Trained (Innate) Immunity (TI) of M1-like Foamy Macrophages: Key Role of HERV-K102 Particles

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Introduction

The term 'trained immunity' (TI) was first coined by Professor Mihai Netea and colleagues in 2011 to describe the enhancement of a secondary innate immunity response after a primary infection or vaccination [1]. Unlike adaptive immunity, TI lacks specificity for any pathogen-specific antigens and thus, invariably involves 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 different pathogens including tuberculosis. The protection furnished by the BCG vaccine was mediated by macrophages. Since in humans, macrophages cannot replicate (unlike mice), this has led to the concept of central TI in the hematopoietic stem and progenitor cells (HSPCs) in the bone marrow [2-4]. Accordingly, TI involves peripheral (monocytes in the blood that turn into macrophages in the tissues) and central (myeloid HSPCs) compartments. Most notably the memory aspect of TI involves metabolic (a switch to glycolysis) and epigenetic changes (changes in the histone methylation and acetylation in chromatin providing access to macrophage lineage and inflammatory genes)[4].

TI refers to a short-term enhancement (usually 3 to 12 months) of the release of core cytokines (such as TNF-α, IL-1β, IL-6) from M1-like macrophages upon rechallenge but which is

also associated with enhanced heterologous anti-pathogen and anti-tumor activity *in vivo*. However, how TI in M1-like proinflammatory macrophages relates to enhanced pathogen and tumor control *in vivo* is unclear and remains to be fully elucidated.

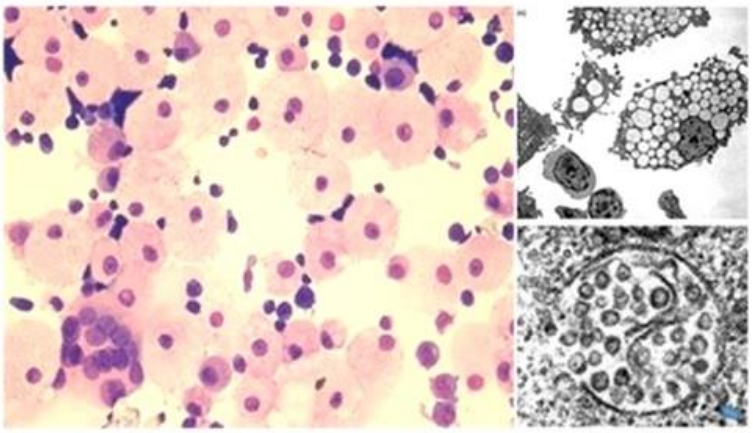


Figure 1. M1-like foamy macrophages express high levels of HERV-K102 particles [5]. When placenta derived cord blood mononuclear cells are cultured in non-RPMI media, M1-like foamy macrophages become strongly activated (left panel Hematoxylin and Eosin stain from cytospins, day 11). These lacy macrophages that are highly vacuolated are negative for Oil Red O which stains lipid bodies of esterified cholesterol that instead are found in M2-like foamy macrophages that are morphologically very different. Here the foam formation results from the budding of the HERV-K102 particles into the vacuoles and which generates immature particles typical of non-pathogenic foamy retroviruses [5]. Release is by cell lysis. Note the presence of a very rare multinucleated giant cell which have been reported for macrophages from the placenta.

Nevertheless, Laderoute has described a novel, virus anti-virus, potent defence system called human endogenous retrovirus K102 (HERV-K102) that gets activated in M1-like macrophages [5]. HERV-K102 is a non-pathogenic foamy retrovirus encoded on chromosome 1q22 that launches in proinflammatory M1-like foamy macrophages (**Figure 1**). Notably, this system allegedly provides recovery from COVID-19, prevents the acquisition of HIV-1, may have

contributed to human survival over other hominins (Neanderthal and Denisovans), and is well established to protect against cancers and HIV-1 progression as demonstrated with innate T and B cell responses to HERV-K102 envelope [reviewed in 5]. The full details of this relatively obscure yet incredibly potent innate protection system launched in the foamy macrophages which putatively mediates trained (innate) immunity, is provided elsewhere [5].

Since TI reportedly occurs in M1-like macrophages with or without the induction of inflammatory cytokines [6,7] this presents somewhat of a conundrum for the functional definition of TI. 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 generates the TI heterologous protection that is associated with foam cell formation. Indeed Li et al., have indicated the transcription factors (TFs) critical to training in all monocyte subsets including those that lack the induction of inflammatory cytokines include the following: SPI1, CEBPB, IRF1, IRF9, STAT1/2, RELA/B, NFKB1/2 which as will be discussed, appears to implicate the full-length expression of HERV-K102 proviral transcripts.

Furthermore, as will be discussed, these immature particles which contain double-stranded (ds) cDNA genomes and are studded with envelope protein [5 and see **Figure 1**] may activate innate T and B cells that recognize HERV-K102 envelope protein expressed on virally transformed and tumor transformed cells. It is anticipated by the end of this narrative; readers may become convinced of the powerful heterologous protection offered by the HERV-K102 protector system against deaths related to infectious agents, tumors and somewhat unexpectantly, also chronic diseases [8].

Molecular Mechanisms Involved in Generating Trained Immunity (TI)

Commonly used inducers of trained immunity include microbial products such as beta glucan and muramyl dipeptide, but also oxLDL, uric acid, the BCG vaccine, other live vaccines or exposures to viruses [6,7]. The differences in epigenetic marks by the different TI inducers are reviewed elsewhere [9]. The myeloid specific enhancers SPI1 and CEBPB [10] are trained immunity specific enhancers of macrophages [11,12].

The metabolic and epigenetic changes associated with TI are mediated via the Akt/mTOR/HIF-1α pathway [11,13,14]. Glycolysis is necessary to drive the PI3K/Akt/mTOR/HIF-1α pathway [4]. In M1 macrophages, activation leads to the accumulation of succinate in the Krebs cycle which leads to the stabilization of the transcription factor (TF) hypoxia inducible factor 1 alpha (HIF-1α). HIF-1α induces the transcription of glycolysis genes [15]. In contrast M2 macrophages primarily use oxidative phosphorylation.

TI involves foam cell formation and creates foamy macrophages [16]. 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 [17]. Trained macrophages uptake lipids such as oxLDL through 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 [18] associated with glycolysis [20]. Interestingly, SARS-COV-2 infection disrupts the mevalonate pathway [20] showing that it directly targets foam cell formation and thus trained immunity.

HIF-1α plays a key role in initiating and promoting the formation of foam cells in macrophages [21]. NF-κβ1 which induces the inflammatory response in macrophages is required for the transcription of HIF-1α [22]. A critical role of HIF-1α in foam cell formation in macrophages was demonstrated by the inhibition of foam cell formation by small interfering RNAs against HIF-1α [23]. Thus, it is very clear TI critically involves the induction of foam in proinflammatory macrophages related to NF-κβ1 and HIF-1α expression.

The PI3K/Akt/mTOR pathway plays a role in autophagy, apoptosis, metabolism and cell

growth but is commonly hyperactivated in tumors where it contributes to malignant potential [24]. It is also hyperactivated upon SARS-CoV-2 infection such as in the hepatocellular cell line Huh7 associated with ERBB2 hyperactivity [25] and significantly elevated alpha-fetoprotein (AFP) mRNA and protein expression [Prof. Ujjwal Neogi, personal communication]. In macrophages, this pathway is used by the epidermal growth factor receptor (EGFR) to generate foam cell formation [26]. For example, gene deletion of EGFR in macrophages in murine models limits the production of IL-6 and TNF-α, reduces lipid uptake by reducing the expression of the scavenger receptor CD36, reduces macrophage accumulation and inhibits the development of atherosclerosis which involves foamy macrophages [27]. Similarly for human macrophages, the EGFR is activated by TLR4 and disruption of TLR4 or EGFR reduced inflammation and foam cell formation [27,28]. Triggering TLR4 activates HIF-1α, IRF1 (interferon response factor 1 that induces HERV-K102 transcription [5]), VDR (the vitamin D receptor transcription factor), S100A9 and NR3C1 (the glucocorticoid receptor) while downregulating PPARG and IFNGR1 [29]. EGFR antagonists were also shown to block oxLDL induction of inflammation and foam cell formation in macrophages with the downregulation of IL-6 and TNF-α [28]. 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 TF HIF-1α include PLAUR, HK2, NAGK, CXCR4, and others [30]. While PLAUR (the plasminogen activator urokinase receptor) and these other genes strongly correlate with progression of atherosclerosis (a disease related to dysfunctional foamy macrophages [31]), interestingly, PLAUR was only expressed in M0 macrophages [30]. Curiously, the M1-like macrophages do not display any markers that correlate with atherosclerosis[1] while the M2-like macrophages express CXCR4 and NAGK [30]. In CD8 T cells,

[1] This is an extremely important observation substantiating that the macrophages producing HERV-K102 particles do not cause cardiovascular or other diseases as they alleviate disease. Instead, pathogens, toxins or active AFP may convert the protector M1-like foamy macrophages to M2-like foamy macrophages with dire consequences (see later and **Figure 6**).

NK cells, monocytes, and naïve B cells, atherosclerosis corelates with pyruvate dehydrogenase kinase 3 (PDK3) expression [30]. PDK3 is part of a multienzyme complex in mitochondria that converts pyruvate to acetyl-CoA and CO_2 and provides a link between glycolysis and the TCA cycle (which regulates glucose metabolism). For example, PDK3 promotes the burning of fat as an energy source when there is insufficient glucose under fasting conditions.

Alpha-fetoprotein (AFP) Expression Is Essential to Foam Cell Formation

In hepatitis B infection, the viral X protein expressed in hepatocytes induces AFP which inhibits PTEN allowing the activation of the PI3K/Akt/mTOR pathway [32]. This pathway regulates gene transcription via mTOR which results in the transcription of HIF-1α and as mentioned, is needed for glycolysis. In hepatocellular carcinoma cells, the phosphorylation of mTOR at serine 2448 synergises with HIF-1α to regulate such genes as CXCR4, Src, and Ras. Small interfering RNA to AFP (AFP-siRNA) which inhibited the production of AFP mRNA and protein, blocked mTOR migration to the nucleus and was associated with the downregulation of p-mTOR (phosphoserine 2448), HIF-1α, Src, CXCR4 and Ras [32]. Thus, TI involving PI3K/Akt/mTOR/HIF-1α activation in human macrophages along with foam cell formation, is likely co-dependent on AFP expression.

