatocytes induces AFP, which inhibits phosphatase and tensin homolog (PTEN), thereby activating the PI3K/Akt/mTOR pathway.⁷⁹ This pathway regulates gene transcription via mTOR, which leads to HIF-1 α transcription and, as mentioned, is needed for glycolysis. In hepatocellular carcinoma cells, the phosphorylation of mTOR at serine 2448 synergizes with HIF-1 α to regulate genes such as *CXCR4*, *SRC*, and *RAS*. Small-interfering RNA targeting

AFP (AFP-siRNA), which inhibits the production of AFP mRNA and protein, blocks mTOR migration to the nucleus and is associated with the downregulation of p-mTOR (phosphoserine 2448), HIF-1 α , *SRC*, *CXCR4*, and *Ras*. Thus, TI involving PI3K/Akt/mTOR/HIF-1 α activation in human macrophages, along with foam cell formation, is potentially co-dependent on AFP expression.

The TLR4 signaling in macrophages induces the glucocorticoid receptor, NR3C1.⁸⁰ AFP expression is induced by glucocorticoids in humans, while in direct contrast, it is repressed by glucocorticoids in rodent models.⁸⁰ Interestingly, rodents lack dehydroepiandrosterone (DHEA), a steroid hormone that counteracts the effects of cortisol on AFP. There are many ways in which rodent immune systems differ from those of humans, especially regarding macrophages, making predictions about immunity, pathogenesis, and therapy based on murine models unreliable.

It is noteworthy that DHEA, but not its inactive form, DHEA-S, specifically binds and inactivates AFP in humans.⁷⁸ This is important because it is known that DHEA levels decline with stress or aging and that chronic disease initiation and/or progression correlate with a declining DHEA/cortisol ratio. Accordingly, with age or stress, more of the AFP induced by cortisol, such as that released by macrophages, would be active and able to promote ISM and the malignant potential of tumors and infectious agents. The well-known immunosuppressive effect of AFP on macrophages was confirmed using two AFP agonist monoclonal antibodies targeting the 67 kD AFP receptor.⁸¹ More importantly, the fact that AFP confers apoptosis resistance was discovered and confirmed with the same monoclonal antibodies.^{81,82} AFP was the first secreted apoptosis inhibitor identified in 1991⁸¹ and was published in 1994.⁸² This added to the historical significance of AFP as the first tumor marker/oncofetal antigen (1963), first immunosuppressive factor (1975), first secreted protein able to generate negative signaling (1991), first secreted protein able to confer apoptosis resistance (1991,1994), first to unify a theory on cancer of how the malignant potential of tumors relates to immunosuppression of the host (1994), and, by the latter, led to the first proposal that the malignant nature of tumors was not genetically determined but a reversible phenotype as early as 1994.⁸³

The transfection of AFP is known to polarize macrophages to the M2 phenotype.⁸⁴ For example, upon triggering of the M1 phenotype by LPS and IFN- γ , AFP transfection into M0 macrophages co-induces CD163 and IL-10, which are considered markers of M2. However, CD163, IL-10, and the M1/M2 hybrid phenotype⁸⁵ characterize the normal FMs illustrated in Figure 1, exhibiting high levels of vacuoles and HERV-K102

particles.⁶⁻⁸ This may further substantiate a role of AFP expression in the training of M1-like macrophages associated with foam cell formation.

2.7. Foamy macrophages, trained immunity, and glycolysis

The formation of foam in macrophages displayed in Figure 1 has been shown to involve high levels of HERV-K102 particles, which bud into intracellular vacuoles rather than through the cell surface membrane.^{7,8} Instead, particle release occurs through lysis of the FMs during a major wave in cultured cord blood cells on day 6–7. The foamy retrovirus particles and the vacuoles are lipid bilayers that require high cholesterol levels. Thus, it seems that HERV-K102 particle production (Figure 1) is a critical component of “training” in M1-like macrophages, requiring elevated cholesterol levels due to foam cell formation.^{62,63}

Trained immunity is associated with the induction of glycolysis, similar to the Warburg effect observed in tumors. At the risk of being an oversimplification, a reason why glycolysis is needed for tumorigenesis (the Warburg effect) is so the mitochondria can produce the substrate acetyl-CoA/citrate (from glycolysis) needed for cholesterol production through the mevalonate pathway.⁸⁶ It should be appreciated that this cholesterol pathway also generates vitamin D, DHEA, cortisol, and the steroid hormones, and so, is intrinsic to the promotion of health. Replenishing the cell surface membrane and other membranes via increased cholesterol production would be needed to support tumor replication or expansion. Indeed, mevalonate initiates DNA synthesis and cell proliferation.⁸⁶ In human monocyte-derived macrophages, which incidentally do not proliferate (although they do in rodent models), excess cholesterol would be required for foam cell formation, as it supports the replication of the protective foamy virus HERV-K102. Hence, glycolysis is linked to TI to support the generation of cholesterol required for the production of vacuoles and HERV-K102 particles during M1 macrophage training.

2.8. M1-like macrophage activation in trained immunity and IRF-1 induction of HERV-K102

As mentioned, the enhancer transcription factors SPI1 and C/EBP β drive myeloid differentiation and TI.⁵⁶⁻⁵⁸ As a matter of fact, SPI1 is considered a pioneering transcription factor (also called a lineage-determining transcription factor) that, in this case for macrophage differentiation, opens chromatin, enabling inflammation-related transcription factors and other TI-associated transcription factors to bind to response elements in the appropriate genes.⁸⁷ Macrophage inflammation involves networks of STAT factors, IRFs, and NF- κ B transcription factors.

Monocytes exposed to LPS and IFN- γ undergo classical M1-like (pro-inflammatory) macrophage activation with upregulation of SPI1, IRF-1, IRF-5, IRF-8, STAT1, STAT2, and NF- κ B1. The alternative activation with IL-4 and IL-13 generates M2-like (anti-inflammatory) cells featuring SPI1, IRF-4, STAT6, KDM6B, PPAR γ , PPAR δ , and C/EBP β . However, PPAR γ plays an important role in monocyte differentiation into FMs, and C/EBP β is a TI enhancer. Accordingly, macrophages that confer TI express M1- and M2-like markers, including C/EBP β and PPAR γ , which are associated with foam cell formation. As mentioned, AFP expression may also contribute to the expression of M2 hybrid markers in inflammatory macrophages.

It is noteworthy that IRF-1 and NF- κ B1 bind to two ISREs in the promoter of HERV-K102, which are found in the 5' LTR.^{38,39} TNF- α is a potent activator of canonical NF- κ B1 transcription factor activity, while IFN- γ and TNF- α synergize to activate IRF-1. Indeed, newer evidence confirms that M1 polarization of macrophages in humans, explicitly in response to IFN- γ signaling, is promoted via HERV-K102 expression.⁴⁰ More recently, the key role of IFN- γ in TI induction *in vivo* following BCG vaccination was confirmed by single-cell RNA sequencing.³⁷

In patients with systemic lupus erythematosus (SLE), the expression of HERV-K HML-2 *env* transcripts (HERV-K102, HERV-K106, HERV-K18, and the polymorphic HERV-K115) was inversely correlated with *TRIM28* expression in PBMCs.⁸⁸ The expression of these HML-2 envelope mRNAs correlated with increased type I IFN signaling in SLE patients. Tripartite motif-containing protein 28 (*TRIM28*) represses endogenous retroviruses in part via epigenetic marking of H3K9.⁸⁹ However, Schmidt *et al.*⁹⁰ provided evidence that it is SUMOylated (small ubiquitin-like modified) *TRIM28*, which strongly represses the expression of endogenous retroviruses, whereas with influenza A viral infection, *TRIM28* becomes inactivated by the loss of SUMOylation. The dsRNA of HERV-K HML-2 then triggers the activity of retinoic acid-inducible gene 1 (*RIG-1*), mitochondrial antiviral-signaling protein (*MAVS*), TANK-binding kinase 1 (*TBK1*), and Janus kinase 1 (*JAK1*).

Most importantly, Schmidt *et al.*⁹⁰ showed, in addition to Russ *et al.*^{40,41}, that endogenous virus activation is a protective response because they amplify antiviral/antimicrobial gene expression, including interferon responses. In influenza A infection, the DEGs induced by derepression of endogenous retroviruses⁹⁰ strongly induced a plethora of interferon-stimulated genes (ISGs), such as *IRF1*, *IRF7*, *IFNB1*, *OAS1*, *ISG15*, *CD274* (PD-L1), and *DDX58* (*RIG-1*, a sensor of double-stranded RNA). Other genes, such as *CXCL8*, *IL-6*, *CCL5*, *MX1*, *MX2*, the

complement-related genes *C1R*, *C1S*, and *CFI*, and *CSF2* (granulocyte-macrophage colony-stimulating factor), were also strongly induced. *CXCL8* expression, which activates and attracts neutrophils, was correlated with HERV-K102 expression in PBMCs in aged but not young individuals *in vivo*.⁹¹ With the induction of the interferon response and given that many of these genes have antiviral activity, it is clear that the expression of HERV-K HML-2 group member sequences helps protect the host through innate (non-antigen-specific) mechanisms.

Others have also validated that HERV-K102 particles amplify the IFN type I and inflammatory response involved in TI induction, as may be associated with the RIG-I/MDA5/MAVS system, TLRs, and the cGAS–STING system.^{92–94}

In other words, the immune system of humans exploits the expression of HERV-K102 viral genomic transcripts, along with proteins/RNAs corresponding to other HML-2 members, to greatly enhance the antiviral TI response as part of the virus-anti-virus protector “alarm” system. However, since the HERV-K102 genomes in the particles released from macrophages by lytic infection are reverse-transcribed into cDNA,^{7,8} these particles can also induce cGAS–STING upon entry into other cells. This provides an alternative (back-up) pathway for spreading and triggering type I interferon antiviral response. This is particularly useful when emerging pathogenic RNA viruses, such as SARS-CoV-2, are encountered, which tend to compromise the foreign RNA activation of the IFN response. This

alternative backup response to generate the critical IFN host defenses could be lifesaving.⁴⁴

Other data, such as a comprehensive single-cell sequencing study of bronchoalveolar lavage fluids from COVID-19 patients in various stages of disease by Ren *et al.*,⁹⁵ have clearly implicated the M1-like proinflammatory macrophages (WDR74+) in recovery from COVID-19.⁶ As well, macrophages mediated recovery (and/or prevented the onset of more severe disease) in mild cases of COVID-19 in a humanized mouse model by activating and amplifying the type I interferon response.⁴²

This means products that function as activators of TI or which can reverse TI inhibition, such as AFP antagonists, and not adaptive vaccines producing antibodies against the spike protein, would have been the preferred main public health intervention to minimize morbidity and mortality related to the emergence of SARS-CoV-2, to spread herd immunity, and to more quickly end the pandemic.⁶ In this regard, ivermectin has been identified, based on protein–protein interaction studies, as a potent AFP antagonist⁹⁶ and has reportedly rescued or prevented millions of humans from severe COVID-19 disease.⁹⁷

2.9. How mortality rate data of the Pfizer-BioNTech spike mRNA gene therapy vaccine in England illuminated the role of horizontal spreading of trained immunity in generating herd immunity

An important aspect of HERV-K102's contribution to TI

Table 1. Temporal changes (%) to COVID-19 and non-COVID-19 mortality rates per 100,000 person years in England by dose for the vaccinated and the unvaccinated⁹⁹

Parameter	A: 1st dose		B: 2nd dose		C: 3rd dose		D: 4th dose (75+ years of age)		E: Control (Omicron)	
Change period	March to April 2021		June to July 2021		October to November 2021		May to June 2022		January to February 2022	
Mortality rate type	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19
% change in the vaccinated (%)	–35	24	156	0	27	20	–32	8	–51	–31
% change in the unvaccinated (%)	–75	–21	292	–9	31	–1	–19	29	–56	–8

Notes: Dates for doses were based on the approximate date at which 50% of those aged 65 to 74 years received that dose. The percentage change refers to the change in mortality rates per 100,000 person-years by the end of the first month indicated. Total monthly mortality rates from the Office for National Statistics (ONS) in England for the vaccinated were recompiled (subgroups added up) based on the subgroup data, as the summary monthly totals did not add up correctly. Recompiling was not needed for the unvaccinated, as explained elsewhere.⁹⁸ Monthly mortality rate data (deaths per 100,000 person-years) by cause are presented in Table S1, from which the changes were calculated. Positive percentages reflect increases in mortality rate, while negative percentages reflect decreases in mortality rate. Omicron, which infected both the vaccinated and unvaccinated, served as a positive control, showing a pan-decrease in mortality rates for both groups relative to COVID-19 and non-COVID-19 mortality. More details are available at Laderoute⁹⁸. ONS data from <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland>

concerns the notion that secretion of HERV-K102 particles from lysed sebocytes as sebum to the external mucosal surfaces,⁶ which may have led to HERV-K102 shedding from the URT, such as by exhalation,^{98,99} could have been instrumental in the generation of herd immunity in the unvaccinated in England following the first Pfizer-BioNTech spike mRNA dose. The first mRNA dose is known to stimulate trained innate immunity⁶ and reduce all-cause mortality,⁵⁵ as shown for COVID-19 and non-COVID-19 deaths among the unvaccinated. (Table 1, column A)

First, in Table 1, column E, Omicron infection is shown as a positive control for the induction of TI, with both COVID-19 and non-COVID-19 mortality (per 100,000 person-years) being reduced in both the vaccinated and unvaccinated. This establishes that the methodology can detect reductions in COVID-19 and non-COVID-19 mortality among vaccinated and unvaccinated individuals.