As just mentioned, TLR4 signaling in macrophages induces the glucocorticoid receptor, NR3C1 [29]. AFP is induced by glucocorticoids in humans although in direct contrast, is repressed by the same in rodent models [33]. Interestingly, rodents also do not have dehydroepiandrosterone (DHEA) a steroid hormone to counter the effects of cortisol/AFP [33]. There are many ways that rodent immune systems differ from humans especially when it comes to macrophages, making immunity and pathogenesis predictions based on murine models unreliable.

It is noteworthy that DHEA but not the inactive form DHEA-S specifically binds and inactivates AFP in humans [34]. This is important since it is known the DHEA levels decline with stress or aging and that chronic disease initiation and/or progression correlates with a

declining DHEA/cortisol ratio [34]. Accordingly with age or stress more of the AFP induced by cortisol such as released by macrophages would be active and able to promote the malignant potential of tumors and infectious agents. The well-known immunosuppression of macrophages by AFP was confirmed with two AFP agonist monoclonal antibodies (MAbs) to the 67 kD AFP receptor (AFPr) [35]. More importantly that AFP confers apoptosis resistance (related to unexpected growth enhancement) was discovered and confirmed with the same MAbs [35,36]. AFP was in fact the first secreted apoptosis inhibitor described in 1991[35] and as published in 1994 [36]. This added to its historical significance as the first: tumor marker/oncofetal antigen (1963), first immunosuppressive factor (1975), first secreted protein able to generate negative signalling (1991), first secreted protein able to confer apoptosis resistance (1991,1994), first to unify a theory 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 originally proposed in 1994 [37].

As referred to earlier in footnote 1, AFP transfection is known to polarize macrophages to the M2 phenotype [38]. For example, upon LPS and IFN-γ triggering of the M1 phenotype, AFP transfection into M0 macrophages co-induces CD163 and IL-10 which are considered markers of M2 [38]. However, CD163, IL-10 and the MI/M2 hybrid phenotype [39] characterize the normal foamy macrophages illustrated in **Figure 1** which exhibit high levels of vacuoles and HERV-K102 particles [40,41]. This may further substantiate a role of AFP expression in the training of macrophages associated with foam cell formation.

Foamy Macrophages, TI and Glycolysis

The formation of foam of macrophages displayed in **Figure 1** has been shown to involve high levels of human endogenous retrovirus K102 (HERV-K102) particles which bud into the intracellular vacuoles but not through the cell surface membrane [40,41]. Instead, particle release is through lysis of the foamy macrophages that occurs in a major wave in cultured cord blood cells

on day 6-7. The foamy virus particles and the vacuoles are lipid bilayers composed of and requiring high levels of cholesterol. Thus, it seems HERV-K102 particle production (**Figure 1**) is a critical and salient component of 'training' in the M1-like macrophages requiring high levels of cholesterol because of foam production [17].

TI associates with the induction of glycolysis which is similar to the Warburg effect described for 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 [42]. 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 of the cell surface membrane and other membranes in the cell via higher cholesterol production would be needed in order to support tumor replication or growth. Indeed, mevalonate initiates DNA synthesis and cell proliferation [42]. In human monocyte derived macrophages, which incidentally do not proliferate (although they do in rodent models), excess cholesterol would be needed and utilized instead for foam cell formation pertaining to the replication of the protector foamy virus HERV-K102. Hence, glycolysis is linked to TI to support the generation of cholesterol needed to produce vacuoles and HERV-K102 particles during M1 macrophage training.

M1-like Macrophage Activation in TI and IRF1 Induction of HERV-K102

As mentioned, drivers of myeloid differentiation are the enhancer TFs SPI1 and CEBPB which also drive TI [11-13]. SpI1 is considered a pioneering transcription factor (also called lineage determining transcription factors) that opens up the chromatin in this case for macrophage differentiation which enables inflammation and other TFs to bind to response elements in the appropriate genes [43]. Macrophage inflammation involves networks of signal transducer and activator of transcription (STAT) factors, interferon response factors (IRFs) and NF-κβ TFs [43]. Monocytes exposed to LPS and interferon gamma (IFN-γ) undergo classical M1-like (pro-

inflammatory) macrophage activation with upregulation of SPI1, IRF1, IRF5, IRF8, STAT1, STAT2 and NF-κβ1. The alternative activation with IL4 and IL13 generates M2-like (anti-inflammatory) cells featuring SPI1, IRF4, STAT6, KDM6B, PPARγ, PPARδ, and CEBPB [43]. However, PPARγ plays an important role in the differentiation of monocyte to foamy macrophages [43] and CEBPB is a TI enhancer. Accordingly, the macrophages conferring TI express M1 and M2-like markers including CEBPB and PPARG which are associated with foam cell formation. As just mentioned, AFP expression may also contribute to M2 hybrid marker expression in the inflammatory macrophages.

It is noteworthy that IRF1 and NF-κβ1 bind to two interferon stimulated response elements (ISREs) in the promoter of HERV-K102 which are found in the 5' long terminal repeat (LTR) [44,45]. TNF-α is a potent activator of canonical NF-κβ1 transcription factor activity while IFN-γ and TNF-α synergize to activate IRF1. Indeed, newer evidence confirms that M1 polarization of macrophages in humans explicitly in response to IFN-γ signalling is promoted via HERV-K102 expression [46]. More recently the key role of IFN-γ in TI induction *in vivo* in response to BCG vaccination was affirmed by scRNA sequencing [7].

In patients with systemic lupus erythematosus (SLE) the expression of HERV-K HML-2 envelope transcripts (HERV-K102, HERV-K106, HERV-K18, and the polymorphic HERV-K115) were inversely correlated to the expression of TRIM28 in peripheral blood mononuclear cells (PBMCs). The expression of these HML-2 envelope mRNAs correlated with an increase in type I IFN signalling in SLE patients [47]. TRIM28 represses endogenous retroviruses in part via epigenetic marking of H3K9 [48]. However, Schmidt et al [49] provided evidence that it is SUMOylated TRIM28 which strongly represses the expression of endogenous retroviruses as associated with influenza A viral infection.

Most importantly, Schmidt et al [49] were able to show that endogenous virus activation is a protective response because they amplify antiviral/antimicrobial gene expression including interferon responses. With infection by influenza A, the DEGS induced by the derepression of

endogenous retroviruses [49] strongly induced a plethora of interferon stimulated genes (ISGs) such as IRF1, IRF7, IFNB1, OAS1, ISG15, CD274 (PD1L1) and DDX58 (RIG-1 a sensor of double stranded RNA). Other genes such as CXCL8, IL6, CCL5, MX1, MX2, the complement related genes C1R, C1S, and CF1, and significantly CSF2 (granulocyte-macrophage colony stimulating factor, GM-CSF) were also very strongly induced. CXCL8 expression (which activates and attracts neutrophils) also was strongly induced and has been shown to correlate with HERV-K102 expression in PBMCs *in vivo* [50]. With the induction of the interferon response and where many of these genes have antiviral activity, it is very clear the expression of HERV-K HML-2 group members is to help protect the host through innate (non-antigen specific) means.

HERV-K102 particles amplify the IFN type I and inflammatory response involved in TI induction as may be associated with the RIG-1/MDA5/MAVS system, Toll-like receptors (TLRs) and the cGAS-STING system [51-53]. That HERV-K102 has been implicated in generating the cGAS-STING response that induces type I interferons has been reported in COVID-19 patients [54]. Indeed Russ et al., have suggested that HERV-K102 which activates antiviral and interferon responses in cells such as through cGAS (dsDNA), RIG-1 (ssRNA) and MDA-5 (dsRNA) provides this antiviral protection by mimicking the effects of the entry of (pathogenic) viruses (i.e., via viral mimicry) [55]. Moreover, this same research group showed that a scan of publicly available transcriptomes of the activation of macrophages with retroelement sequencing tools revealed HERV-K102 at 1q22 was associated with the M1 polarization of macrophages in response to IFN gamma treatment [46]. Here, STAT1 and IRF1 were implicated in the induction of HERV-K102 transcripts [46].

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 member proteins to greatly enhance the antiviral TI response as part of the virus-anti-virus protector 'alarm' system. I think this is ingenious of Mother Nature. It may involve dsRNA in the cells producing the proviral genomic transcripts from genomic DNA. However, since the genomes in the HERV-K102

particles upon lytic release from the macrophages are reversed transcribed into cDNA [40,41] means these released particles can induce cGAS-STING upon entry into other cells, providing an alternative (back-up) pathway for spreading and triggering the type I interferon antiviral responses.

There are about 30 trillion (ie., 30 x 10^{12}) cells in the body and HERV-K102 frequently reaches 10^{12} particles per ml of plasma in response to viral infections [40 and see more details in 56]. If one also considers the particles constitutively made and produced by sebocytes (highly specialized M1-like foamy macrophages found in sebaceous glands that line the mucosa and skin [5]), then it would seem there would be sufficient particles to protect all the cells in the body, and then some!

The genes described by Schmidt et al [49] induced via the derepression of endogenous retroviruses were first, genes involved in the macrophage lineage and second, those identified to be involved in the training of macrophages *in vivo* [7]. Of 4 macrophage TI profiles recently discerned by Li et al. [7], the endogenous retrovirus activated DEGS matched the TM1 (type I IFN stimulated) the best, followed by the TM2 (IL-1 inflammatory response). Although there could be other endogenous retroviruses involved, when considered with the findings by Russ et al cited above [46,55], it appears that HERV-K102 genomic expression serves to greatly enhance both the IFN type I responses and the IFN-γ enhancement of TI while clearly contributing to foam cell formation in macrophages.

Consistent with the findings by Schmidt et al [49], Kenney et al [57] found that the launch of the type I interferon response known to be needed for recovery from SARS-CoV-2 and/or the prevention of severe COVID-19 disease, was by M1-like proinflammatory macrophages as demonstrated in a special humanized mouse model involving infection by SARS-CoV-2. As discussed elsewhere [5] this and other data such as a comprehensive single cell sequencing study of bronchoalveolar lavage fluids from COVID-19 patients in various stages of recovery by Ren X et al, 2021 [58] have clearly implicated the M1-like proinflammatory macrophages (WDR74+) in recovery from COVID-19. This means that activators of TI and not antibodies to spike protein

would have been the preferred main public health intervention to minimize morbidity and mortality related to the SARS-CoV-2 pandemic!

IRF1 activation is crucial to the control of innate immunity and is phylogenetically very old (Eumetazoan, one of the earliest multicell organisms where tissues are organized into germ layers and the embryo goes through a gastrula stage). Interferon based innate immunity with IRF1 activation is relatively new and present only in vertebrates (bony fish, birds, mammals, humans) [54]. Receptors that can induce IRF1 include TNF, the RIG like Receptors (RLR) including RIG-1 (DDX58) and MDA5 (IFIH1) which are sensors of dsRNA genomes, cGAS-STING for cDNA genomes, TLRs, and IFN type I and II receptors. The IFN I receptors use JAK and a complex of STAT1/2 and IRF9 (called ISGF3) which activates AIM and the inflammasome, NLRP3. The IFN II (gamma) receptors use STAT1 homodimers and more potently activate IRF1 [55].

HERV-K102 Particle Shedding in the Mucosa and Herd Immunity

As mentioned, IRF1 expression is strongly associated with TI [7] and with the induction of TI related genes by endogenous retroviruses expression [49]. This implies HERV-K102 RNA expression itself may induce TI and that it exhibits a feedback loop for its own upregulation and induction of TI. This might help explain how the foamy macrophages in **Figure 1** accrue very high levels of vacuoles filled with HERV-K102 particles prior to cell lysis that occurs in a first major wave around day 6-7 [40,41].

The unusual mechanism of programmed cell death being initiated in the cytoplasm when there are maximal levels of the HERV-K102 particles and vacuoles made (**Figure 1**), has been elucidated by Fischer and colleagues for sebocytes [59]. Sebocytes are highly specialized M1-like foamy macrophages found in sebaceous glands located in the skin and mucosa and are known to produce HERV-K102 transcripts [reviewed in 5]. The sebocytes undergo cell death by this novel mechanism of lysis and this sebum is then exuded to the surface where it coats the mucosa. In murine sebocytes, this cell death process involves LAMP1, and a lysosomal DNase 2. Accordingly,

the protector HERV-K102 particles exuded to the surface of the mucosa from the sebaceous glands could then be shed to others such as by exhalation, which could spread herd immunity. This would be accomplished by the particles which bear the double stranded cDNA HERV-K102 genomes, activating the cGAS-STING and thus the interferon type I response in all cell types in the new host. However, it is also possible upon integration and mRNA expression in macrophages/sebocyte progenitor cells in the new host that the expression of double stranded RNA would likely induce IRF-1 and thus initiate a cascade that could also pre-activate the HERV-K102 in the new host. Presumably the ideal goal of herd immunity would be to have the HERV-K102 protector system fully activated in those not yet infected with the emerging pathogen or pandemic virus.

Population Based Evidence for Beneficial (or Harmful) Shedding

The first dose of the SARS-CoV-2 spike mRNA vaccine is known to activate innate immunity but without triggering adaptive immunity and antibodies to spike protein [5]. Xu et al., [60] reported for age standardized *NON-COVID-19 deaths* per 100 person years from December 14, 2020, to July 31, 2021, that following dose 1, the non-COVID-19 mortality rate per person years was about 82 - 83 % reduced for people who received Pfizer and Moderna spike mRNA gene therapy products when compared with the unvaccinated (**Figure 2**). Following the second dose this protection fell to about 23 % and 33 % for Pfizer and Moderna respectively when compared with the unvaccinated.

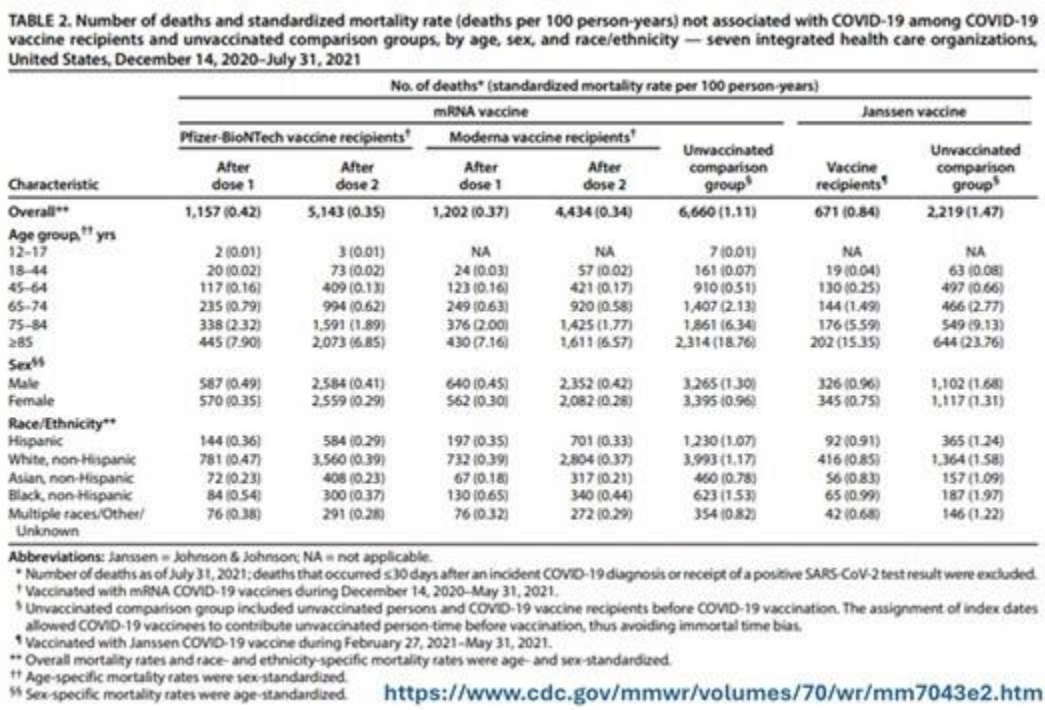


TABLE 2. Number of deaths and standardized mortality rate (deaths per 100 person-years) not associated with COVID-19 among COVID-19 vaccine recipients and unvaccinated comparison groups, by age, sex, and race/ethnicity — seven integrated health care organizations, United States, December 14, 2020–July 31, 2021

	No. of deaths* (standardized mortality rate per 100 person-years)						
	mRNA vaccine					Janssen vaccine	
	Pfizer-BioNTech vaccine recipients†		Moderna vaccine recipients†				
Characteristic	After dose 1	After dose 2	After dose 1	After dose 2	Unvaccinated comparison group§	Vaccine recipients¶	Unvaccinated comparison group§
Overall**	**1,157 (0.42)**	**5,143 (0.35)**	**1,202 (0.37)**	**4,434 (0.34)**	**6,660 (1.11)**	**671 (0.84)**	**2,219 (1.47)**
Age group,†† yrs							
12–17	2 (0.01)	3 (0.01)	NA	NA	7 (0.01)	NA	NA
18–44	20 (0.02)	73 (0.02)	24 (0.03)	57 (0.02)	161 (0.07)	19 (0.04)	63 (0.08)
45–64	117 (0.16)	409 (0.13)	123 (0.16)	421 (0.17)	910 (0.51)	130 (0.25)	497 (0.66)
65–74	235 (0.79)	994 (0.62)	249 (0.63)	920 (0.58)	1,407 (2.13)	144 (1.49)	466 (2.77)
75–84	338 (2.32)	1,591 (1.89)	376 (2.00)	1,425 (1.77)	1,861 (6.34)	176 (5.59)	549 (9.13)
≥85	445 (7.90)	2,073 (6.85)	430 (7.16)	1,611 (6.57)	2,314 (18.76)	202 (15.35)	644 (23.76)
Sex§§							
Male	587 (0.49)	2,584 (0.41)	640 (0.45)	2,352 (0.42)	3,265 (1.30)	326 (0.96)	1,102 (1.68)
Female	570 (0.35)	2,559 (0.29)	562 (0.30)	2,082 (0.28)	3,395 (0.96)	345 (0.75)	1,117 (1.31)
Race/Ethnicity**							
Hispanic	144 (0.36)	584 (0.29)	197 (0.35)	701 (0.33)	1,230 (1.07)	92 (0.91)	365 (1.24)
White, non-Hispanic	781 (0.47)	3,560 (0.39)	732 (0.39)	2,804 (0.37)	3,993 (1.17)	416 (0.85)	1,364 (1.58)
Asian, non-Hispanic	72 (0.23)	408 (0.23)	67 (0.18)	317 (0.21)	460 (0.78)	56 (0.83)	157 (1.09)
Black, non-Hispanic	84 (0.54)	300 (0.37)	130 (0.65)	340 (0.44)	623 (1.53)	65 (0.99)	187 (1.97)
Multiple races/Other/ Unknown	76 (0.38)	291 (0.28)	76 (0.32)	272 (0.29)	354 (0.82)	42 (0.68)	146 (1.22)

Abbreviations: Janssen = Johnson & Johnson; NA = not applicable.

* Number of deaths as of July 31, 2021; deaths that occurred ≤30 days after an incident COVID-19 diagnosis or receipt of a positive SARS-CoV-2 test result were excluded.

† Vaccinated with mRNA COVID-19 vaccines during December 14, 2020–May 31, 2021.

§ Unvaccinated comparison group included unvaccinated persons and COVID-19 vaccine recipients before COVID-19 vaccination. The assignment of index dates allowed COVID-19 vaccinees to contribute unvaccinated person-time before vaccination, thus avoiding immortal time bias.