While the first dose was associated with a reduction in both COVID-19 and non-COVID-19 mortality rates in the unvaccinated (Table 1, column A), upon the second dose (Table 1, column B), an extremely large increase in the COVID-19 deaths is evident in the unvaccinated (292% increase in death rate), which even superseded the increased mortality rate found for the vaccinated at 156%. This may have been due to the recent induction of TI by the first Pfizer dose in the vaccinated, which could result in more residual protection than in the unvaccinated. The worsening of COVID-19 mortality following the second dose is thought to be generally due to antibody-dependent enhancement (ADE) of SARS-CoV-2 infection of macrophages, driven by the induction of spike-specific IgG1/3.⁶ However, the generation of spike IgG1/3 in the URT, uniquely induced by the spike mRNA gene therapy lipid nanoparticles (LNPs),¹⁰⁰ was unusually pathogenic. This led to two additional death mechanisms, namely mRNA gene therapy “shedding” (bioweaponized HERV-K102, see Figure 4) unique to Pfizer-BioNTech^{98,99} and “bioweaponized SARS-CoV-2.”⁹⁹ Both Moderna and the Pfizer-BioNTech spike mRNA gene therapy products induced “bioweaponized SARS-CoV-2.”

Interestingly, Bowe et al.¹⁰¹ characterized cases of SARS-CoV-2 reinfections and breakthrough infections but refrained from identifying the problem as SARS-CoV-2 transmitted from the URT in a complex with spike complement-binding antibodies. It should be noted that the mechanism of death of the two bioweapons pertains not to infection per se, but to microclotting and vasculitis due to complement binding in the complex transmitted from the URT when the antigen-antibody complex reaches the microcirculation deep in the lungs of third parties.⁹⁹ For

the most part, immunity per se does not protect against clotting/vasculitis-related injuries or deaths, with one potential exception related to TI.

Apparently, IRF-1, such as that generated during the induction of HERV-K102 particles that generate TI, upregulates PD-L1 (CD274) on vascular endothelial cells,¹⁰²⁻¹⁰⁶ which could protect against vasculitis and complement/clotting injuries.¹⁰³ It is known that high levels of testosterone (such as in younger males) block the ability of IRF-1 to upregulate PD-L1 on vascular endothelium,¹⁰⁵ leaving them more prone to microclotting, vasculitis, and/or myocarditis than other sectors of the population. The induction of IRF-1 has also been reported to be associated with the derepression of endogenous retroviruses.⁹⁰ It could be inferred from the data of Grippin *et al.*¹⁰⁶ and Bowe *et al.*¹⁰¹ (both studies that pertained largely to bioweaponized SARS-CoV-2) that IRF-1-mediated upregulation of PD-L1 on vascular endothelium may also help protect against injuries and death associated with transmitted spike IgG1/3 bioweapon complexes. Accordingly, the unvaccinated adult, unlike the vaccinated, may not have had the TI memory response recently activated. This would help explain why the unvaccinated were more sensitive to death induction than the vaccinated related to bioweaponized SARS-CoV-2, during the first 30 days following the second dose in the vaccinated (Table 1, column B).

For subsequent doses (Table 1, columns C & D), the shed protector HERV-K102 became progressively less potent, as illustrated by changes in non-COVID-19 mortality rates in the unvaccinated. For example, with subsequent doses in the vaccinated, the changes in non-COVID-19 mortality rates in the unvaccinated were: -21%, -9%, -1%, and +29% (for the first, second, third, and fourth doses, respectively), showing a progressive loss of protection. This means that the use of the Process 2 Pfizer-BioNTech spike mRNA technology for vaccination purposes potentially compromised the natural spreading of herd immunity, prolonging the pandemic and expanding the level of carnage.

Figure 4 is a plausible mechanism illustrating how the Pfizer-BioNTech Process 2 (but not Process 1 used for the clinical trials) could lead to shedding (compromised and bioweaponized HERV-K102) that diminished herd immunity with each subsequent dose in England (Table 1, measured by the sequential loss of negative mortality changes for non-COVID-19 deaths in the unvaccinated). As discussed elsewhere,⁹⁹ only Pfizer-BioNTech LNPs, but not Moderna's, were inferred to be contaminated with spike protein and/or endotoxin based on indirect evidence.^{107,108} For the former, the evidence included detection of spike protein on days 0 and 1 after injection,

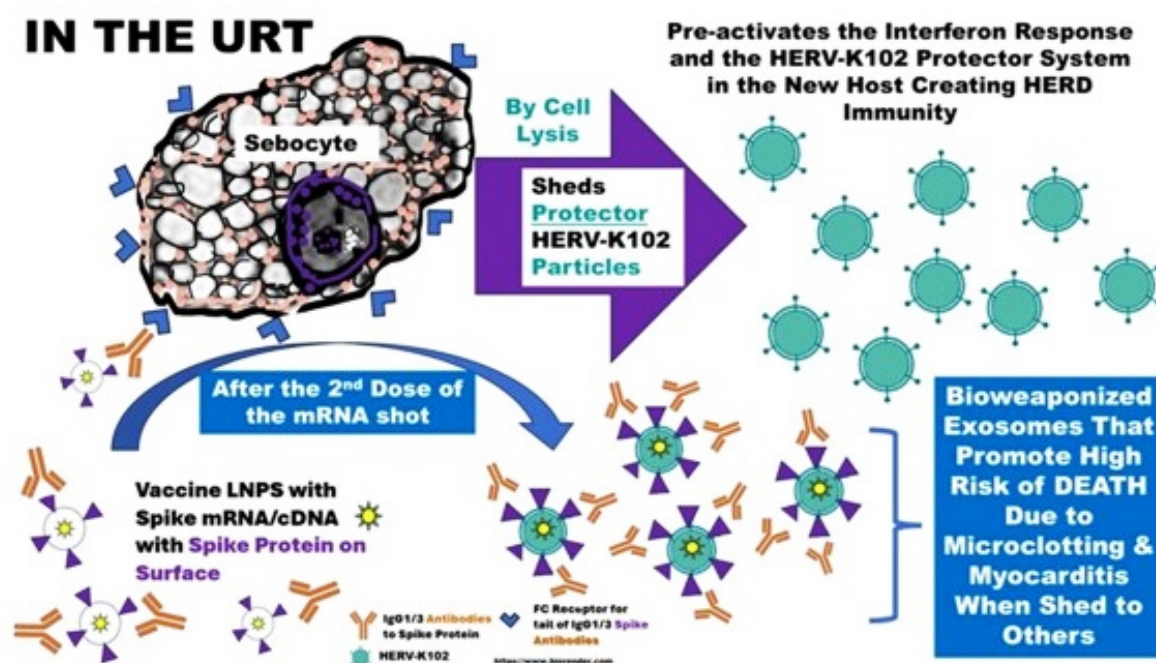


Figure 4. Proposed mechanism by which lipid nanoparticles (LNPs) from Pfizer-BioNTech Process 2, uniquely contaminated with spike protein or endotoxin^{107,108} during manufacturing, may have been targeted to sebocytes in the upper respiratory tract (URT), compromising putative herd immunity.⁹⁸ Since Moderna did not use *Escherichia coli* (*E. coli*) to generate complementary DNA (cDNA) encoding the messenger RNA (mRNA) for its COVID-19 spike mRNA gene therapy product, there was no possibility that their LNPs would be contaminated with spike protein or endotoxin. In contrast, for Process 2, Pfizer-BioNTech used *E. coli* transfected with spike cDNA plasmids, which could have generated spike protein, as well as contamination with high levels of endotoxin, cDNA, and/or mRNA/cDNA hybrids. The author retained the copyright to the image from a PowerPoint presentation given as sworn testimony at the National Citizens Inquiry on June 1, 2024.⁹⁸

which correlated with the Pfizer-BioNTech spike mRNA gene therapy product but not with the Moderna shot.¹⁰⁷ In the second case, only the Pfizer-BioNTech mRNA gene therapy LNPs, but not the Moderna mRNA LNPs, directly stimulated macrophages *in vitro* to release IL-10, CXCL8, and IL-6,¹⁰⁸ consistent with only the Pfizer-BioNTech LNPs being contaminated with endotoxin and/or spike protein, where either could target the LNPs to sebocytes and/or macrophages. However, direct testing of the spike mRNA gene therapy product vials for spike protein and quantitation of endotoxin has not been reported and is clearly warranted to validate this premise. Regardless, another group has tentatively determined that the Pfizer-BioNTech spike mRNA product was associated with a substantially increased risk of non-COVID-19 deaths and a much smaller increase in COVID-19 deaths compared with the Moderna spike mRNA product in the Florida population.¹⁰⁹ Indeed, the ratio of increased

non-COVID-19 mortality to increased COVID-19 mortality over the first 12 months following vaccination was 6.6-fold, indicating that the bulk of the excess risk of the Pfizer-BioNTech spike mRNA product pertained to non-COVID-19 deaths. These non-COVID-19 deaths pertaining to and unique to the Pfizer-BioNTech mRNA gene therapy product would be consistent with the mechanism depicted in Figure 4, referred to as shedding.

In Figure 4, the HERV-K102 particles, known to be produced in sebocytes in the URT²⁶, are targeted by the Pfizer-BioNTech spike mRNA LNPs via ADE of infection in macrophages by the IgG1/3 spike antibodies.⁶ However, a similar role for antibodies to endotoxin or endotoxin itself binding to TLR4 on macrophages in targeting LNPs to sebocytes and macrophages in tissues cannot be excluded at present. The latter is a very great concern because once endotoxin (derived from the cell walls of *Escherichia coli*) is in a product, it becomes impossible to remove.

Generally, for good manufacturing processes, there are limits on the amount of endotoxin permissible, which in all likelihood would have been greatly exceeded here. A less likely explanation would be that some spike protein could have been produced in the live *E. coli* bacteria, but since the expression vectors would have employed mammalian promoters, this would have greatly reduced the risks of spike protein production. Once targeted to sebocytes in the URT, the mRNA encodes and overexpresses the spike protein, which is incorporated into HERV-K102 particles. Presumably (and see Section 2.9.1), at least rarely, the spike mRNA, or incompletely digested cDNA, or mRNA/cDNA hybrids may be incorporated into the modified HERV-K102 particles. Since the spike mRNA gene therapy products are well known to cause the unnatural high production of IgG1 and IgG3 complement binding antibodies in the URT,⁹⁹ this means the spike complement binding IgG1/3 in the URT would also transform the protector HERV-K102 particles (which resemble exosomes) expressing spike proteins¹¹⁰

into bioweapons capable of causing vasculitis and microclotting upon transmission to the microcirculation deep in the lungs of the recipients.