¶ Vaccinated with Janssen COVID-19 vaccine during February 27, 2021–May 31, 2021.

** Overall mortality rates and race- and ethnicity-specific mortality rates were age- and sex-standardized.

†† Age-specific mortality rates were sex-standardized.

§§ Sex-specific mortality rates were age-standardized.

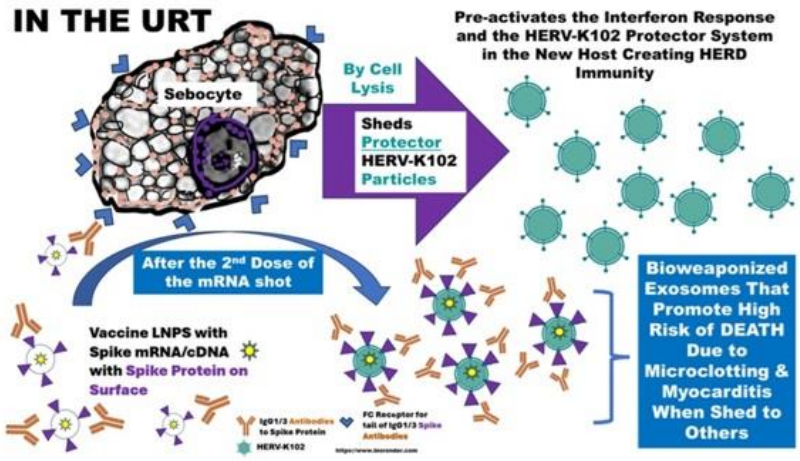
https://www.cdc.gov/mmwr/volumes/70/wr/mm7043e2.htm

Figure 2. USA age standardized Non-COVID-19 mortality data from the CDC [60]. This data substantiates the notion that trained innate immunity was strongly induced following the first spike mRNA gene therapy shot as it likely provided heterologous protection against non-COVID-19 mortality (about 82 to 83 % protection overall when compared with the unvaccinated).

The reduction in heterologous protection against death following the second dose would have been associated with the onset of the spike IgG antibodies following the second dose, which are known to mediate antibody dependent enhancement (ADE) of infection into macrophages [reviewed in 5]. This blocks and/or jeopardizes trained innate immunity [5]. Nevertheless, the data in **Figure 2** for Americans can be taken to support the contention that TI direct induction by the mRNA gene therapy shots and/or as enhanced by way of HERV-K102 shed particles from the URT after *the first dose* is protective against non-COVID-19 causes of death.

However, the reduced heterologous protection against non-COVID-19 mortality following the second shot in the USA, could also be due to shed bioweaponized HERV-K102 particles from

the URT of the vaccinated (**Figure 3**). The spike laden CD9 exosomes [61] from sebocytes are likely coated with spike IgG1/3 that is made in the URT [62] and this complex would be transferred [62,63] deep into the lung microcirculation of the new host [62,63]. There, due to the complement binding spike IgG1 and IgG3 antibodies bound to spike protein in the shed complex, this would set off complement activation and promote clotting and microclotting in the new host's circulation. This could result in severe cardiovascular injuries including myocarditis, permanent disability and even death [63,64]. The people who would be most at risk would be those who received two doses of the spike mRNA gene therapy products as they would likely have much higher IgG1/3 spike antibodies in the blood than the unvaccinated. However, by the third dose or by 6 months after the second dose (roughly around January 2022) many people who were infected with SARS-CoV-2 after receiving the spike mRNA gene therapy shots, would convert their IgG1/3 to IgG4 in the blood, reducing their risk of death by shedding. On the other hand, those who were infected with SARS-CoV-2 before receiving the spike mRNA shots, do not convert to IgG4 [65] and remain at increased risk of a shedding death. Generally, medical staff and younger age groups were more likely to be infected before getting the spike mRNA shot than the rest of the population and so, sudden death seemed to be more commonly reported in medical doctors and athletes despite their inherent good health and younger age.



Putatively How the mRNA Gene Therapy Products May Convert
HERV-K102 Protector Particles that Provide HERD Immunity to
Bioweaponized Exosomes Expressing Spike Protein
That May Cause Death from the Activation of Complement, Coagulation
(Microclotting) and/or Myocarditis

Figure 3. Plausible mechanism for how the protector HERV-K102 particles that spread herd immunity could be bioweaponized following the second dose of the spike mRNA gene therapy shots [63]. Those with the highest levels of the spike IgG1 and IgG3 antibodies in the bloodstream (those who received the 2 doses of the spike mRNA shots for the time period before January 2022) would be most at risk of myocarditis, sudden death, cerebral vascular accidents, and other serious outcomes related to microclotting. After the third dose, those who were infected with SARS-CoV-2 prior to receiving the spike mRNA gene therapy shot (and who retained spike IgG1/3 in the blood and did not convert to IgG4, [65]), are thought to be more prone to death caused by shedding.

Note also that via shedding of the protector HERV-K102 particles after the first dose either via autologous ingestion or as shared within household members, this could strongly protect against both COVID-19 and non-COVID-19 deaths in close contacts that were not vaccinated. Data provided in **Figure 4** for England [63] are strongly supportive of this notion. For example, in **Figure 4A**, following the first dose and aside from immediate non-COVID-19 deaths associated

with being vaccinated, the reduction in COVID-19 and non-COVID-19 mortality in the unvaccinated was notable and is consistent with beneficial shedding spreading herd immunity. I have included the period in which Omicron seemingly infected many people, as a positive control for the reduction in mortality rates across the board in **Figure 4E**. However, with the second and subsequent shots the level of TI protection becomes smaller and smaller for the non-COVID-19 deaths in the unvaccinated. This is consistent with more and more of the protector HERV-K102 particles being targeted and compromised by the spike mRNA gene therapy in the sebocytes in the upper respiratory tract with each dose (such as by ADE). It could also be due to higher levels of IgG1/3 antibodies in a complex with the compromised exosomes shed from the URT that bind complement (**Figure 3**). Note that the famous Cleveland Clinic Data [66] suggested there is no conversion of the spike IgG1/3 in the URT to non-complement binding IgG4 and that the levels of IgG increase with each dosage. This is because an increased risk of being infected with COVID-19 followed a dose responsive manner.

Laderoute MP. The Marvels of the HERV-K102 Virus-Anti-Virus Protection System of Humans Including Shed (Horizontal) Population Protection (and the Harms of Gene Therapy Shedding), March 5, 2024. https://hervk102.substack.com/p/the-marvels-of-the-herv-k102-virus. ONS Data For England

Around the time that about 50% of the 65 to 75 years of age had received a particular dose, what immediately happened to the mortality rates about 10-14 days later ?

Temporal changes to C19 and non-C19 Mortality Rates By Dose

	A: 1st Dose		B: 2nd Dose		C: 3rd Dose		D: 4th 75+ Dose		E: Omicron	
change period	Mar to Apr 2021		Jun to Jul 2021		Oct to Nov 2021		May to Jun 2022		Jan to Feb 2022	
	C19	non-C19	C19	non-C19	C19	non-C19	C19	non-C19	C19	non-C19
vaxed	-35%	24%	156%	0%	27%	16%	-32%	8%	-51%	-31%
unvaxed	-59%	-22%	74%	-10%	31%	-1%	-20%	29%	-56%	-8%

NB: **Omicron [E] decreased mortality rates in both the vaxed and unvaxed for C19 and non-C19.** The same thing happened for the first Pfizer-BIoNTech mRNA dose [A] except the vaccine was toxic and induced non-C19 deaths. **The data in A is the first evidence consistent with HERV-K102 particle protection being horizontally transmitted. On the other hand,** these exosomes can be contaminated by gene therapy products and can be deadly when shed especially related to the generation of the spike IgG1/3 after the second dose (B & C) to the unvaccinated.

Figure 4. Temporal Changes to COVID-19 (C19) and non-COVID-19 (non-C19) Mortality Rates by Dose [63]. Dates for the various doses were based on the time around which about 50% of the 65 to 75 years of age would have received that dose.

As explained elsewhere [63] the ratio of age standardized non-COVID-19 mortality rates per person years over the COVID-19 mortality rates per person years provided a surrogate marker of shedding risks. As shown in **Figure 5,** the dates at which about 50% of the 65 to 75 years of age were immunized with each dose in England are given in the graph. Note with the exception of the first dose around February 10, 2021, where a shedding risk causing death was not observed due to the lack of spike IgG1/3, in all other cases the peaks appeared to last 3-4 months as expected [63]. The fourth injection featured primarily the 75 + although those with chronic diseases of any age also received the 4^{th} dose. The most likely explanation for the mirror image of shedding risk in the unvaccinated would be due to shedding of the compromised HERV-K102 particles as illustrated in **Figure 3** from the URT in the spike mRNA gene therapy injected.