Spike protein (at least S2) was detected on CD9 exosomes (meaning derived from FMs of the same size as HERV-K102 particles and potentially representing them) from about 14 days after the second dose, and this production of contaminated exosomes lasted 3–4 months.¹¹⁰ A surrogate marker or index of shedding was developed, consisting of non-COVID-19 mortality rates divided by COVID-19 mortality rates (per 100,000 person-years) for the English population based on the Office for National Statistics (ONS) published data, and the results were plotted for the vaccinated in blue and the unvaccinated in orange, as shown in Figure 5.^{98,99} As anticipated, shedding lasted 3–4 months after the second and all subsequent booster doses. However, in the unvaccinated in orange, the shedding index showed an identical pattern over time to that for the vaccinated

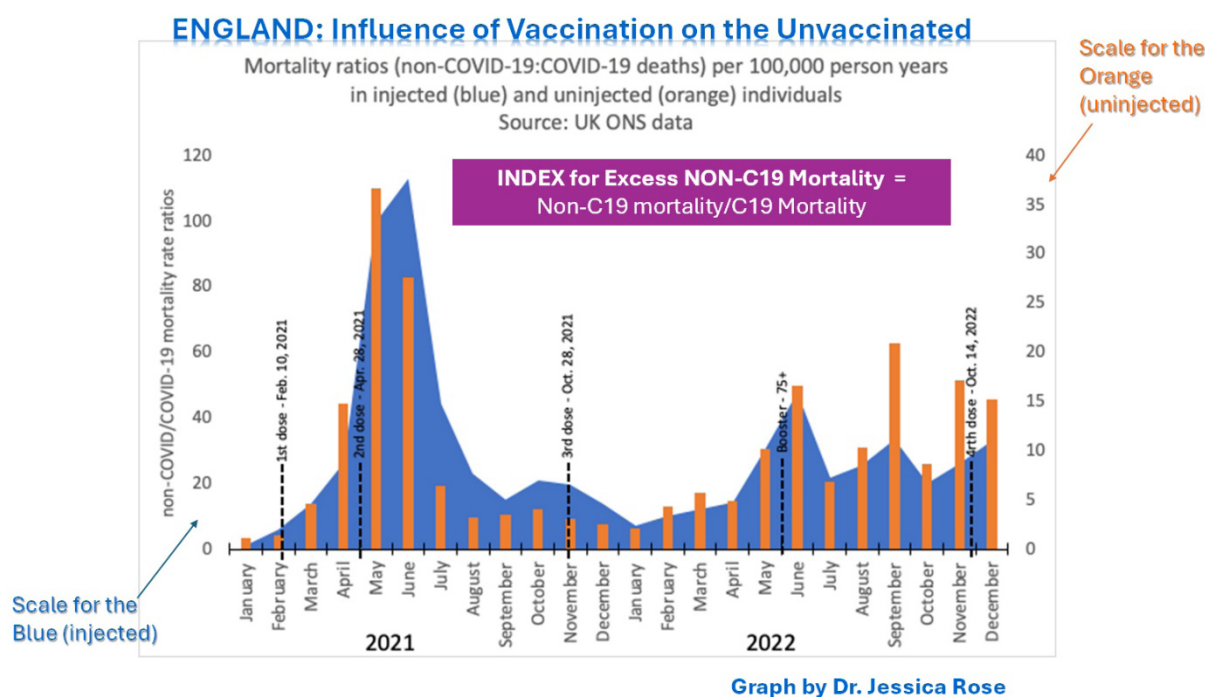


Figure 5. The ratio of non-COVID-19-to-COVID-19 mortality rate appears to provide an index of deaths putatively due to shedding of the Pfizer-BioNTech spike messenger RNA (mRNA) gene therapy product in England.⁹⁸ As detailed elsewhere and based on released and recompiled totals for mortality rates in the vaccinated based on data from the Office for National Statistics (ONS) of the United Kingdom, the Pfizer-BioNTech Process 2 manufacturing of the spike mRNA in *Escherichia coli* likely resulted in contamination of the lipid nanoparticles with spike protein and/or endotoxin which may have uniquely promoted shedding for the Pfizer-BioNTech spike mRNA but not for Moderna (also see Vaccine Adverse Event Reporting System [VAERS] data in Table S3). Corrected ONS monthly vaccinated and directly quoted unvaccinated mortality rates by cause for England are provided in Table S1 and were used to plot this graph for the vaccinated (blue) versus the unvaccinated (orange). Graph by Dr. Jessica Rose. The author retained the copyright to the image from a PowerPoint presentation given as sworn testimony at the National Citizens Inquiry on June 1, 2024.⁹⁸

from January 2021 to December 2022, but at a 3-fold lower frequency, where the scale on the right for the unvaccinated was enlarged 3-fold. It is hard to imagine why the ratio of non-COVID-19 death rate to the COVID-19 death rate (a putative index for shedding) in the unvaccinated should precisely mirror that in the vaccinated, unless one invokes the notion of shedding from the Pfizer-BioNTech fully vaccinated. Nevertheless, with the second dose, shedding deaths among the unvaccinated may have occurred slightly earlier (April-May) relative to the vaccinated. This may be because the second dose would have provoked TI memory, which would have protected the vaccinated more so than the unvaccinated, potentially for up to 60 days from the harms of shedding exposures relating to IRF-1 upregulated PD-L1 on vascular endothelium.¹⁰²⁻¹⁰⁶ The data in Table 1 Column B show almost a doubling of the risk of COVID-19 death around the second dose in the unvaccinated when compared with the vaccinated, consistent with relatively less TI present in the unvaccinated at this time. As well, in Figure S1, based on mortality data from VAERS for the vaccinated, from day 0 to day 30 following the second dose, is when the best induction of TI memory occurs (comparing across the 3 doses).

Overall, the data in Table 1, column A, suggest that transmission of putative protector HERV-K102 particles to third parties after the first dose provides heterologous protection against all-cause mortality, as illustrated for the unvaccinated. As such, these data may be the first evidence of trained innate immunity transmission contributing to herd immunity. With subsequent mRNA doses, the potency of the transmitted TI from the URT appears to decline (relative to non-COVID-19 deaths), potentially due to interference from the Pfizer-BioNTech LNPs, which compromise this form of herd immunity. By the 4th dose, it appears most of the protective HERV-K102 particles have been converted to harmful bioweapons in the URT. These observations make it very clear that the formation of IgG1/3 antibodies to respiratory pathogens in the URT, such as via mRNA gene therapy, must be avoided, if not banned, if one wishes to preserve the usefulness of immunity during pandemics or to end the pandemic sooner.

2.9.1. Messenger RNA vaccine shedding of the Pfizer-BioNTech messenger RNA gene therapy product could increase the risk of integration

To date, we have not received clarification on whether mRNA/cDNA encoding the spike may have contaminated macrophage-produced exosomes *in vivo*.¹¹⁰ Since HERV-K102 is a replication-competent foamy retrovirus and undergoes amplified integration associated with clinically significant protection against infection (Figure 2)⁸ or cancer-related death,¹⁹ this points to the possibility

of a higher risk of spike integration associated with the shedding of the “bioweaponized HERV-K102.” This shedding is a property of the Pfizer BioNTech spike mRNA gene therapy product but not the Moderna mRNA product. Due to spike and/or excessive endotoxin contamination, as shown indirectly^{107,108} for the Pfizer-BioNTech product, these LNPs may preferentially target sebocytes, which are specialized M1-like FM cells constitutively expressing HERV-K102 and known to express FCGR2A for binding activated IgG1/3.²⁶

Indeed, recent evidence by Catanzaro *et al.*¹¹¹ showed that a 20-base-pair (bp) sequence identical to that reported for the Pfizer-BioNTech spike mRNA was found to be integrated at 19p12 in an advanced bladder cancer of a 31-year-old female who, interestingly, had only received the Moderna spike mRNA gene therapy products (3 doses). Remarkably, although only a 20 bp insert, this sequence was highly oncogenic. Unfortunately, the Moderna spike mRNA sequence is not publicly available, so we cannot definitively determine whether integration was solely due to exposure to the Pfizer-BioNTech spike mRNA gene therapy product (such as through shedding).

In this regard, one might consider making it mandatory that any approved gene therapy product must contain the exact sequence of the mRNA in the product insert (USA) or product monograph (Canada), since mRNA gene therapy products are inherently prone to integration and thus genetic modification of the host, which is very dangerous and requires closer scrutiny.

Mobile elements in the human genome leave signatures in the flanking DNA, providing clues to the mechanisms used for integration. In further substantiation of this original finding of spike sequence integration *in vivo* was the finding that the 3' flanking sequence of the Catanzaro *et al.*¹¹¹ spike mRNA insert (3' TAG GAG TGGGT) at 19p12 in the bladder cancer patient's tumor (JA Catanzaro, personal communication, November 30, 2025) matched a 3' flanking sequence reported for a HERV-K102-similar sequence (i.e., based on a consensus sequence of the most recently acquired HERV-K HML-2 LTR5Hs, which would be about 99% identical in the region of the enzymes). This 3'-matching flanking sequence had been observed for an *in vitro* integration event in HeLa cells (a tumor cell line), also at 19p12 (3' TG TAG GGG TGGGT). This target site duplication sequence was reported by Monde *et al.*¹¹² in 2022. Thus, this *in vivo* integration event, reported by Catanzaro *et al.*,¹¹¹ apparently involved a HERV-K102-based integration mechanism that we know is active *in vivo* (Figure 2).^{7,8} Accordingly, mRNA gene therapy product shedding, which is unique to the Pfizer-BioNTech manufacturing process (Figure 4), might be associated

Table 2. Raw death counts (age 10+) for the first 17 months of the COVID-19 vaccine rollout (January 1, 2021, to May 31, 2022): Office for National Statistics (ONS) data released July 6, 2022, for England⁹⁹

Death category	All deaths ^a	COVID-19	ALL non-COVID-19 ^a	Background non-COVID-19 ^b	Total iatrogenic non-COVID-19 ^c	Iatrogenic early vaccine (deaths < 21 days)	Average shedding deaths in the vaccinated ^d	Estimated shedding deaths in the unvaccinated ^e	Ratio of iatrogenic to COVID-19 deaths
Raw numbers of deaths	749,115	87,472	661,643	101,013	559,553	60,917	426,602	72,034	6.4
% of total death (%) ^f	100	11.7	88.3	13.5	74.7	8.1	57.1	9.6	
% of total iatrogenic non-COVID-19 death (%)					100	10.9	76.2	12.9	

Notes: ^a Includes 1,436 non-COVID-19 deaths in the vaccinated. These were not included in the July 6, 2022, ONS data release. Note that the additional number of shedding deaths was estimated at 75%, or 1,077. ^b Includes 359 non-COVID-19 deaths in the additional 1,436 deaths not included in the July 6, 2022, ONS data release. Background refers to other expected causes of death unrelated to the pandemic or vaccination. ^c Includes 1,077 estimated additional shedding deaths not included in the July 6, 2022, ONS data release. ^d Two methods for analyzing shedding deaths in the vaccinated were used: raw death counts with onset intervals > 63 days (420,194), and excess monthly deaths above nadir counts of January 2021 (430,855), which averaged to 425,525 shedding deaths.⁹⁸ With the additional 1,077 shedding deaths not included in the July 2022 ONS data release, the total is 426,602. ^e Estimated shedding deaths in the unvaccinated used monthly deaths above a nadir of May 2022. ^f Percentages may not add up due to rounding. Based on VAERS data (Figure S1, Table S3), shedding likely contributed to many of the iatrogenic early vaccine deaths under 21 days and were thus included in the ratio of iatrogenic to COVID-19 deaths (last column). More details are available at Laderoute⁹⁸. ONS data from <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland>

with an increased risk of host genetic integration. This is thought to be due to the proximity of the spike mRNA/cDNA or undigested spike mRNA/cDNA hybrids to the HERV-K102 functional integration enzymes, putatively within the HERV-K102 particles (Figure 2). However, further work is needed to substantiate this proposed shedding mechanism, to assess the risks of integrating and genetically modifying the host, and specifically to exclude a role for Moderna mRNA exposures in this individual.

2.9.2. Pfizer-BioNTech iatrogenic non-COVID-19-to-COVID-19 death ratios in England at 6.4-fold corroborate the same reported for the excess deaths in Florida, ascribed to Pfizer-BioNTech at 6.6-fold

As shown in Table 2, there were 559,553 total iatrogenic non-COVID-19 deaths during the first 17 months of the COVID-19 vaccine rollout in England. The mRNA used during the first year primarily pertained to the Pfizer-BioNTech mRNA vaccine. Thus, about 75% of all deaths in the population aged 10 years and older in England during this time may have pertained to non-COVID-19 deaths (over 500,000). The non-COVID-19-to-COVID-19 mortality ratio was 6.4-fold in England (Table 2). This was corroborated by the Levi *et al.*¹⁰⁹ matched-cohort study of Floridians, which reported a 6.6-fold increase over a similar time frame. Kirsch¹¹³ estimated from the Levi *et al.*¹⁰⁹ paper that about 470,000 Americans may have experienced non-COVID-19 deaths over the first 12 months following the first dose of the Pfizer-BioNTech vaccine. This magnitude in the USA, wherein only about 2/3 of the mRNA injected received the Pfizer-BioNTech vaccine relative to the 1/3 that received the Moderna vaccine, is on the same scale of death reported for England, although the latter is on a smaller population reported over a similar time frame (but where the Moderna mRNA vaccine was not introduced until later). Taken altogether, it seems very hard to believe that public health agencies in England and in the USA overlooked the catastrophic loss of around half a million lives related to the Pfizer-BioNTech spike mRNA gene therapy product during the first 14 to 17 months of the mRNA vaccine rollout associated with “non-COVID-19 deaths.”