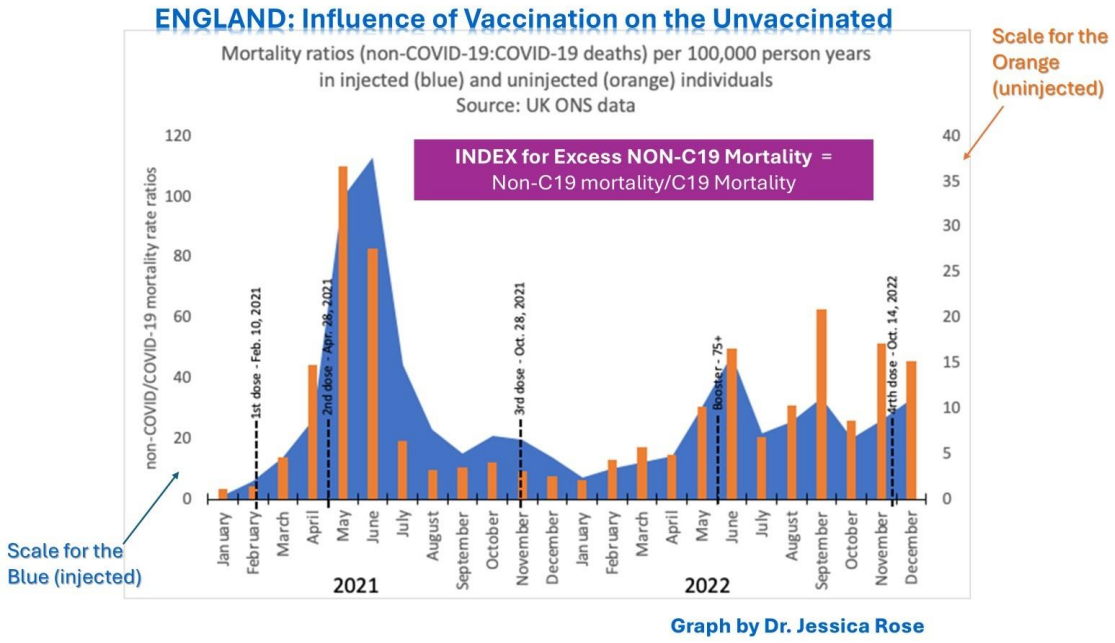


Figure 5. Influence of spike mRNA gene therapy vaccination on the unvaccinated [63]. Dates for the various doses were based on the time around which about 50% of the 65 to 75 years of age would have received that dose. Note the scales for the unvaccinated were about 3- fold less than for the vaccinated implying the vaccinated were at higher risk of death related to shedding. Data shows the putative risk of shedding deaths in the unvaccinated mirrored that for the vaccinated and the worse period was right after the second dose. Reduction thereafter in the vaccinated is thought to relate to the conversion of spike IgG1/3 to IgG4 in the blood which would have reduced the risk of death.

How Pathogens Like SARS-CoV-2 Circumvent TI

It should be appreciated that IRF1 is considered a tumor suppressor factor. The induction of the malignant phenotype 'epithelial mesenchyme transition' (EMT) leads to silencing of IRF1 transcription by repressive H3K27me3 histone marks [67]. Many viruses exploit the downregulation of IRF1 by triggering the hyperactivation of the EGFR/ERBB2 pathway in

macrophages[2] which induces EMT [67]. For example, this was reported for SARS-CoV-2 upon infection of Huh7 cells [25]. Presumably entry of viruses and/or other intracellular pathogens into the protector foamy macrophages by activating EMT would abrogate TI. Thus, it seems human pathogenic viruses borrow the malignant phenotype to circumvent TI [67].

Ren X et al., [58] demonstrated in patients with severe disease that upon SARS-COV-2 infection *in vivo* into the macrophages the following were upregulated: FKBP5,[3] WDR74, CXCL8, TNF, NFKB1, IFNGR1, VDR, and CEBPB (enhancer for TI) while APLP2, CD274, RSAD2, MX1, LAMP2, IFNGR2, IRF1 (the major TF for TI induction), and SPI1 (pioneering enhancer for TI) were downregulated. These changes would be consistent with 1) apoptosis resistance and the loss of lytic release of the HERV-K102 particles and 2) the induction of EMT and the loss of expression of HERV-K102 proviral genomic transcripts by IFN-γ or IRF1. Accordingly, this culminates in the loss of TI by SARS-CoV-2 infection of macrophages. The WDR74 macrophages are the only ones in bronchoalveolar lavage fluids (BALF) involved in the recovery from moderate disease and were also depleted with progression to severe COVID-19 [58]. These macrophages likely represent the foamy macrophages shown in **Figure 1**.

Another aspect of how important these macrophages are to recovery from COVID-19 concerns the fact that of the 64 different cell types characterized by Ren et al., [58] in the BALF of the lungs, there were only two cell types with highly activated vitamin D receptor (VDR) regulons; the WDR74 macrophages putatively producing the HERV-K102 particles with release through cell lysis and their progenitors the CD14+CD16 (intermediate) monocytes [58]. Since vitamin D sufficiency (over 50 ng/ml) is known to protect against COVID-19 death (see **Figure 6**) and more generally against all cause mortality [69] this finding confirms the M1-like foamy

[2] Where the virus often gains access to macrophages via antibody dependent enhancement (ADE) of infection of macrophages [5].

[3] Which prevents the nuclear signaling of the NR3C1 glucocorticoid (GC) receptor thereby inducing GC resistance and critical illness related corticosteroid insufficiency (CIRCI) which is associated with NFKB1 pathological upregulation and cytokine storm [68].

macrophages that generate TI are in fact the critical cell type mediating recovery from COVID-19.

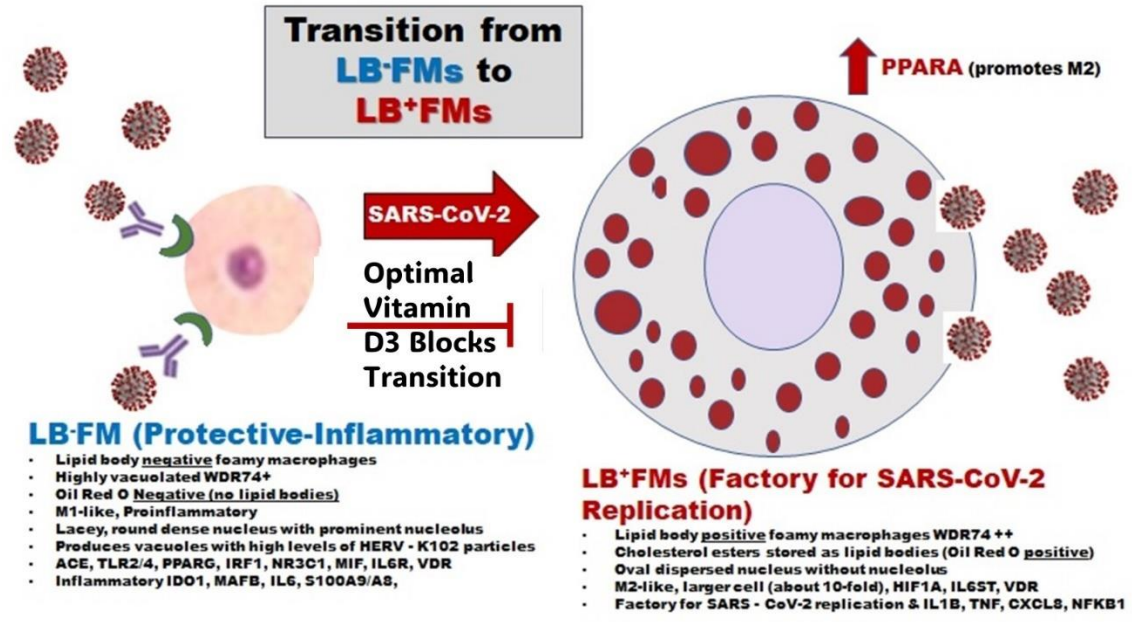


Figure 6. Optimal vitamin D3 levels block the ability of SARS-CoV-2 to transition the lipid-body negative foamy macrophages that produce the protector HERV-K102 particles to the lipid-body positive foamy macrophages (that are Oil Red O positive) and provide an immunologically privileged site for SARS-CoV-2 replication [5]. This transition is via the phosphorylation of MAPK8 (JNK) which is abrogated when vitamin D levels are sufficient [70]. Many human intracellular pathogens (viruses and Mycobacteria) attempt to convert the lipid-body negative foamy macrophages that produce the protector HERV-K102 particles to the lipid-body positive foamy macrophages which become an immunologically privileged site for their unimpeded replication [71].

In the upper respiratory tract (URT) as demonstrated from nasopharyngeal swabs, the core TFs for TI namely SPI1, CEBPB, and IRF1 were downregulated in the activated sebocytes

(inflammatory macrophages) upon SARS-CoV-2 infection [72]. The latter was also associated with upregulation of the RIG1-MDA5 with the induction of a number of ISGs. Three genes known to be associated with apoptosis in the sebocytes were downregulated (LAMP1, LAMP2 and LCN2, [72-74]). Thus, in the URT it seems SARS-CoV-2 infection blocked HERV-K102 particle production and most likely also prevented its release.

In the lower respiratory tract (LRT) HERV-K102 particle production and release were probably also blocked but in the BALF there was a notable difference in that several inflammatory factors were upregulated (TNF, NFKB1, IFNGR1) and including CXCL8 which recruits and activates neutrophils (**Figure 6**). There was an upregulation of CEBPB associated with this proinflammatory response in the SARS-CoV-2 infected macrophages [58].

Thus, it seems SARS-CoV-2 infection of macrophages *in vivo*, likely abrogates both TI and HERV-K102 expression, creates dysfunctional macrophages and can lead to dysregulated inflammation.

In animals BCG vaccination which induces TI has been shown to protect against SARS-CoV-2 [4]. The induction and release of interferon gamma (IFN-γ) from CD8+ T cells was also crucial for the establishment of TI following BCG vaccination in animal models [6]. Rivas et al., [75] reported a history of BCG but not influenza vaccination was associated with decreased SARS-CoV-2 seroconversion (i.e., protection against symptomatic infection). However, not all clinical trials have demonstrated that BCG vaccination protects against COVID-19 infection or severity.

It should be noted that a recent claim that BCG vaccination failed to protect against COVID-19 in a randomized clinical trial (RCT) [76] was misleading. Rather, this trial did not exclude COVID-19 vaccination which regrettably obscured the results. The correct interpretation of this clinical trial would be that the results could not be interpreted due to confounding by administration of other vaccines in most of the participants. Nevertheless, Netea et al., [77] have additionally commented on some of the other reasons it may be difficult to show that recent BSG vaccination protects against SARS-CoV-2.

Be that as it may, a number of groups have shown COVID-19 severity is linked to defective trained innate immunity [5,77] and/or the delay or loss of the early interferon response [reviewed in 78] .