Over the 2020 to 2025 time period, almost 30% of the deaths (8,584 out of 28,728 persons) reported to the Vaccine Adverse Event Reporting System (VAERS) by January 2, 2026, for mono- and bivalent spike mRNA gene therapy products occurred within the first two days (Table S3). This onset interval precedes the time when the spike protein can be detected in the blood after vaccination.¹⁰⁷ Accordingly, for the most part, these deaths are likely related to the shedding from the vaccinator who was likely recently fully vaccinated with two doses from the Pfizer-

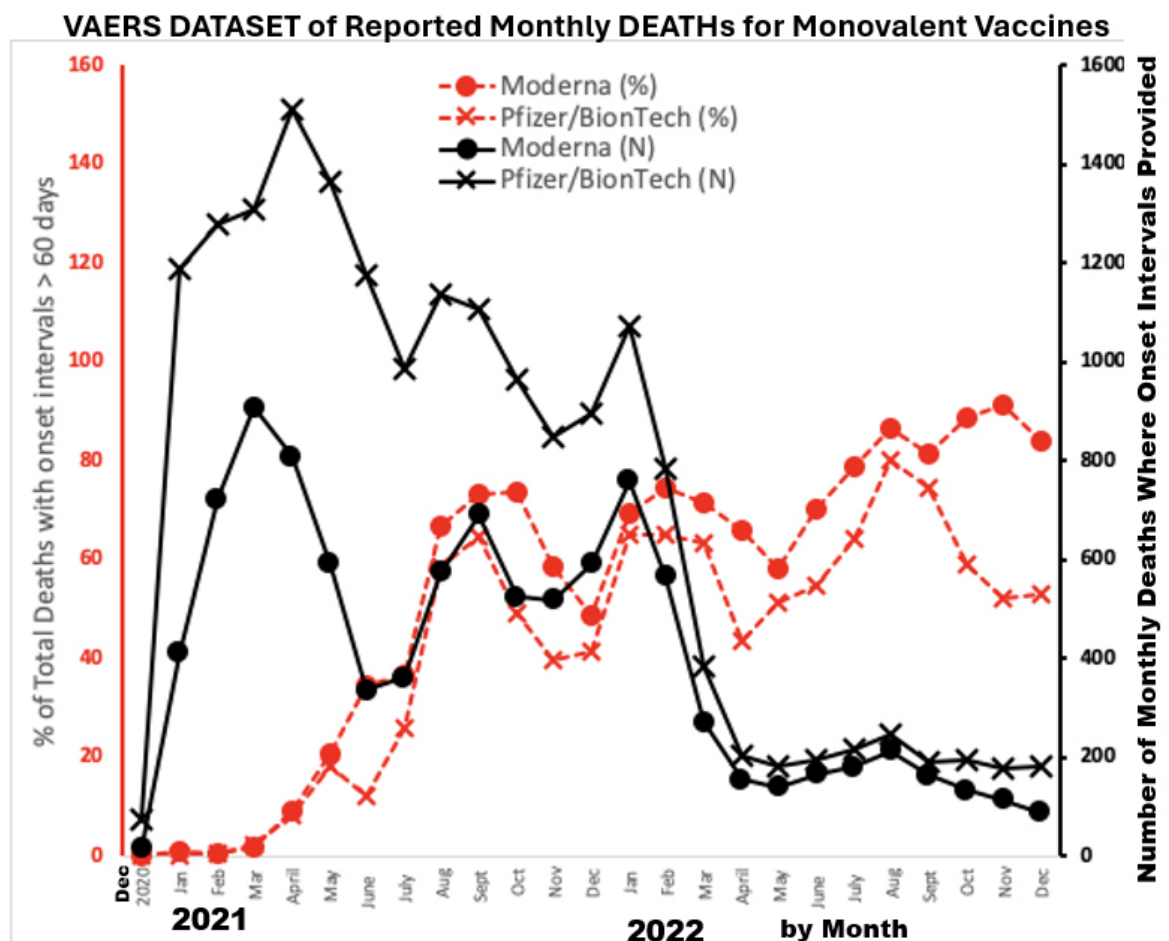


Figure 6. Center for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS) data reveal evidence corroborating at least two modes of death with onset intervals over 60 days, common to both Pfizer-BioNTech and Moderna (red plots). Both shedding (bioweaponized HERV-K102) and bioweaponized SARS-CoV-2 can cause death reported to VAERS beyond 60 days (Table S3) and the percentage of deaths with onset intervals beyond 60 days are provided by the plots in red cross symbols (X) for Pfizer-BioNTech and the solid red circles for Moderna. It is rare for a vaccine to have reports of deaths beyond 60 days unless there was involvement of ADE, which increases the subsequent risk of death often one to two years later. Since the mRNA adaptive vaccines were administered during an active pandemic, it was not surprising that after the selection⁶ and subsequent emergence of the Delta variant dominating the infections (i.e., over 50 % of the cases) around the end of June 2021,¹¹⁴ that the % of cases with onset intervals of deaths beyond 60 days also exceeded 50% as observed in July 2021. Roughly with each new round of doses administered, there was a dip of 10–30% in the percentage of deaths with onset intervals over 60 days that lasted 3–4 months as observed for both Pfizer-BioNTech and Moderna. Onset intervals less than 60 days are thought to be due to shedding from the vaccinator, which allegedly generated deaths within the first 48 h. Other deaths up to 60 days could have been due to household or workplace shedding (Table S3) from persons injected with the Process 2 Pfizer-BioNTech gene therapy product. Please note that only the Pfizer-BioNTech gene therapy product seemed to compromise the protector HERV-K102 particles, leading to the shedding of spike protein and/or mRNA, cDNA, and/or mRNA–DNA hybrids with the compromised, spike laden HERV-K102 particles. Shedding may or may not carry an increased risk of integration of spike sequences, as discussed in Section 2.9.1. Shedding lasted for 3–4 months after each round of vaccination and could affect not only those injected with the Pfizer-BioNTech gene therapy shot but also Moderna and even the unvaccinated. The cutoff date of VAERS data was August 30, 2025. Graph by Dr. Jessica Rose. The author retained the copyright to the images from a PowerPoint presentation given as sworn testimony at the National Citizens Inquiry on November 7, 2025.⁹⁹

BioNTech LNPs and who would shed for 3 to 4 months. However, it is possible that accidental injection directly into the bloodstream could also cause death. Clearly, regulatory agencies were somehow indifferent to these early deaths and did not report these deaths as suspicious, which should have sparked an intensive investigation, mandatory autopsies, and a halt to the further administration of the mRNA shots.

Many of these vaccine-associated deaths were “bioweapon-related” deaths that occurred beyond 60 days,⁹⁹ as reported to VAERS (Figures 6 & S1). In Table S3, the VAERS data for Figure 6 indicated that by January 2, 2026, 34.51% of the mRNA-associated deaths reported to VAERS occurred beyond 60 days. Deaths with onset intervals larger than 60 days are almost never reported to VAERS, except that it was common for the COVID-19 vaccines. Indeed, this initial finding should have also stalled the mRNA vaccination program, having reached over 100 deaths with onset intervals over 60 days by the end of April 2021 for Pfizer-BioNTech, by the end of May 2021 for Moderna, and by the end of August 2021 for Janssen. One could argue that even at 10 cases per manufacturer (March 13, 2021, for Pfizer-BioNTech, March 5, 2021, for Moderna, and the end of June 2021 for Janssen), the immunization campaign should have been interrupted for investigation and to require autopsies. The highest percentage of all deaths with onset intervals over 60 days occurred in January 2022 for all three manufacturers (11% associated with Pfizer-BioNTech, 10% with Moderna, and 13% with the Janssen vaccine). This was the month when many people were infected with Omicron, which, in many cases, would involve bioweaponized SARS-CoV-2 being transmitted from those who received two doses of the mRNA gene therapy shots.

2.9.3. Further evidence of the two types of bioweapons generated by spike IgG1/3 antibodies in the upper respiratory tract: Vaccine Adverse Event Reporting System data

The data used to construct the plots in Figure 6 are provided in Table S2 and were obtained from the easily searchable CDC Wonder Database for the VAERS [<https://wonder.cdc.gov/vaers.html>]. The plots shown in Figure 6 were first disclosed on November 7, 2025, at the National Citizens Inquiry.⁹⁹

The onset of both types of bioweapons would, in theory, occur simultaneously, as both depended on the generation of spike IgG1/3 in the URT, which coincided with the selection of the Delta variant by these antibodies.⁶

The results portrayed in Figure 6 confirm that (i) both

the Pfizer-BioNTech and the Moderna mRNA gene therapy shots contributed to “bioweaponized SARS-CoV-2” deaths, as denoted by the percentage of deaths with onset intervals greater than 60 days (see further details in Table S3), and (ii) that the delay in recognition of these SARS-CoV-2 deaths, as reported by *Bowe et al.*¹⁰¹, was likely due to 3–4 month masking of “bioweaponized SARS-CoV-2” deaths by the more frequent non-COVID-19 deaths (related to shedding by the Pfizer-BioNTech shots, see Figure 6). The separate plots of mortality data by manufacturer clearly indicated there were at least 2 types of bioweapons contributing to deaths beyond 60 days during 2021 and 2022 (Table S3), as explained below.

The black lines in Figure 6 refer to the total deaths reported to VAERS, separately for Moderna and Pfizer-BioNTech, for which the onset interval was known (the X-axis labeling is shown on the right in black). The Pfizer-BioNTech product was used twice as often as the Moderna product, so this explains in part why the total number of death reports of Pfizer-BioNTech deaths was higher. In the USA, the Delta variant emerged in late June 2021.¹¹⁴ With the induction of TI at the first dose of the mRNA vaccines, we see that from May 2021 to July 2021, the total number of deaths reported to VAERS declined steadily, consistent with TI protection against all-cause mortality. However, following the second dose, there were smaller peaks in total reported deaths (September to October 2021), consistent with ADE (Figure 7) and an increased risk of death. The natural and widespread Omicron exposure in January 2022, which broadened TI activation in both vaccinated and unvaccinated populations (Table 1, column E), appears to have significantly reduced pandemic fatalities (Figure 6) based on VAERS data. Thus, we see that the total number of deaths reported to VAERS dropped substantially after January–February 2022.

In Figure 6, the red lines indicate the percentage of total deaths reported to VAERS (i.e., those with onset intervals provided) that had onset intervals > 60 days. The increase in the percentage of deaths with onset intervals > 60 days first emerged in March 2021, when the very first cases of the Delta variant were selected by spike IgG1/3 in the URT (for example, Delta variants detected at <0.1% on March 1, 2021 [<https://ourworldindata.org/coronavirus>]¹¹⁴). As shown in Figure 6, each time a coordinated dose of mRNA was administered, the percentage of total deaths with onset intervals beyond 60 days decreased by 10–30% for 3–4 months, across both Moderna and Pfizer-BioNTech deaths reported to VAERS. It can be argued that this drop pertained to Pfizer-BioNTech spike mRNA gene therapy “shedding” from the vaccinator (who was likely recently vaccinated, most commonly with the Pfizer-BioNTech

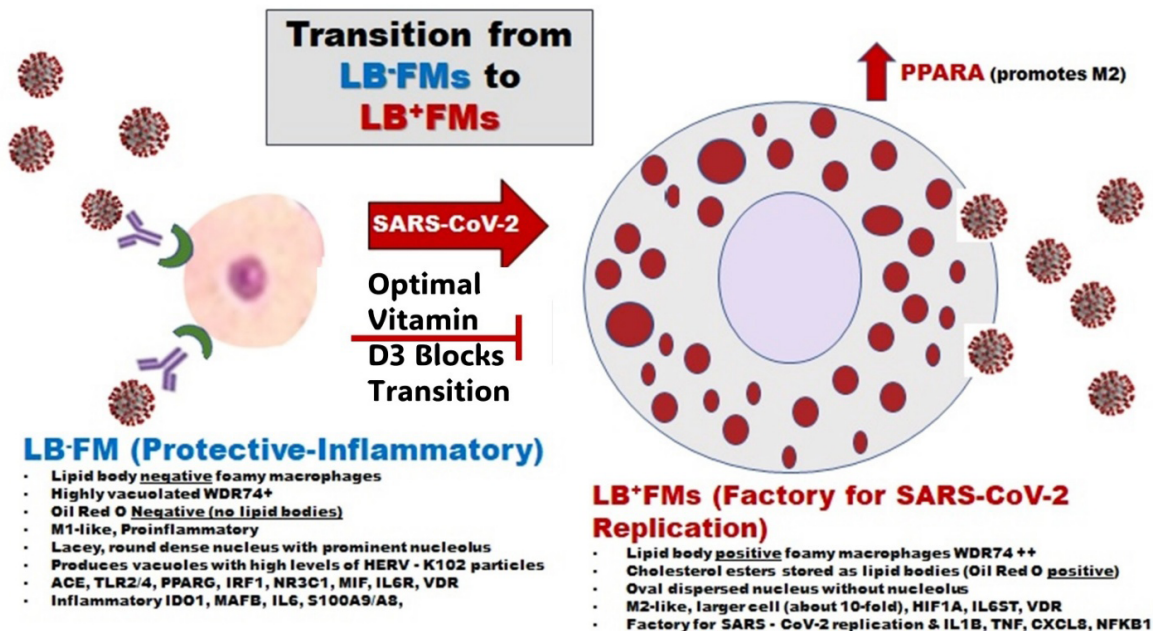


Figure 7. Optimal vitamin D3 levels block SARS-CoV-2's ability to convert lipid-body-negative (LB⁻) M1-like foamy macrophages (FMs) that produce the protective human endogenous retrovirus (HERV)-K102 particles into lipid-body-positive (LB⁺), dysfunctional M2-like FMs. This is a newer concept of the immunosenescence of macrophages (ISM) than that presented in 2015 and 2020 which simply defined ISM as the failed release of HERV-K102 particles from M1-like FM.⁷⁷⁻⁷⁸ SARS-CoV-2 gains entry to the FMs via antibody-dependent enhancement (ADE) of macrophage infection. In the presence of SARS-CoV-2, immunoglobulin G (IgG)1/3 antibodies (purple Ys) bind to the spike protein on SARS-CoV-2 virions, inducing a conformational change that reveals the fragment crystallizable (FC) receptor recognition domain of the antibodies. The Fc gamma receptor IIa (FCγRIIa; green) on LB⁻ FMs enables uptake and, thus, infection by SARS-CoV-2, even though LB⁻ FMs do not express ACE2. However, in the presence of adequate levels of active vitamin D, the conversion of M1-like FMs to dysfunctional M2 macrophages (oil red O-positive) is blocked.¹¹⁷ Only the intermediate monocytes and WD repeat domain 74 (WDR74)+ macrophages exhibit highly active vitamin D regulons among 64 cell types in the bronchoalveolar lavage fluid of COVID-19 patients.⁹⁵ Many human pathogens gain access to the M1 macrophages via ADE,⁶ which, upon transition to M2 macrophages, allows their replication in an immunologically privileged site for extended periods due to resistance to apoptosis.¹¹⁵ It is important to note that chronic disease relates to the functional status of macrophages,^[77,78,123] and where immunosenescence (dysfunction) of macrophages, as caused by active alpha-fetoprotein, has been implicated.^{77,78} Modified with permission from Laderoute.⁶ Copyright 2024 Jaypee Brothers Medical Publishers (P) Ltd.

product), where more of the deaths occurred under 60 days, and commonly on day 0 and day 1 (Figure S1, Table S3). It is also possible that shedding (from Pfizer-BioNTech), causing non-COVID-19 deaths (or injuries, see Table S4 for myocarditis/pericarditis cases), occurred in households or workplaces, particularly after 14 days and up to 60 days.

Overall, the data in Figure 6 corroborate the presence of two unexpected mechanisms: shedding unique to Pfizer-BioNTech products, and “bioweaponized SARS-CoV-2” common to both mRNA vaccines, both of which contributed to deaths beyond 60 days. Data in Table S3 indicate some post-vaccination deaths reported to VAERS did involve a diagnosis of COVID-19. For example, 36.17% of the deaths reported for 2020 to 2025 overall involved COVID-19; during the shedding peaks in June–July 2021, it was reduced to 7.97%; and in August–September 2022,

it was 56.20%.

Regarding the 60-day delay in deaths observed with the bioweapons, it is tempting to speculate that, for each dose starting with the second dose, despite the induction of IgG1/3 antibodies in the URT, some measure of TI would still be induced (Table 1, Figure S1). TI would be associated with the release of HERV-K102 particles and the concomitant release of IRF-1, which induces HERV-K102 particles. The IRF-1 in the blood could upregulate PD-L1 (CD274) on vascular endothelial cells, protecting against complement activation, microclotting, and vasculitis, as may be associated with either bioweapon.¹⁰²⁻¹⁰⁶ Vasculitis and/or myocarditis are expected to be more common with shedding than with bioweaponized SARS-CoV-2, as HERV-K102 particles induce inflammation and the level of spike protein in the bioweaponized HERV-K102 particles

would be much higher due to the overproduction of spike protein with the entry of the mRNA from the LNPs into the sebocytes. Indeed, as shown in Table S4, over 99% of cases of myocarditis injury were non-COVID-19 cases, and 29% (Moderna) to 35% (Pfizer-BioNTech) involved injuries within the first 48 h. This time limit of 48 hours for a serious adverse event is consistent with shedding (referring to bioweaponized HERV-K102) from the vaccinator as measured for deaths reported to VAERS (Figure S1, Table S3). This strongly suggests that shedding caused many, if not most, of the myocarditis and/or pericarditis cases. As such, this finding may suggest that the risk of myocarditis/pericarditis was significantly elevated with shedding caused by the Pfizer-BioNTech mRNA vaccine, compared with SARS-CoV-2 infection or even bioweaponized SARS-CoV-2. As well, there was a predilection for male cases in the 18–29 age group (Table S4), especially for the Pfizer-BioNTech vaccine, as has been reported for myocarditis and/or pericarditis risks where high testosterone could limit the upregulation of protective PD-L1 on vascular endothelium by IRF-1.¹⁰⁵

The results in Table S5, facilitated by inferences made from Table S3, show that the year with the most reported COVID-19 vaccine-associated deaths in VAERS was by far 2021 (70.70%), which was when shedding deaths dominated (Table S3). Even in 2021, a significant proportion of the reported deaths (3,684/20,313 or 12.82%) represented breakthrough infections, clearly indicating the COVID-19 vaccines were not preventing infections (lethal or not) and therefore were clearly not safe and effective. However, the year in which the highest relative level of COVID-19-associated deaths occurred was in fact 2022 (Table S5). Here, of the 6,222 deaths reported to VAERS, 2,802 cases (45.03%) involved COVID-19 breakthrough infections. These breakthrough infections were studied by *Bowe et al.*¹⁰¹, and unlike typical SARS-CoV-2 deaths associated with pneumonias, the rates of injury, hospitalization, and deaths were highly increased and involved cardiovascular issues affecting all ages (although there was still a predilection for the older age groups). The latter findings validate the implication of bioweaponized SARS-CoV-2 and microclotting-vasculitis in the injuries and deaths.⁹⁹ However, it should be appreciated that the highest monthly level of COVID-19-associated deaths in 2022 was in January 2022, associated with the common transmission of Omicron. When transmitted from the URT of the unvaccinated, it would have been a normal SARS-CoV-2 infection. When transmitted from persons who had at least 2 doses of the mRNA gene therapy products, this would have involved the bioweaponized SARS-CoV-2 with dire outcomes. Regardless of the outcomes, it is clear from the VAERS data in Figure 6 that Omicron, and not

the COVID-19 vaccines, more or less ended the pandemic. TI appears to have been causally associated with negative excess mortality following the onset of Omicron worldwide (data not shown¹¹⁴). In Canada, due to the postponement of the second dose in elders by four months, the negative excess all-cause mortality associated with TI lasted a long time and resulted in a greatly reduced cumulative COVID-19 deaths per million population. By September 28, 2025, the cumulative deaths per million for the USA, the UK, and Canada were 3,596, 3,404, and 1,424, respectively (Figure S2). The USA did not postpone the second dose, while the UK did, with at least a three-month delay at the beginning. This provides direct proof that immunity related to TI did flatten the curve, while the adaptive immunity conferred by COVID-19 vaccines did not, as was entirely anticipated.⁶

2.10. Important role of vitamin D3 in innate immunity and other protective measures

As shown in Figure 7, SARS-CoV-2 enters FMs, including sebocytes, via the ADE phenomenon as described in detail elsewhere.⁶ Presumably, by inducing AFP mRNA and protein and/or promoting the overactivity of the EGFR/ERBB2 malignancy-conferring pathway,⁷¹ this triggers the conversion of M1-like FMs to M2 with serious consequences. This causes the loss of host TI heterologous protection against all-cause mortality, including pathogens and cancers, while providing a haven for ongoing pathogen replication.¹¹⁵ This exploitation of the PI3K/Akt/mTOR epithelial–mesenchymal transition (EMT) pathway is not only common to many human pathogens but also to cancers and chronic diseases, including cardiovascular disease,⁷⁷ autoimmunity, allergies, and even neurodegenerative diseases.⁷⁸ It has been proposed that active AFP, which mediates ISM by binding to the 67 kD AFP receptor,^{81,82} causes chronic disease and an increased susceptibility to cancer and pathogens.^{77,78} Importantly, DHEA, the youth hormone that essentially provides an anti-stress response to cortisol,⁷⁸ and not DHEA-S (the inactive form of DHEA), binds and inactivates active AFP, reducing the risk of ISM. As we age or become exposed to stress, DHEA levels decline, increasing the likelihood of developing ISM with the next viral infection. This causes chronic disease, which is likely to reduce PD-L1 expression on vascular endothelium due to lower circulating IRF-1 levels.¹⁰² This reduction would make the host more prone to the spike mRNA gene therapy-generated bioweapons.

A priori, a substantial way to avoid ADE-mediated SARS-CoV-2 infection of macrophages/sebocytes is to avoid adaptive immunity vaccines that generate IgG1 and IgG3 ADE-mediating antibodies to the spike protein (Figure 7), especially those inappropriately created in the

URT by the spike mRNA gene therapy technology. This should help establish and maintain herd immunity, TI, and prevent the selection of variants to end the pandemic sooner.⁶ To prevent the creation of deadly bioweapons, such as bioweaponized HERV-K102 (shedding causing non-COVID-19 injuries and deaths) and bioweaponized SARS-CoV-2 (transmission causing COVID-19 associated injuries and deaths), where both types of bioweapons via activation of complement generate microclotting, vasculitis, and serious cardiovascular diseases, the simple solution is to ban the use of mRNA for immunization purposes. As well, maintaining a healthy lifestyle, supplementing with nutrients, sunbathing, and spending time outdoors to benefit from near-infrared exposure, while implementing stress-reduction interventions like yoga, would probably help maintain sufficient DHEA levels to prevent the age-related onset of ISM.^{77,78} Additionally, readily available AFP antagonists such as zinc, genistein, vitamin D3, and, in the USA, 7-keto-DHEA could be used, particularly when hypertension lasting more than two weeks is observed (DHEA/7-keto-DHEA is banned in Canada). A growing number of states are providing over-the-counter access to ivermectin, which might be the most potent AFP antagonist known,⁹⁶ and thus may reduce chronic disease and health care costs more generally. It should be noted that epigallocatechin-3-gallate (EGCG) of green tea is now known to favor M2-like polarization of macrophages and should not be utilized to promote recovery from chronic diseases.¹¹⁶

The proposal that optimal plasma levels of vitamin D3 would be sufficient to prevent serious disease and death, generally from ISM and specifically from SARS-CoV-2 infection, as shown in [Figure 7](#), may be game-changing. When vitamin D3 levels are sufficient, the activated VDR can prevent mitogen-activated protein kinase 8 (MAPK8) phosphorylation, blocking the transition from lipid body-negative FMs to lipid body-positive FMs ([Figure 7](#)).¹¹⁷ Interestingly, among the 64 cell types in the BALF of patients with COVID-19, only the CD14/CD16 intermediate monocytes and the M1-like macrophages producing HERV-K102 particles displayed a highly activated VDR regulon.⁹⁵ This confirms that the main mechanism by which optimal vitamin D3 blood levels protect the host against severe disease and death is by promoting TI, which protects against and reverses chronic disease.

More recently, ivermectin has been identified as a highly potent AFP antagonist based on overlapping protein-protein interaction networks in SARS-CoV-2 infection shared with an ovarian breast cancer cell line, as discussed elsewhere.⁹⁶ As mentioned, many studies support the contention that ivermectin prevents or promotes recovery

from SARS-CoV-2 infection.⁹⁷ Additionally, evidence suggests that flavonoids and benzimidazoles may interfere with the signaling pathway of AFP by reversing EMT, i.e., the PI3K-Akt-mTOR pathway,^{118,119} and may synergize with ivermectin in preventing and treating diseases, infectious or not.