Yamaguchi et al., [79] provided interesting evidence on the ability of the BNT162b2 Pfizer BioNTech COVID-19 vaccine to induce 'differentially accessible regions (DARs)' consistent with TI induction. These markings were especially enhanced as measured at one day after the second dose. Notably, these motifs were enriched for SPI1 and IRF1 and/or IRF8 response elements. However, by day 49, these DARs were no longer detectable which implied the expression of persistent spike associated with the mRNA gene therapy technology and/or antibody-antigen complexes may have adversely altered the programming of the myeloid lineage by abrogating TI. In juxtaposition to this, COVID-19 patients presenting with acute respiratory distress syndrome (ARDS) exhibited a loss in the expression of the same type I IFN stimulated genes associated with TI when assessed in monocytes by single cell RNA (scRNA) sequencing. These genes included: IRF1, IFITM1, APOBEC3A, ISG15, WARS, GBP1, IFI6, FCGR1A, IFITM3, TNFSF10, and GBP4. Note that APOBEC3A does not lead to deamination of HERV-K nucleotides during the reverse transcription step and so it does not introduce mutations as was shown with an artificial HERV-K HML-2 consensus construct called Phoenix [80].

The Yamaguchi et al., [79] data also suggests that it may well be TI induced in monocyte-macrophages which protects against severe COVID-19 disease. Furthermore, unlike natural infection, the TI protection boosted by the second dose of the COVID-19 vaccine expired at 28 days thereafter (day 49). It is entirely plausible that the induction of the spike specific antibodies by the second dose of vaccine [81,82] likely peaked around day 28 after the second dose. It remains to be determined if immune complexes or spike protein alone might abrogate TI such as through tolerance, immunosenescence induction or by the direct entry of SARS-CoV-2 spike protein into the macrophages by ADE.

The fact that persons who have recovered from COVID-19 display DARS associated with

TI along with IRF1 expression in CD14+ monocytes in blood [79] also implicated TI in recovery. Here chromatin accessibility was demonstrated at NR4A1, IRF1, IRF8, SPIB, HoxA9 and BCL11A. Others have also implicated TI in recovery from COVID-19 by examining the epigenomic landscape of peripheral immune cells [83].

As discussed elsewhere, in addition to TI, direct evidence also shows that HERV-K102 expression inversely correlates with COVID-19 severity [5]. This is not surprising given its implied critical role in foam cell formation and in TI generation in foamy macrophages.

Taken altogether, for the functional definition of TI, it is not so much that it involves the heightened release of inflammatory cytokines, but that TNF-α, IFN-γ and NF-κβ1 converge with IRF1 at ISREs to induce the transcription of a protector foamy retrovirus identified as HERV-K102 [40,41] which not only promotes TI but serves to greatly amplify it. Glycolysis is needed to support cholesterol production for foam cell formation related to HERV-K102 replication and particle production. It should be noted while the PI3K/Akt/mTOR pathway induces foam cell formation associated with BSG expression in macrophages such as induced by oxLDL, interfering with NFKB1 does not block foam cell formation [84]. This means the inflammatory component such as by NFKB1 is not an absolute requirement for TI as has been observed by others [6,7]. Perhaps foam cell formation involving HERV-K102 particle production in foamy macrophages would better characterize and thus define TI.

TI in Cancer Patients: Introduction

While the discussion so far has focussed on trained immunity in response to infectious agents, it goes without saying that M1 polarized macrophages also play a key role in immunosurveillance against cancer [8]. In particular we have just discussed how pathogenic infectious agents upon entry into macrophages induce EMT to counteract TI and downmodulate IRF1 to block the specific induction of HERV-K102 protector particles. Recall that IRF1 is considered a tumor suppressor [67]. So, there may be some truth to the notion that tumor transformation and the viral transformation of cells are similar and involve EMT overlapping mechanisms. Before we discuss TI in cancer patients let us first address the question of what cancer is. The various cancer theories tended to focus on certain aspects of tumor biology meaning they attempted to try and establish the primary characteristic governing the behaviour of cancer cells and will briefly be reviewed here.

Perhaps the oldest theory on cancer adopted early in the 20th century is the somatic mutation theory where it is said mutations in tumor suppressor genes and oncogenes cause cancer [85,86]. In other words, cancer is genetically determined which means not much can be done about it except slash and burn. This has been and remains the basis for chemotherapy and radiation therapy along with surgical removal of the primary tumor which is still the standard of therapy today. Next was the tissue organization field theory in 1999 where it was stated proliferation is the default state of all cells and carcinogenesis is a disease of tissue organization [87]. Then along came the atavistic theory of cancer in 2011 that proclaimed that cancer was a reversion to an ancient program of survival (cell versus organism) [88]. The cancer stem cell theory of 2010 [89] stated the cancer stem cells acquired the tumor initiating mutations. On the other hand, Warburg maintained as early as 1956 that tumor cells have an (variably) altered metabolism in which dysfunctional mitochondria may play a role [90]. Not to be outdone, Baghli and colleagues recently published their mitochondrial stem cell connection (MSCC) theory that states cancer arises from chronic oxidative insufficiency in cancer stem cells [91]. There was even an egg cell genetic program of

cancer origins (2022) which was loosely based on the notion of parthenogenesis in germ cells and fetal metabolism programming [92].

The Important Concept of EMT and the Cancer Phenotype

In my opinion, the most important development of our understanding of cancer came when it was realized that the malignant nature of tumors was not genetically determined but a phenotype, called epithelial mesenchymal transition (EMT) and which could be reversed by mesenchymal epithelial transition (MET) [93]. An excellent overview of the mechanisms was provided by Lamouille et al., in 2014 [94]. This meant that the slash and burn approach to cancer therapies was outdated, no longer needed and literally, overkill. Despite this advance being widely acknowledged by 2006, it is surprising that to this day, chemotherapy and radiation therapy are still the first line of treatment for cancer patients with or without surgical removal of the primary tumor. This status quo is maintained despite the fact that not unlike childhood vaccines, there have been no placebo controlled randomized clinical trials that conclusively demonstrate a significantly elevated clinical benefit on *overall survival* (ie., more than 15% -20% improvement in absolute values representing a clinically significant response), by either of these therapies alone or together. The progression-free or disease-free survival statistics commonly used to warrant regulatory approval are frankly immaterial, since it makes no sense to "cure cancer" but at the same time cause a higher risk of death due to non-cancer causes. Replacing one cause of death for another should never be the basis for the regulatory authorization of any marketed product for any purpose!

Fortuitously, the first person in the world to suggest that cancer was not genetically determined but a phenotype and therefore amenable to pharmacological interventions was myself in 1994 [37]. For my Ph.D. thesis, I had discovered and characterized the 67 kD AFPr which was expressed on macrophages and overexpressed on the common solid tumors, the adenocarcinomas (like breast, lung, prostate, colorectal cancer, and so on) [35]. I had made and identified two MAbs to the 67 kD AFP receptor which behaved as AFP agonists. As mentioned, this enabled me to

unequivocally validate the immunosuppressive effects of AFP on macrophage tumor cytotoxicity, and general inhibition of immune reactivity which had remained controversial [35]. I also discovered that AFP blocked apoptosis in a macrophage cancer cell line which has implications both for the malignant potential of tumor cells and for failed apoptosis of macrophages. Unbeknownst to me at the time this apoptosis resistance of macrophages had significant implications for immunosenescence of macrophages and the cause of chronic disease [31,34] while at the same time jeopardizing TI (**Figure 7**).

The New Immunosenescence Paradigm of 2015 (What Happens When TI in Foamy Macrophages is Inhibited by Active AFP)

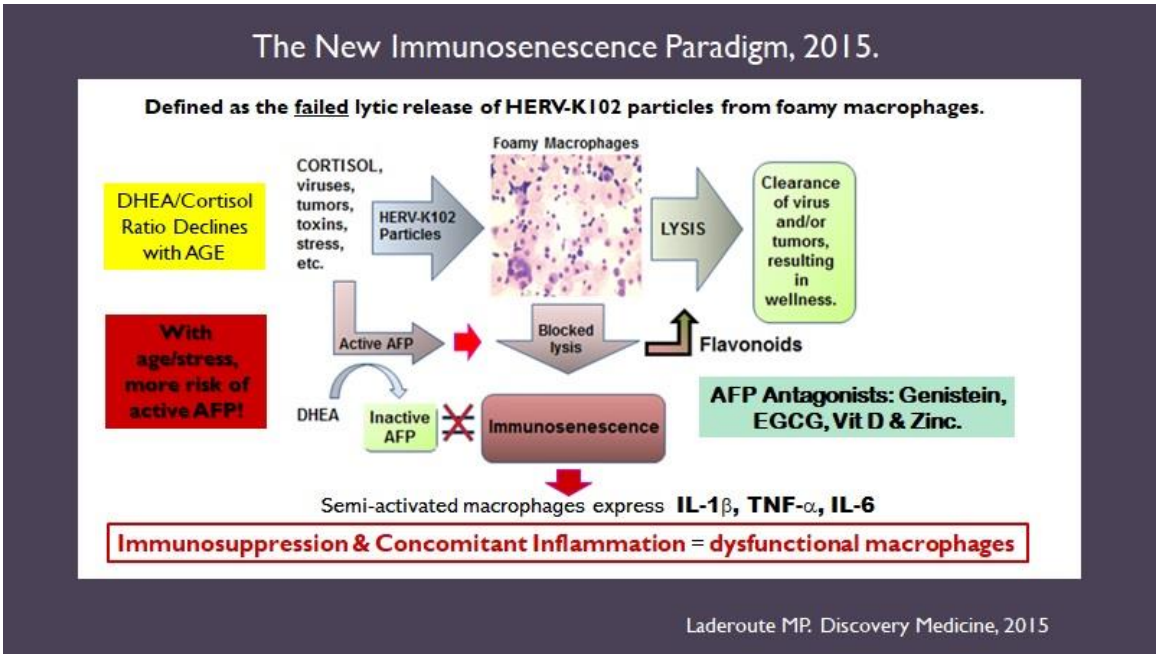


Figure 7. The New Immunosenescence Paradigm of Macrophages , 2015 [34].