3. Conclusion

Without consideration of the release of the protector HERV-K102 particles by lysis from FMs, it would be very hard indeed to explain how a cell that disappears could generate potent TI protection against all-cause mortality, including the generation of sterilizing immunity. The latter has been inferred based on the increased integration of HERV-K102 correlated with resistance to HIV-1 acquisition ([Figure 2](#)).⁸ One might consider that this disappearing act may have thwarted the ability to fully understand what TI really is and how it mediates potent protection against emerging pathogens and cancers. Certainly, it explains the late discovery of TI in 2011¹ and the HERV-K102 protector system in 2007^{7,8}, which was elaborated further in 2015⁷⁸, 2018¹⁴, and again in 2024.⁶ This is despite the fact that the M1 versus M2 tumor-associated macrophage paradigm associated with recovery versus disease progression (respectively) has been known and evaluated in the cancer field since at least the early 1990s.¹²⁰

Taken altogether, for the functional definition of TI, single-cell sequencing has revealed that enhanced cytokine and chemokine activation upon rechallenge may be optional and not necessary for TI. Rather, it seems that the cytokines TNF- α , IFN- γ , and/or the transcription factor NF- κ B1 converge with IRF-1 at ISREs to induce transcription of a protective foamy virus, HERV-K102, which generates FMs.⁶⁻⁸ This replication-competent endogenous foamy retrovirus, encoded on Chromosome 1 at 1q22 and unique to humans, not only generates TI but also greatly amplifies it through epigenetic and genomic changes in the human genome, reflecting, in part, increased integration. Thus, TI can be as vital and rigorous as adaptive immunity, including the use of recombination events in the human genome to amplify and enhance the memory response. Glycolysis is required to support cholesterol production for foam cell formation associated with HERV-K102 replication and particle production. It should be noted that although the PI3K/Akt/mTOR pathway induces foam cell formation, interfering with NF- κ B1 does not block it.¹²¹ This means the inflammatory component, such as that induced by NF- κ B1, is not an absolute requirement for TI, as others have observed in single-cell sequencing studies.^{36,37} Therefore, the current definition of TI should be revised to emphasize the salient role of HERV-K102 particles in mediating protection.

A summary of the multitude of ways that HERV-K102 particles manifest their potent anti-viral stance and the broader protection of *H. sapiens* against morbidity and mortality is captured in the graphic abstract. These innate immunity mechanisms have been broadened to include protection against microclotting and vasculitis associated with the bioweapons created by the spike mRNA gene therapy products. TI, unlike adaptive immunity, may protect the vascular endothelium from complement activation, microclotting, and vasculitis through the upregulation of PD-L1 (CD274) by the release of IRF-1¹⁰²⁻¹⁰⁶ and also HERV-K102 particles⁹⁰ associated with TI. IRF-1 is germane to the expression of the full-length HERV-K102 provirus, its replication, and thus TI.

It should be noted that the inappropriate and dangerous generation of IgG1/3 anti-spike antibodies in the URT using mRNA gene therapy technology shifted a pandemic involving SARS-CoV-2 infection, in which the aged and sick were preferentially susceptible to death, to one in which all age groups became susceptible regardless of health or immunity status,^{99,101} although the elderly were still at a higher risk of any cause of death. For the most part, adaptive immunity did not offer much protection against injury such as myocarditis (Table S4) or microclotting-related death (i.e., from either of the two bioweapons). Most certainly, the spike IgG antibodies in the URT or circulation, the latter of which was the industry-standard measure of immunity to SARS-CoV-2, were erroneously used as a surrogate marker of vaccine efficacy when ironically, these spike IgG antibodies caused the majority of injuries and deaths, including to younger and healthy individuals and even the unvaccinated.^{98,99,101} On the other hand, recent TI activity did serve to provide some level of protection against vasculitis and microclotting-associated injury and death, which apparently lasted up to 60 days. Infants and children were still less susceptible to bioweapons than healthy adults (Tables S3 and S4), probably due to the frequent activation of TI with each new virus they commonly encountered.

The limitations of this discovery that HERV-K102 mediates the protection associated with TI induction primarily stem from our gaps in knowledge. This includes how to clinically exploit this new finding and the current lack of randomized clinical trials to demonstrate the efficacy of HERV-K102 induction in promoting overall health and/or reducing the risks of pandemics, rapidly advancing cancers, and other chronic diseases. Clearly, more research is needed to better understand HERV-K102 protector mechanisms, including the direct demonstration of its putative oncolytic and virolytic activity, how best to screen populations for ISM issues that inhibit TI so remedies can

be taken proactively, and the discovery of additional AFP antagonists. At present, to significantly reduce health care costs and prepare for the next pandemic, populations need to optimize their vitamin D3 and DHEA levels. This means that most hospitals and private laboratories should offer these prognostic tests. For DHEA, it is more specifically the ratio of DHEA to cortisol that is prognostic, but invariably only the DHEA-S inactive form is tested in hospitals and private laboratories. This needs to change if we wish to improve health care rather than stay the course with the existing “modus operandi” of disease care. For overall general health protection and in anticipation of future pandemics, it would be very useful for ivermectin, benzimidazoles, and 7-keto-DHEA to be made available over the counter across all of North America. The 7-keto-DHEA is preferred over DHEA as it cannot be converted to sex hormones, which, in women, DHEA may result in increased testosterone side effects.

In conclusion, it is strongly suggested that foam cell formation involving HERV-K102 particle production in FMs would better characterize and thus define TI since TI does not necessarily involve a heightened production of proinflammatory factors upon rechallenge. Furthermore, the HERV-K102 protector system can explain how sterilizing immunity is possible, and this discussion has revealed a novel mechanism that promotes herd immunity, giving the TI concept new meaning. From Figure 6 and Tables S3 and S5, it is clear that Omicron infections in vaccinated and unvaccinated individuals ended the pandemic, not the COVID-19 vaccines. Indeed, one might argue that boosting with the advent of the bivalent mRNA vaccines only served to prolong the pandemic and enhance the risk of death among the elderly. On the other hand, Canada, by postponing the second dose of the mRNA gene therapy products by 4 months, did seem to flatten the curve somewhat (Figure S2) when compared with the USA or the United Kingdom, which had a 2.53- and 2.39-fold higher number of cumulative COVID-19 deaths per million, respectively, than Canada (by September 28, 2025). Since, for the most part, the first dose induced only TI and not the dangerous spike IgG antibodies, this may not only have saved lives but also enhanced protection in the unimmunized through the novel herd immunity mechanism proposed here. Thus, to some extent, this data validates the power of TI to control a pandemic.

It is imperative that future work elucidate how HERV-K102 and the various HERV-K HML-2 elements participate in establishing and maintaining TI, and explore how HERV-K102 particle production might be induced not by vaccination but by nutraceutical means, for example, beta-glucans found in simple foods like oatmeal.¹²² Given

the fact that macrophage dysfunction (defined here as the failed lytic release of HERV-K102 particles from M1-like FMs [see Figure 7]) is increasingly recognized as the cause of chronic disease,^{77,78,123} the exploration of HERV-K102 particles in health and disease should have important ramifications for future health care and public health more generally. The time has come to rigorously test AFP antagonists and TI initiators in randomized clinical trials for their utility in chronic disease prevention and treatment, particularly given the current heightened incidence of rapidly progressing tumors and infections resulting from the inappropriate use of mRNA technology for immunization.⁶

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References

1. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9(5):355-361. doi: 10.1016/j.chom.2011.04.006
2. Mitroulis I, Ruppova K, Wang B, *et al*. Modulation of myelopoiesis progenitors is an integral component of trained immunity. *Cell*. 2018;172(1-2):147-161.e12. doi: 10.1016/j.cell.2017.11.034
3. Cirovic B, de Bree LCJ, Groh L, *et al*. BCG vaccination in humans elicits trained immunity via the hematopoietic progenitor compartment. *Cell Host Microbe*. 2020;28(2):322-334.e5. doi: 10.1016/j.chom.2020.05.014
4. Al B, Suen TK, Placek K, Netea MG. Innate (learned) memory. *J Allergy Clin Immunol*. 2023;152(3):551-566. doi: 10.1016/j.jaci.2023.06.014
5. Vuscan P, Kischkel B, Joosten LAB, Netea MG. Trained immunity: General and emerging concepts. *Immunol Rev*. 2024;323(1):164-185. doi: 10.1111/imr.13326
6. Laderoute MP. Chapter 17. Controversies Concerning the Immunology of the COVID-19 Adaptive Immunity Vaccines. In: J Varon, PE Marik, M Rendell, J Iglesias, C de Souza, P Prabhudesai, eds. *Controversies in the Pandemic*. New Delhi: Jaypee Brothers Medical Publishers Ltd.; 2024.

7. Laderoute MP, Giulivi A, Larocque L, *et al.* The replicative activity of human endogenous retrovirus K102 (HERV-K102) with HIV viremia. *AIDS*. 2007;21(18):2417-2424.
doi: 10.1097/QAD.0b013e3282f14d64
8. Laderoute MP, Larocque LJ, Giulivi A, Diaz-Mitoma F. Further evidence that human endogenous retrovirus K102 is a replication competent foamy virus that may antagonize HIV-1 replication. *Open AIDS J*. 2015;9(1):112-122.
doi: 10.2174/1874613601509010112
9. Fischer H, Fumicz J, Rossiter H, *et al.* Holocrine secretion of sebum is a unique DNase2-dependent mode of programmed cell death. *J Invest Dermatol*. 2017;137(3):587-594.
doi: 10.1016/j.jid.2016.10.017
10. Brinzevich D, Young GR, Sebra R, *et al.* HIV-1 interacts with human endogenous retrovirus K (HML-2) envelopes derived from human primary lymphocytes. *J Virol*. 2014;88(11):6213-6223.
doi: 10.1128/JVI.00669-14
11. Subramanian RP, Wildschutte JH, Russo C, Coffin JM. Identification, characterization, and comparative genomic distribution of the HERV-K (HML-2) group of human endogenous retroviruses. *Retrovirology*. 2011;8(1):90.
doi: 10.1186/1742-4690-8-90
12. Bodem J, Schied T, Gabriel R, Rammling M, Rethwilm A. Foamy virus nuclear RNA export is distinct from that of other retroviruses. *J Virol*. 2011;85(5):2333-2341.
doi: 10.1128/JVI.01518-10
13. Bhardwaj N, Maldarelli F, Mellors J, Coffin JM. HIV-1 infection leads to increased transcription of human endogenous retrovirus HERV-K (HML-2) proviruses in vivo but not to increased virion production. *J Virol*. 2014;88(19):11108-11120.
doi: 10.1128/JVI.01623-14
14. Laderoute MP. Clues to finding correlates of risk/protection for HIV-1 vaccines [version 2; peer review: 2 approved with reservations]. *F1000Research*. 2018;6:868.
doi: 10.12688/f1000research.11818.2
15. Morozov VA, Dao Thi VL, Denner J. The transmembrane protein of the human endogenous retrovirus--K (HERV-K) modulates cytokine release and gene expression. *PLoS ONE*. 2013;8(8):e70399.
doi: 10.1371/journal.pone.0070399
16. Rivas SR, Valdez MJM, Govindarajan V, *et al.* The role of HERV-K in cancer stemness. *Viruses*. 2022;14(9):2019.
doi: 10.3390/v14092019
17. Wang-Johanning F, Rycaj K, Plummer JB, *et al.* Immunotherapeutic potential of anti-human endogenous retrovirus-K envelope protein antibodies in targeting breast tumors. *J Natl Cancer Inst*. 2012;104(3):189-210.
doi: 10.1093/jnci/djr540
18. Li M, Radvanyi L, Yin B, *et al.* Downregulation of human endogenous retrovirus type K (HERV-K) viral *env* RNA in pancreatic cancer cells decreases cell proliferation and tumor growth. *Clin Cancer Res*. 2017;23(19):5892-5911.
doi: 10.1158/1078-0432.CCR-17-0001
19. Ng KW, Boumelha J, Enfield KSS, *et al.* Antibodies against endogenous retroviruses promote lung cancer immunotherapy. *Nature*. 2023;616(7957):563-573.
doi: 10.1038/s41586-023-05771-9
20. Nguyen QTT, Shin SG, Nguyen TTT, Lee KY, McClelland M, Lee EJ. Human endogenous retrovirus-K envelope protein is aberrantly expressed in serous ovarian cancer and promotes chemosensitivity via NF- κ B/P-glycoprotein pathway inhibition. *J Ovarian Res*. 2025;18(1):146.
doi: 10.1186/s13048-025-01722-2
21. Gong Q, Xu R. Subtype-specific human endogenous retrovirus K102 envelope protein is a novel serum immunosuppressive biomarker of cancer. *Front Immunol*. 2025;15:1533740.
doi: 10.3389/fimmu.2024.1533740
22. Li M, Zheng S, Gong Q, *et al.* HERV-K TM subunit elicits CD8⁺ T cell anergy and tumor immune evasion via targeting CD3 coreceptor ϵ in AML and PDAC. *Adv Sci*. 2026;13(1):e17432.
doi: 10.1002/advs.202417432
23. Linial ML. Foamy viruses are unconventional retroviruses. *J Virol*. 1999;73(3):1747-1755.
doi: 10.1128/JVI.73.3.1747-1755.1999
24. Meiering CD, Comstock KE, Linial ML. Multiple integrations of human foamy virus in persistently infected human erythroleukemia cells. *J Virol*. 2000;74(4):1718-1726.
doi: 10.1128/jvi.74.4.1718-1726.2000
25. Fowke KR, Nagelkerke NJ, Kimani J, *et al.* Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. *Lancet*. 1996;348(9038):1347-1351.
doi: 10.1016/S0140-6736(95)12269-2
26. Nelson AM, Zhao W, Gilliland KL, Zaenglein AL, Liu W, Thiboutot DM. Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells. *J Clin Invest*. 2008;118(4):1468-1478.
doi: 10.1172/JCI33869
27. Diaz-Mitoma F, Turgonyi E, Kumar A, Lim W, Larocque L, Hyde BM. Clinical improvement in chronic fatigue syndrome is associated with enhanced natural killer cell-mediated cytotoxicity: the results of a pilot study with

- isoprinosine*. *J Chronic Fatigue Syndr*. 2003;11(2):71–95.
doi: 10.1300/J092v11n02_06
28. Stevens DL. Chronic fatigue. *West J Med*. 2001;175(5):315–319.
doi: 10.1136/ewjm.175.5.315
 29. Magiorkinis G, Blanco-Melo D, Belshaw R. The decline of human endogenous retroviruses: extinction and survival. *Retrovirology*. 2015;12(1):8.
doi: 10.1186/s12977-015-0136-x
 30. Meiering CD, Linial ML. Historical perspective of foamy virus epidemiology and infection. *Clin Microbiol Rev*. 2001;14(1):165–176.
doi: 10.1128/CMR.14.1.165-176.2001
 31. Heinkelein M, Hoffmann U, Lücke M, *et al*. Experimental therapy of allogeneic solid tumors induced in athymic mice with suicide gene-transducing replication-competent foamy virus vectors. *Cancer Gene Ther*. 2005;12(12):947–953.
doi: 10.1038/sj.cgt.7700855
 32. Mikovits JA, Hoffman PM, Rethwilm A, Ruscetti FW. In vitro infection of primary and retrovirus-infected human leukocytes by human foamy virus. *J Virol*. 1996;70(5):2774–2780.
doi: 10.1128/JVI.70.5.2774-2780.1996
 33. Watkins TBK, Lim EL, Petkovic M, *et al*. Pervasive chromosomal instability and karyotype order in tumour evolution. *Nature*. 2020;587(7832):126–132.
doi: 10.1038/s41586-020-2698-6
 34. Apostolou E, Rizwan M, Moustardas P, *et al*. Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgic-encephalomyelitis/chronic fatigue syndrome. *Front Immunol*. 2022;13:949787.
doi: 10.3389/fimmu.2022.949787
 35. Wolfel R, Corman VM, Guggemos W, *et al*. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020;581(7809):465–469.
doi: 10.1038/s41586-020-2196-x
 36. Zhang B, Moorlag SJ, Dominguez-Andres J, *et al*. Single-cell RNA sequencing reveals induction of distinct trained-immunity programs in human monocytes. *J Clin Invest*. 2022;132(7):e147719.
doi: 10.1172/JCI147719
 37. Li W, Moorlag SJCFM, Koeken VACM, *et al*. A single-cell view on host immune transcriptional response to in vivo BCG-induced trained immunity. *Cell Rep*. 2023;42(5):112487.
doi: 10.1016/j.celrep.2023.112487
 38. Manghera M, Ferguson-Parry J, Lin R, Douville RN. NF- κ B and IRF1 induce endogenous retrovirus K expression via interferon-stimulated response elements in its 5' long terminal repeat. *J Virol*. 2016;90(20):9338–9349.
doi: 10.1128/JVI.01503-16
 39. Manghera M, Douville RN. Endogenous retrovirus-K promoter: a landing strip for inflammatory transcription factors? *Retrovirology*. 2013;10(1):16.
doi: 10.1186/1742-4690-10-16
 40. Russ E, Mikhalevich N, Iordanskiy S. Expression of human endogenous retrovirus group K (HERV-K) HML-2 correlates with immune activation of macrophages and type I interferon response. *Microbiol Spectr*. 2023;11(2):e0443822.
doi: 10.1128/spectrum.04438-22
 41. Russ E, Iordanskiy S. Endogenous retroviruses as modulators of innate immunity. *Pathogens*. 2023;12(2):162.
doi: 10.3390/pathogens12020162
 42. Kenney DJ, O'Connell AK, Turcinovic J, *et al*. Humanized mice reveal a macrophage-enriched gene signature defining human lung tissue protection during SARS-CoV-2 infection. *Cell Rep*. 2022;39(3):110714.
doi: 10.1016/j.celrep.2022.110714
 43. Grow EJ, Flynn RA, Chavez SL, *et al*. Intrinsic retroviral reactivation in human preimplantation embryos and pluripotent cells. *Nature*. 2015;522(7555):221–225.
doi: 10.1038/nature14308
 44. Guo Y, Yang C, Liu Y, *et al*. High expression of HERV-K (HML-2) might stimulate interferon in COVID-19 patients. *Viruses*. 2022;14(5):996.
doi: 10.3390/v14050996
 45. Plochmann K, Horn A, Gschmack E, *et al*. Heparan sulfate is an attachment factor for foamy virus entry. *J Virol*. 2012;86(18):10028–10035.
doi: 10.1128/JVI.00051-12
 46. Robinson-McCarthy LR, McCarthy KR, Raaben M, *et al*. Reconstruction of the cell entry pathway of an extinct virus. *PLoS Pathog*. 2018;14(8):e1007123.
doi: 10.1371/journal.ppat.1007123
 47. Wang Q, Yu Y, Zhuang J, Liu R, Sun C. Demystifying the cGAS-STING pathway: precision regulation in the tumor immune microenvironment. *Mol Cancer*. 2025;24(1):178.
doi: 10.1186/s12943-025-02380-0
 48. Mensurado S, Blanco-Domínguez R, Silva-Santos B. The emerging roles of $\gamma\delta$ T cells in cancer immunotherapy. *Nat Rev Clin Oncol*. 2023;20(3):178–191.
doi: 10.1038/s41571-022-00722-1
 49. Schönefeldt S, Wais T, Herling M, *et al*. The diverse roles

- of $\gamma\delta$ T cells in cancer: from rapid immunity to aggressive lymphoma. *Cancers*. 2021;13(24):6212.
doi: 10.3390/cancers13246212
50. Cieslak SG, Shahbazi R. Gamma delta T cells and their immunotherapeutic potential in cancer. *Biomark Res*. 2025;13(1):51.
doi: 10.1186/s40364-025-00762-6
 51. Hajishengallis G, Netea MG, Chavakis T. Trained immunity in chronic inflammatory diseases and cancer. *Nat Rev Immunol*. 2025;25(7):497-514.
doi: 10.1038/s41577-025-01132-x
 52. Drummer C 4th, Saaoud F, Shao Y, *et al*. Trained immunity and reactivity of macrophages and endothelial cells. *Arterioscler Thromb Vasc Biol*. 2021;41(3):1032-1046.
doi: 10.1161/ATVBAHA.120.315452
 53. Maslova A, Ramirez RN, Ma K, *et al*. Deep learning of immune cell differentiation. *Proc Natl Acad Sci USA*. 2020;117(41):25655-25666.
doi: 10.1073/pnas.2011795117
 54. Benjaskulluecha S, Boonmee A, Pattarakankul T, Wongprom B, Klomsing J, Palaga T. Screening of compounds to identify novel epigenetic regulatory factors that affect innate immune memory in macrophages. *Sci Rep*. 2022;12(1):1912.
doi: 10.1038/s41598-022-05929-x
 55. Xu S, Huang R, Sy LS, *et al*. COVID-19 vaccination and non-COVID-19 mortality risk—seven integrated health care organizations, United States, December 14, 2020–July 31, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(43):1520–1524.
doi: 10.15585/mmwr.mm7043e2
 56. Saeed S, Quintin J, Kerstens HH, *et al*. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science*. 2014;345(6204):1251086.
doi: 10.1126/science.1251086
 57. Arts RJW, Joosten LAB, Netea MG. The potential role of trained immunity in autoimmune and autoinflammatory disorders. *Front Immunol*. 2018;9:298.
doi: 10.3389/fimmu.2018.00298
 58. Cheng SC, Quintin J, Cramer RA, *et al*. mTOR- and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science*. 2014;345(6204):1250684.
doi: 10.1126/science.1250684
 59. Arts RJW, Moorlag SJCFM, Novakovic B, *et al*. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. *Cell Host Microbe*. 2018;23(1):89–100.e5.
doi: 10.1016/j.chom.2017.12.010
 60. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. *Front Immunol*. 2019;10:1462.
doi: 10.3389/fimmu.2019.01462
 61. Arts RJW, Novakovic B, Ter Horst R, *et al*. Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. *Cell Metab*. 2016;24(6):807-819.
doi: 10.1016/j.cmet.2016.10.008
 62. Bekkering S, Quintin J, Joosten LA, van der Meer JW, Netea MG, Riksen NP. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. *Arterioscler Thromb Vasc Biol*. 2014;34(8):1731-1738.
doi: 10.1161/ATVBAHA.114.303887
 63. Bekkering S, Arts RJW, Novakovic B, *et al*. Metabolic induction of trained immunity through the mevalonate pathway. *Cell*. 2018;172(1-2):135-146.e9.
doi: 10.1016/j.cell.2017.11.025
 64. Wang J, Liu YM, Hu J, Chen C. Trained immunity in monocyte/macrophage: novel mechanism of phytochemicals in the treatment of atherosclerotic cardiovascular disease. *Front Pharmacol*. 2023;14:1109576.
doi: 10.3389/fphar.2023.1109576
 65. Keating ST, Groh L, Thiem K, *et al*. Rewiring of glucose metabolism defines trained immunity induced by oxidized low-density lipoprotein. *J Mol Med*. 2020;98(6):819-831.
doi: 10.1007/s00109-020-01915-w
 66. Gomez Marti JL, Wells A, Brufsky AM. Dysregulation of the mevalonate pathway during SARS-CoV-2 infection: An in silico study. *J Med Virol*. 2021;93(4):2396-2405.
doi: 10.1002/jmv.26743
 67. Gao L, Chen Q, Zhou X, Fan L. The role of hypoxia-inducible factor 1 in atherosclerosis. *J Clin Pathol*. 2012;65(10):872-876.
doi: 10.1136/jclinpath-2012-200828
 68. Rius J, Guma M, Schachtrup C, *et al*. NF- κ B links innate immunity to the hypoxic response through transcriptional regulation of HIF-1 α . *Nature*. 2008;453(7196):807-811.
doi: 10.1038/nature06905
 69. Jiang G, Li T, Qiu Y, Rui Y, Chen W, Lou Y. RNA interference for HIF-1 α inhibits foam cells formation in vitro. *Eur J Pharmacol*. 2007;562(3):183-190.
doi: 10.1016/j.ejphar.2007.01.066
 70. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov*. 2014;13(2):140-156.