DHEA but not the inactive DHEAS binds and inhibits the ability of AFP to cause apoptosis resistance in primary cells [34]. With age, stress and/or infections the levels of DHEA diminish

and now when TI is induced in the macrophage in response to viruses, toxins or tumors, the active AFP can bind to the 67 kD AFPr on macrophages and this block the lysis of the foamy macrophages. This essentially mediates EMT causing immunosenescence (dysfunction) in the macrophages. However, because this cell type is partially activated it means it is already producing proinflammatory factors, and as a result, AFP activity prevents their downregulation. So now the macrophages are completely dysfunctional being immunosuppressed by AFP and paradoxically also exhibiting a pro-inflammatory phenotype. The treatment for this condition would be the use of *AFP antagonists* (such as zinc, vitamin D, genistein, EGCG, 7-keto DHEA and now ivermectin [95]. In contrast the use of anti-inflammatories[4] would only treat the symptoms and not the cause, and in the long run would do more harm than good by immunosuppressing the M1-like foamy macrophages. Commonly used anti-inflammatories that interfere with the clinical reversion of immunosenescence by nutraceuticals (personal observations at Immune System Management in Ottawa, Ontario Canada as Lab and Research Director) include statins, turmeric, and melatonin over 2 mg per night. It should be noted that the adverse effects of active AFP is more akin to that presented **Figure 6** rather than **Figure 7.** In **Figure 6,** SARS-CoV-2 which upregulates AFP and results in the hyperactivation of the ERBB2 mediated PI3K/Akt/mTOR signalling pathway [25, and Prof. Ujjwal Neogi, personal communication] causes the conversion of the M1-like foamy macrophages (producing the HERV-K102 particles) to the M2-like dysfunctional foamy macrophages. The latter cells are resistant to apoptosis and no longer produce the HERV-K102 particles. However, it should be appreciated that this conversion is likely blocked by vitamin D3 levels over 50 ng/ml.

[4] Most allopathic and naturopathic approaches to chronic disease use anti-inflammatories that are in fact immunosuppressive and make things worse and not better. To treat the cause, one has to use AFP antagonists.

The Unified Theory of Cancer, 1994

However, no matter what the signal was (apoptosis, adherence, detachment, proliferation, differentiation, cytotoxicity of macrophages on tumor cells, etc.) AFP or the anti-AFP receptor MAbs always inhibited the concurrent signaling [35]. This led to the *novel* discovery that AFP imparts a negative signal that abrogates any incoming signal. This in fact could help explain how malignant cells appear to have their own rogue agenda and are able to ignore normal signalling. So, the hypothesis that I put forth in 1994 [37] was an attempt to unify how it is that AFP released by the tumor could in an autocrine fashion confer malignant potential of the tumor (including apoptosis resistance) and at the same time this secreted AFP could also mediate the immunosuppression of macrophages in the host. I have dubbed this my 'unified theory of cancer'[37]. So not only was I the first to propose that the malignant nature of tumor was a phenotype but also attempted to explain what controlled this phenotype and therefore identified what would be a suitable target for cancer. Regrettably since it was heretical at the time to suggest the malignant nature of tumors was *not* genetically determined, my paper [37] was met with disbelief and was and still is largely ignored.[5]

AFP and AFP Receptors As Targets for Cancer Cures

According to my unified theory of cancer [37], the cure for cancer (ie., to reverse malignant potential) would be the use of AFP and/or AFPr antagonists. This was predicted in 1994. Today (more than three decades later) we do have strong evidence that ivermectin appears to be a very potent AFP antagonist [95]. It is a rather effective treatment not only against pandemic viruses [96-98] but as an intervention even for late-stage cancers [91]. Dr. William Makis tells us daily on X [https://x.com/MakisMD] and on substack [https://makismd.substack.com] of his success with combining ivermectin with benzimidazoles typically clearing the advanced and rapidly

[5] Except the Editor of Molecular Carcinogenesis who was excited that 'potentially' the cure for cancer had been discovered.

progressing cancer within 3 months [91].

Recent evidence suggests that benzimidazoles may inhibit the activation of Her/2 (ERBB2) [99,100]. While the identity of the 67kD AFPr remains elusive, a candidate gene would be herstatin, an alternative splice variant and truncated transcript of ERBB2 [101]. This protein is also 67 kD and utilizes novel nucleotide sequences from intron 8. It binds and keeps ERBB2 in the off position in the cell membrane [101]. Presumably AFP binding to the 67 kD herstatin (putative AFPr) causes this complex to dissociate from the cell surface membrane. In this regard, the AFP and AFP binding protein complex has been found to be elevated in the blood or pleural effusions of breast cancer patients [35]. Alternatively, or in addition, AFP binds MUC4 which triggers ERBB2 [102] meaning ERBB2 comprises an important component of at least one AFP receptor. At the very least, because the main pathway for AFP to confer malignant potential is through the same PI3K/Akt/mTOR pathway for ERBB2 [95] as was shown with SARS-CoV-2 infection [25] means there could be great synergy in effectiveness with using an AFP antagonist (ivermectin) and an AFPr/ERBB2 antagonist (benzimidazole). Together they would knock out malignant potential and equally important, immunosenescence in the foamy macrophages promoting recovery (**Figures 6 and 7**).

In other words, accumulating evidence seems to corroborate my unified theory of cancer proposed in 1994 [37] that (active) AFP through AFP receptors confers malignant potential on tumors. No less significantly to the current discussion, active AFP would also diminish pertinent and critical host immunity against cancers namely TI in foamy macrophages by way of the 67 kD AFPr expressed on macrophages.

Before I examine the evidence pointing to γ δ T cells in mediating recovery from cancer and why the WDR74 M1-like protector foamy macrophages needed for recovery from COVID-19 [58] are generally glossed over in cancer patients, it would be useful to briefly discuss the innate T and B cells recognition of HERV-K102 envelope in cancer patients and other diseases.

Innate T and B cell Recognition of HERV-K102 Envelope

It all started in 2001 when Wang-Johanning et al., [103] first reported HERV-K102 splice envelope RNA transcripts as well as the full length HERV-K102 proviral RNA transcripts commonly in patient breast cancer tumors but not in the adjacent normal tissues by Northern blotting.

As a technical note and which is explained elsewhere [5] the protein P61567 corresponding to the splice envelope transcript that may be expressed on its own in cancer tissues, lacks the 'KRASTE' amino acids and has a different conformation than the full proviral *pol-env* sequence corresponding to protein P63135. Note that of the HERV-K HML-2 group members only HERV-K102 is replication competent *in vivo* and *in vitro* [40,41], and so it is not surprising that HERV-K102 uniquely has two entries for envelope protein in GenBank (NCBI): one encoded from the full-length provirus *pol-env* RNA and one from the alternative spliced envelope. A conformational difference in the two sources of envelope protein was needed to explain why the existence of antibodies to envelope on the surface of cancer cells (the putative P61567 envelope) did not clear the HERV-K102 particles from the circulation which clearly have envelope protruding from the surfaces of particles (**Figure 1**) [5].

By 2007 Wang-Johanning et al., had shown in ovarian cancer cell lines and in ovarian cancers that the HERV-K102 envelope protein was expressed at the cell surface (in about 55% of ovarian cancers) but not in ovarian tissues from healthy normal females [104]. This was quickly followed by the finding of T and B cell responses to HERV-K102 envelope protein in breast cancer patients [105]. About 88% of breast cancer tumors expressed HERV-K102 (or similar) envelope protein as detected with their new MAb to the surface unit component of the HERV-K102 envelope called 6H5. IgG antibodies were commonly detected in the serum of breast cancer patients but not normal healthy controls. Multiple T cell responses to HERV-K102 envelope were demonstrated including proliferation, IFN-γ production as determined by ELISPOT assays, multiple Th1 cytokine responses involving IL-2, IL-6, IL (CXCL8) and IP-10 (CXCL10), and also cytotoxic

T cell responses. They noted at this time that others had reported CTLs to HERV-K gag antigens that cross-reacted with HIV-1 gag protein which seemed to control HIV-1 replication [106].

By 2007 our research team had reported that antibodies to the ML4 (KRASTEMVTPVTWMDN) and ML5 (LETRDCKPFYTIDLNSS) HERV-K102 (AF164610) surface unit envelope protein derived peptides were detected in 80% and 70 % of HIV-1 patients, respectively while marginal reactivity to these peptides were detected in about 2% of healthy normal controls [40]. The reactivity was at much higher levels in HIV-1 patients than patients with herpes infections seemingly to compensate for the very low levels of HERV-K102 particles in HIV-1 patients that on average was about 8,200 particles per ml of plasma [56]. In contrast, 10^{12} HERV-K102 particles per ml of plasma were commonly detected in patients viremic for other bloodborne pathogens [40]. Moreover, induction of HERV-K102 particles was very fast at 2.55 x 10^{11} particles per ml of plasma at 84 hours from zero particles per ml of plasma in a patient with a post-viral syndrome (who temporarily stopped therapy for research purposes [56]).

By 2012, Wang-Johanning et al., published on a most remarkable finding that their 6H5 MAb to HERV-K102 envelope protein induced apoptosis (cell death) in breast cancer cell lines *in vitro* and *in vivo* in a xenograft mouse model [107]. This was mediated by p53 and CIDEA activation affecting TP53AIP1 and AFP/caspase 3 interactions freeing caspase 3 for cell death induction. Importantly, TP53 is known to downmodulate AFP expression [108] and this was extended to include other members of this family of TP53 repressive TF like TP63 and TP73 [109]. Moreover, it is well established AFP binds and inactivates caspase 3 [110]. Thus, in 2012 we had our first evidence that HERV-K102 envelope cell surface expression when triggered downmodulates EMT and renders tumor cells *more sensitive to apoptosis via p53*.

It was around this time that Jones et al, 2012 [111] described that they isolated T cell clones from an HIV-1 elite suppressor (naturally controls HIV-1 so no virions detected in serum) that could clear HIV-1 and any other lentivirus infected cells in culture by recognizing a peptide 100% identical to HERV-K102 envelope protein. This further extended the protective effects of T and B

cell responses to HERV-K102 envelope antigens not only in cancer patients but to those harboring pandemic viruses such as HIV-1.