- doi: 10.1038/nrd4204
71. Appelberg S, Gupta S, Svensson Akusjärvi S, *et al.* Dysregulation in Akt/mTOR/HIF-1 signaling identified by proteo-transcriptomics of SARS-CoV-2 infected cells. *Emerg Microbes Infect.* 2020;9(1):1748-1760.
doi: 10.1080/22221751.2020.1799723
 72. Orekhov AN, Oishi Y, Nikiforov NG, *et al.* Modified LDL particles activate inflammatory pathways in monocyte-derived macrophages: transcriptome analysis. *Curr Pharm Des.* 2018;24(26):3143-3151.
doi: 10.2174/1381612824666180911120039
 73. Zeboudj L, Giraud A, Guyonnet L, *et al.* Selective EGFR (epidermal growth factor receptor) deletion in myeloid cells limits atherosclerosis—brief report. *Arterioscler Thromb Vasc Biol.* 2018;38(1):114-119.
doi: 10.1161/ATVBAHA.117.309927
 74. Wang L, Huang Z, Huang W, *et al.* Inhibition of epidermal growth factor receptor attenuates atherosclerosis via decreasing inflammation and oxidative stress. *Sci Rep.* 2017;7:45917.
doi: 10.1038/srep45917
 75. Tallam A, Perumal TM, Antony PM, *et al.* Gene regulatory network inference of immunoresponsive gene 1 (IRG1) identifies interferon regulatory factor 1 (IRF1) as its transcriptional regulator in mammalian macrophages. *PLoS ONE.* 2016;11(2):e0149050.
doi: 10.1371/journal.pone.0149050
 76. Dai C, Lin Y. Comprehensive analysis of the diagnostic and therapeutic value of the hypoxia-related gene PLAUR in the progression of atherosclerosis. *Sci Rep.* 2023;13(1):8533.
doi: 10.1038/s41598-023-35548-z
 77. Laderoute M. The paradigm of immunosenescence in atherosclerosis-cardiovascular disease (ASCVD). *Discov Med.* 2020;29(156):41-51.
 78. Laderoute MP. A new paradigm about HERV-K102 particle production and blocked release to explain cortisol mediated immunosenescence and age-associated risk of chronic disease. *Discov Med.* 2015;20(112):379-391.
 79. Zhu M, Guo J, Li W, *et al.* Hepatitis B virus X protein induces expression of alpha-fetoprotein and activates PI3K/mTOR signaling pathway in liver cells. *Oncotarget.* 2015;6(14):12196-12208.
doi: 10.18632/oncotarget.2906
 80. Nakabayashi H, Koyama Y, Sakai M, Li HM, Wong NC, Nishi S. Glucocorticoid stimulates primate but inhibits rodent α -fetoprotein gene promoter. *Biochem Biophys Res Commun.* 2001;287(1):160-172.
doi: 10.1006/bbrc.2001.5564
 81. Laderoute MP. *The Characterization of a Novel, Widespread, PNA-Reactive Tumor Associated Antigen: The Alpha-fetoprotein Receptor/ Binding Protein.* Doctoral dissertation. University of Alberta; 1991.
doi: 10.7939/R3BC3T56Z
 82. Laderoute MP, Pilarski LM. The inhibition of apoptosis by alpha-fetoprotein (AFP) and the role of AFP receptors in anti-cellular senescence. *Anticancer Res.* 1994;14(6B):2429-2438.
 83. Laderoute MP. A new perspective on the nature of the cancer problem: anti-cellular senescence. *Mol Carcinog.* 1994;10(3):125-133.
doi: 10.1002/mc.2940100303
 84. Zhang M, Liu K, Zhang Q, *et al.* Alpha fetoprotein promotes polarization of macrophages towards M2-like phenotype and inhibits macrophages to phagocytize hepatoma cells. *Front Immunol.* 2023;14:1081572.
doi: 10.3389/fimmu.2023.1081572
 85. Stec M, Weglarczyk K, Baran J, *et al.* Expansion and differentiation of CD14+CD16(-) and CD14+ +CD16+ human monocyte subsets from cord blood CD34+ hematopoietic progenitors. *J Leukoc Biol.* 2007;82(3):594-602.
doi: 10.1189/jlb.0207117
 86. Coleman PS, Parlo RA. Warburg's ghost-cancer's self-sustaining phenotype: the aberrant carbon flux in cholesterol-enriched tumor mitochondria via deregulated cholesterologenesis. *Front Cell Dev Biol.* 2021;9:626316.
doi: 10.3389/fcell.2021.626316
 87. Platanitis E, Decker T. Regulatory networks involving STATs, IRFs, and NF κ B in inflammation. *Front Immunol.* 2018;9:2542.
doi: 10.3389/fimmu.2018.02542
 88. Tokuyama M, Gunn BM, Venkataraman A, *et al.* Antibodies against human endogenous retrovirus K102 envelope activate neutrophils in systemic lupus erythematosus. *J Exp Med.* 2021;218(7):e20191766.
doi: 10.1084/jem.20191766
 89. Tovo PA, Garazzino S, Savino F, *et al.* Expressions of type I and III interferons, endogenous retroviruses, TRIM28, and SETDB1 in children with respiratory syncytial virus bronchiolitis. *Curr Issues Mol Biol.* 2023;45(2):1197-1217.
doi: 10.3390/cimb45020079
 90. Schmidt N, Domingues P, Golebiowski F, *et al.* An influenza virus-triggered SUMO switch orchestrates co-opted endogenous retroviruses to stimulate host antiviral immunity. *Proc Natl Acad Sci USA.* 2019;116(35):17399-17408.
doi: 10.1073/pnas.1907031116

91. Autio A, Nevalainen T, Mishra BH, Jylhä M, Flinck H, Hurme M. Effect of aging on the transcriptomic changes associated with the expression of the HERV-K (HML-2) provirus at 1q22. *Immun Ageing*. 2020;17(1):11.
doi: 10.1186/s12979-020-00182-0
92. Kawai T, Akira S. Toll-like receptor and RIG-I-like receptor signaling. *Ann N Y Acad Sci*. 2008;1143(1):1-20.
doi: 10.1196/annals.1443.020
93. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol*. 2020;20(9):537-551.
doi: 10.1038/s41577-020-0288-3
94. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol*. 2021;21(9):548-569.
doi: 10.1038/s41577-021-00524-z
95. Ren X, Wen W, Fan X, *et al*. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. *Cell*. 2021;184(7):1895-1913.e19.
doi: 10.1016/j.cell.2021.01.053
96. Laderoute M. Ivermectin may prevent and reverse immunosenescence by antagonizing alpha-fetoprotein and downmodulating PI3K/Akt/mTOR hyperactivity. Rapid response. *Open Heart*. 2021. <https://openheart.bmj.com/content/8/1/e001655>
97. Kory PD, McCarthy J. *War on Ivermectin. The Medicine that Saved Millions and Could Have Ended the Pandemic*. New York: ICAN Press, Skyhorse Publishing, Inc.; 2023.
98. Laderoute MP. Shedding of Spike mRNA “Gene Therapy Products”: Potential Mechanisms and Mortality Outcomes. Sworn Testimony to National Citizens Inquiry. 2024. Accessed June 7, 2026. <https://rumble.com/v51idm2-dr-marian-laderoute-jun-01-2024-regina-saskatchewan.html>
99. Laderoute MP. The Catastrophic HARM of Spike Specific IgG1/3 Antibodies in the Upper Respiratory Tract (URT) by the COVID-19 Spike mRNA GENE THERAPY Products (and how this led to widespread injuries and deaths in CHILDREN AND HEALTHY ADULTS). Sworn Testimony to the National Citizens Inquiry; November 7, 2025, Brandon, Manitoba. Accessed June 7, 2026. <https://rumble.com/v72xyrm-dr-marian-laderoute-november-07-2025-brandon-manitoba.html#comment-600000896>
100. Guerra ENS, de Castro VT, Amorim Dos Santos J, Acevedo AC, Chardin H. Saliva is suitable for SARS-CoV-2 antibodies detection after vaccination: A rapid systematic review. *Front Immunol*. 2022;13:1006040.
doi: 10.3389/fimmu.2022.1006040
101. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med*. 2022;28(11):2398-2405.
doi: 10.1038/s41591-022-02051-3
102. Lee SJ, Jang BC, Lee SW, *et al*. Interferon regulatory factor-1 is prerequisite to the constitutive expression and IFN-gamma-induced upregulation of B7-H1 (CD274). *FEBS Lett*. 2006;580(3):755-762.
doi: 10.1016/j.febslet.2005.12.093
103. Veluswamy P, Wacker M, Scherner M, Wippermann J. Delicate role of PD-L1/PD-1 axis in blood vessel inflammatory diseases: current insight and future significance. *Int J Mol Sci*. 2020;21(21):8159.
doi: 10.3390/ijms21218159
104. Padmanabhan S, Gaire B, Zou Y, Uddin MM, Vancurova I. IFN γ -induced PD-L1 expression in ovarian cancer cells is regulated by JAK1, STAT1 and IRF1 signaling. *Cell Signal*. 2022;97:110400.
doi: 10.1016/j.cellsig.2022.110400
105. Puglisi M, May L, Gardiyehewa T, Landry JW. Sex differences in the response to lung cancer and its relation to Programmed Cell Death Protein-1/Programmed Death-Ligand-1 checkpoint therapies. *Cancers*. 2025;17(24):3953.
doi: 10.3390/cancers17243953
106. Grippin AJ, Marconi C, Copling S, *et al*. SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. *Nature*. 2025;647(8089):488-497.
doi: 10.1038/s41586-025-09655-y
107. Bhattacharjee B, Lu P, Monteiro VA, *et al*. Immunological and antigenic signatures associated with chronic illnesses after COVID-19 vaccination (Version 2). *medRxiv*. Preprint Posted online February 25, 2025.
doi: 10.1101/2025.02.18.25322379
108. Cao X, Manhas A, Chen YI, *et al*. Inhibition of CXCL10 and IFN- γ ameliorates myocarditis in preclinical models of SARS-CoV-2 mRNA vaccination. *Sci Transl Med*. 2025;17(828):eadq0143.
doi: 10.1126/scitranslmed.adq0143
109. Levi R, Mansuri F, Jordan MM, Ladapo JA. Twelve-month all-cause mortality after initial COVID-19 vaccination with Pfizer-BioNTech or mRNA-1273 among adults living in Florida (Version 2). *medRxiv*. Preprint Posted online July 22, 2025.
doi: 10.1101/2025.04.25.253264
110. Bansal S, Perincheri S, Fleming T, *et al*. Cutting edge: circulating exosomes with COVID spike protein are induced by BNT162b2 (Pfizer-BioNTech) vaccination prior to development of antibodies: a novel mechanism for immune activation by mRNA vaccines. *J Immunol*. 2021;207(10):2405-2410.
doi: 10.4049/jimmunol.2100637

111. Catanzaro JA, Hulscher N, McCullough PA. Genomic integration and molecular dysregulation in aggressive stage IV bladder cancer following COVID-19 mRNA vaccination. *Int J Inn Res Med Sci*. 2025;10(10):380-386.
doi: 10.23958/ijirms/vol10-i10/2130
112. Monde K, Satou Y, Goto M, *et al*. Movements of ancient human endogenous retroviruses detected in SOX2-expressing cells. *J Virol*. 2022;96(9):e0035622.
doi: 10.1128/jvi.00356-22
113. Kirsch S. New Florida brand differential study show the Pfizer vaccine likely killed over 500,000 Americans. *Steve Kirsch's Newsletter*. 2025. Accessed June 7, 2026. <https://kirschsubstack.com/p/new-florida-brand-differential-study>
114. Our World in Data. Accessed June 7, 2026. <https://ourworldindata.org/coronavirus>
115. Dias SSG, Soares VC, Ferreira AC, *et al*. Lipid droplets fuel SARS-CoV-2 replication and production of inflammatory mediators. *PLoS Pathog*. 2020;16(12):e1009127.
doi: 10.1371/journal.ppat.1009127
116. Cai F, Liu S, Lei Y, *et al*. Epigallocatechin-3 gallate regulates macrophage subtypes and immunometabolism to ameliorate experimental autoimmune encephalomyelitis. *Cell Immunol*. 2021;368:104421.
doi: 10.1016/j.cellimm.2021.104421
117. Oh J, Weng S, Felton SK, *et al*. 1,25(OH)₂ vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation*. 2009;120(8):687-698.
doi: 10.1161/CIRCULATIONAHA.109.856070
118. Quan H, Cheng H, Tang G, *et al*. Flavonoid derivative FB-15 inhibits the progression of nasopharyngeal carcinoma by targeting the PI3K-Akt signaling pathway. *Biochem Biophys Res Commun*. 2025;771:152037.
doi: 10.1016/j.bbrc.2025.152037
119. Lee YT, Tan YJ, Oon CE. Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine. *Acta Pharm Sin B*. 2023;13(2):478-497.
doi: 10.1016/j.apsb.2022.09.010
120. Cassetta L, Pollard JW. A timeline of tumour-associated macrophage biology. *Nat Rev Cancer*. 2023;23(4):238-257.
doi: 10.1038/s41568-022-00547-1
121. Lv JJ, Wang H, Cui HY, *et al*. Blockade of macrophage CD147 protects against foam cell formation in atherosclerosis. *Front Cell Dev Biol*. 2021;8:609090.
doi: 10.3389/fcell.2020.609090
122. Pan W, Hao S, Zheng M, *et al*. Oat-derived β -Glucans induced trained immunity through metabolic reprogramming. *Inflammation*. 2020;43(4):1323-1336.
doi: 10.1007/s10753-020-01211-2
123. Guan F, Wang R, Yi Z, *et al*. Tissue macrophages: origin, heterogeneity, biological functions, diseases and therapeutic targets. *Signal Transduct Target Ther*. 2025;10(1):93.
doi: 10.1038/s41392-025-02124-y