In 2022, a report emerged that inferred antibodies to HERV-K102 envelope were protective against amyotrophic lateral sclerosis (ALS) [112]. Along similar lines, Arru et al., [113] had used two HERV-K102 envelope peptides 19-37 and 109-126 and found that both peptides *stimulated* IFN-γ and CCL3 in B cells while 19-37 stimulated IL-6 production in B cells and TNF-α in CD8 T cells. Thus, it was suggested that HERV-K102 envelope protein such as present on HERV-K102 particles might stimulate innate T and B cells. Recently it was demonstrated that the triggering activation of the innate γ δ T cells was by the cGAS-STING pathway [114] which is well known to be activated by the entry of the HERV-K102 particles that contain cDNA genomes [46, 54, 55]. In this regard it is noteworthy that monocytes were indeed needed for the cGAS-STING activation of the γ δ T cells [115, 116].

γ δ T Cells Appear to Mediate Recovery from CANCER

With the advent of single cell RNA sequencing, accumulating evidence has suggested that the γ δ T cells of innate immunity appear to be necessary and sufficient for recovery from cancer [117-121 and reviewed in 122]. That the γ δ T cells show trained innate immunity has been recently demonstrated [123]. However, TGF-β expression can abort this protection by the γ δ T cells [114]. TGF-β can behave as a tumor suppressor when it activates the smad pathway via TGFBR2 or can be oncogenic through non-Smad pathways such as those involving PI3K/Akt, p38 MAPK, MAPK-ERK, and JNK pathways [124]. For the latter, it is possible that by TGF-β binding to AFP which activates AFP [125,126], that this interaction provides in part, an explanation of how TGF-β expression may correlate with the upregulation of EMT when p53 is altered or lost [127]. Co-incidentally, TGF-β Smad proteins work with p53 to down regulate AFP [128,129] and raises the issue if p53 is non-functional would Smad proteins instead upregulate AFP expression? This possibility may be partially substantiated by the finding that combining TGFB1

overexpression with AFP upregulation improves the specificity for hepatocellular carcinoma (HCC) diagnosis [130]. A similar issue has been observed for ZBTB20 a transcription factor that is responsible for the post-natal downregulation of AFP expression [131]. In this case in the presence of altered TP53, it becomes an oncogene and upregulates AFP in HCC [132].

Why Aren't the M1-like Foamy Macrophages Implicated in Recovery from Cancer?

In terms of the HERV-K102 protection system, it may be somewhat surprising to some that in these investigations generally, the foamy macrophages producing the HERV-K102 particles were not identified as mediating critical protection against tumors. Early analysis of the successes of some patients treated with the immune checkpoint inhibition (ICI) therapies actually pointed towards the T CTLs in recovery from cancer [133]. Occasionally protector macrophages have actually been reported such as in cases of uveal melanoma [134].

There may be several reasons for why the M1-like foamy macrophages are not identified or connected with recovery from cancer. For example, many human studies employ PBMCs for their studies, but macrophages are not generally found in the blood but in tissues. Second even when the immune cell landscape is analysed from tumor biopsies, the lumping together of all the M0, M1, and M2 macrophages into one category called macrophages, would mask any protective effects of M1 or harmful effects of M2 from being discovered [133]. The third reason may be the most significant, and that is when the HERV-K102 particles are launched by lysis of the foamy macrophages (**Figure 1**) means the protective immune cells disappear. Accordingly, it would be difficult to pinpoint a cell type that no longer exists!

An examination of the relative number of the protector WDR74 macrophages in BALF of severe COVID-19 patients showed it comprised a mere 0.5 % of all the macrophages (92 of 18576 cells) [58]. In contrast, the WDR74 positive foamy macrophages were 54% of the macrophages

in the blood (PBMCs) of severe COVID-19 patients (562/1046). This may have been because of their recent differentiation from the CD14+CD16+ monocytes of the blood [58].

To overcome this problem of insufficient numbers of macrophages examined such as in tumor extracts, Zhang et al [135] strictly examined the myeloid subtypes (monocytes and macrophages) where the tumor tissue cells were blended with the myeloid cells in PBMCs. The study was in patients with non small cell lung cancers (NSCLC) and attempted to discern what cell type correlated with ICI therapy success. When compared with the treatment naïve patients there was a notable increase in the M1-like macrophages that were FABP4 and C1q positive in those who responded to ICI therapy. However, the number of these M1- like macrophages was considerably less in those who did not respond to ICI therapy potentially implying there was a depletion mediated by the ICI therapy itself. Importantly those with high levels of the M1-like macrophages displayed a significantly increased overall survival when compared with patients with low levels. Thus, in this manner Zhang et al were able to demonstrate the correlation of M1-like macrophages with the cure of cancer.

Despite the inherent difficulty, early in 2025 a number of groups have confirmed that the CD4+ FCER1G M1-like macrophages (with high levels of HMOX1) [136] and the M1 but not the M0 or M2 macrophages [137] mediated recovery in cancer patients. In the latter case, the cell types associated with low risk were: CD8 T cell, CD4 T cell resting, and the M1-like macrophages while high risk involved: B cell memory cells, activated CD4 memory cells, T regs, M0 macrophages, M2 macrophages and neutrophils. All together with the $\gamma\ \delta$ T cell publications, it seems that adaptive immunity responses may have been detrimental to recovery from cancer, much like what had been observed for COVID-19 recovery and for the prevention of more severe forms of COVID-19 disease [5].

Before we leave the topic of the activation of HERV-K102 in the mediation of trained (innate) immunity needed for recovery from cancer or pandemic viruses, there is one more important paper that clarifies that the HERV-K HML-2 does not cause disease but prevents it. An

unexpected development in oncology was the finding by Liu et al., (2022) that suggested two p53 binding sites in the HERV-K HML-2 LTR5Hs[6] but not found in the LTR5A or LTR5B LTRs were able to amplify the p53 tumor suppressor induction of genes downstream of these promoter sites in a species-specific manner accounting for about 70% of the p53 response [83]. For example, CRP (indicator of inflammation at 1q23.2) was downmodulated and DDX6 (RNA helicase 11q23.3) and MX1 (anti-viral,21q22.3) were upregulated. This clearly implicates the expression of HML-2 group members in cancer or with infections as part of the host innate immunity protection system rather than the cause or promotion of cancer that is frequently and wrongly supposed. This matches the earlier finding that triggering HERV-K102 envelope with antibody on tumor cells induced p53 and apoptosis in cancer cells [107], which cannot be mistaken for promoting harm to the host.

Summary and Conclusions

In this review article the mechanisms and clinical significance of trained (innate) immunity to human survival whether from cancer or infectious diseases has been discussed. The key mechanism by which foamy macrophages generate trained immunity is unequivocally through the induction of the HERV-K102 protector foamy retroviral particles which generates foam cell formation. Once released, it is believed the particles will activate the protector interferon response generally upon entry into cells. Presumably HERV-K102 integrates in these cells which would enhance the next response showing memory. There is some suggestion that the HERV-K102 particles might be necessary and sufficient for $\gamma\,\delta$ T cells activation as their cDNA genomes may activate the cGAS-STING pathway in these critical cells. Moreover, the possibility has been raised

[6] Retroviruses in the human genome have long terminal repeats (LTRs) usually at the 5' and 3' ends of their genomes needed for replication although only HERV-K102 is replication competent *in vivo* and *in vitro* [38,39]. LTR5Hs refers to the human specific LTRs of the HERV-K HML-2 family to which HERV-K102 belongs. Generally, this refers to HML-2 retrovirus acquisitions within the last 5 million years in the genomes of *Homo sapiens*.

that the envelope on the HERV-K102 particles itself could activate innate T and B cells. Not discussed here was the notion that the HERV-K102 particles themselves can cause rapid and intense apoptosis of tumor and/or infected cultured cells because these particles are oncolytic [5]. The fact that antibodies to HERV-K102 envelope can trigger apoptosis in cancer cells through the induction of p53 was rather remarkable along with the finding of recently integrated human specific HML-2 sequences spreading the p53 tumor suppressor phenotype by altering the expression of genes. .

While there have been many theories of cancer, there was only one, the unified theory of cancer, 1994 [37] that contemplated and addressed how is it that the malignant potential of the tumor could be correlated with the suppression of host immunity, specifically macrophages. Given that we now know that the malignant nature of tumors is a phenotype (EMT) and not genetically determined allows us to pursue pharmacological products that could ameliorate the malignant phenotype for bona fide cancer cures. The pharmacological target proposed over 30 years ago for cancer cures, namely AFP and AFP receptors [37] seems not only plausible but miraculously effective judging by preliminary experiences of ivermectin combined with the benzimidazoles by Dr. William Makis. It seems to work so well that having a placebo arm in a randomized clinical trial would surely be judged unethical.

It was recently suggested by Larry Ellison the CEO of Oracle in the Oval office that part of the STARGATE $500 billion initiative would be the application of artificial intelligence for the rapid production (within 48 hours) of personalized custom cancer mRNA gene therapy vaccines based on the identification of cancer mutations and the derivation of sequences encoding the neoantigens to be used in the vectors. The research reviewed in this article implies that adaptive immunity does not cure cancer just like it doesn’t prevent transmission and severity onset of SARS-CoV-2 infections. If anything, because of ADE related to the rapid onset of mutations, adaptive immunity vaccines would make severe outcomes more likely. Many have tried and none have succeeded to create the elusive cancer vaccine that can be used over and over again.

Moreover, the spike mRNA gene therapy technology allegedly killed more than COVID-19 during the first 17 months of the spike mRNA gene therapy shot rollouts, at least in England [63]. In hindsight these treacherous shots were proven not to carry any benefits expected of vaccines and this severely questions why and how they became mandated.

Should ivermectin and the benzimidazoles be made available over the counter then people could stock their medicine cabinets with these miracle drugs in case of emergencies (a new pandemic or new diagnoses of rapidly evolving cancer). Accordingly, within a few minutes of a cancer diagnosis (the time it would take to access the medicine cabinet) and for at most a few hundred dollars (not billions of dollars), and regardless of stage, grade and/or cancer size or type, metastatic or not, most people could expect a complete cure usually within 3 months with the combined use of ivermectin and the benzimidazoles [91]. Furthermore, one doesn't have to be concerned about the technology inadvertently causing cancer or leading to sudden deaths and/or any other serious health problems or adverse events.

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