Review

Low-Dose Interferon I and Iii-Based Nasal Sprays: A Good-Looking Covid-19 Vaccine Candidate?

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Abstract

The COVID-19 pandemic and the recently-emerged highly transmissible SARS-CoV-2 Omicron variants have increased the demands for novel immunising and therapeutic approaches to protect the lives of patients with significant co-morbidities. Following a worldwide campaign of mass vaccination, there is still a significant demand to quell the harmful effects of the novel SARS-CoV-2 variants on people with serious co-morbidities, and there is still a dilemma of how we could prevent potentially catastrophic effects of future pandemics upon the human race. And the concerns intersect at a specific point; a gained evolutionary ability of several viruses over the previous centuries to go undetected during the first stages of infection by means of capping the 5' end of their genetic material, reducing the synthetic rate of Type I and Type III Interferons, temporarily inhibiting the apoptotic pathways of infected cells to facilitate a rapid viral replication, and inhibiting antigenic presentation. Type I and III Interferon-based viral immune evasion may be primarily associated with a delayed clearance of the viral load. Past clinical data also suggests that the SARS-CoV-2 spike glycoprotein is capable of inhibiting the V(D)J antibody gene rearrangement in developing B-lymphocytes, as well as diverse important cellular processes of DNA repair by downregulating the BRCA1 and 53BP1 genes. Furthermore, most traditional methods of vaccination do not particularly boost mucosal immunity and as a result, there is a visible gap that viruses can easily fill in, which implicates a reduced stimulation of a mucosal plasma cell production. Serum plasma antibodies do not cross the nasal epithelium and hence, offer little protection against mucosal inflammation, unlike the antibodies produced by mucosal plasma cells. We acknowledge the existence of a significant challenge to stimulate mucosal immune responses due to the high complexity of its structure-function axis. Nevertheless, over the past half century, numerous scientists developed ways of immunisation and early treatment worldwide that generally showed outstanding levels of success and insignificant risks of adverse events. An important example implicates the administration of human interferons I and III into the nasal mucosa to simulate local infection and train the innate immune system to robustly become activated and transmit essential signals before viruses silence it. Recently, it was discovered that specific plants secrete proteins that also stimulate the production of Type I Interferons. It might be that focusing on directly offering the immune system the information about the genetics and protein structure of the pathogen, rather than training its first-line mechanisms to develop faster, excessively increases its specificity, making it reach a level that brings the virus the opportunity to evolve and escape previously-developed host

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immune mechanisms. Naturally-selected polymorphic viruses had generated long-term evolutionary responses to deeply tackle the ability of the complex human immune system to neutralise viruses during the first stages of cellular infection. It is until the scientific community realises this that we will probably continue to face serious epidemics and pandemics of respiratory diseases over the coming several decades.

Keywords: covid-19; pandemic; immune evasion; first-line immunity; viral evolution; interferon; vaccinology

Introduction

Immune evasion represents the most serious immunological problem of the 21st century, and it is the result of a shift in the evolutionary battle between the human immune system and pathogenic viruses that took place throughout modern and contemporary history. Respiratory viruses represent the pathological category of viruses whose mechanisms of immune evasion are among the most prevalent, and it is likely that regular mutations leading to the development of new seasonal variants of Influenza A and SARS-CoV-2 are caused by the reduced ability of the immune system to locate and lyse the infectious viruses during their initial phases of replication. This explains the significant number of patients that develop symptoms several days after the actual infection took place, and the phenomenon is also known as a silent inflammation. With regards to the COVID-19 pandemic, it is important to acknowledge the methods the novel coronavirus utilise to escape the host immune system by means of replication and spread to several kinds of bodily tissues. Namely, once the virus has entered the host cell, it downregulates the activities of pattern recognition receptors that detect pathogen-associated molecular patterns found on the viral genome, and the expression rate of Type I and III Interferon-encoding genes. Namely, the viral genome also produces a number of non-structural proteins that decrease the amount of produced interferons, either by means of viral self-camouflage or by means of cleaving interferon-producing mRNA. Type I Interferons include interferon-alpha, -beta, -delta, - epsilon, -kappa and -omega, whilst Type III Interferons include interferon-lambda1, -lambda2 and -lambda3. Many of the non-structural proteins are conserved in a viral pocket known as the S-Adenosyl-L-Methionine pocket. Consequently, the virus heavily downregulates the autocrine and paracrine signalling rate of Type I and Type III Interferons during critical stages of infection and replication. Some of the viral non-structural proteins also inhibit products of Interferon-Stimulated Genes that lyse the viral genome. Likewise, the virus often gains a significant stronghold over the ability of the innate immune system to induce an important series of host cell apoptosis and to activate antigen-presenting cells and consequently, the developed viral evolutionary mechanisms are directly antagonising the mechanisms that Type I and Type III Interferons have to robustly induce the apoptosis of the infected cells once they have been released by the newly infected host cells to prevent further viral replication and spread. Moreover, by significantly downregulating interferon synthesis, viruses like SARS-CoV-2 gained a major stronghold over the ability of the innate immune system to create important antiviral

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(PKR-related) and anti-inflammatory signals, which are crucial for the correct development of the necessary further immune defenses. Moreover, the virus produces a structural protein named the spike glycoprotein, which has recently been discovered to weaken the activity of the BRCA1 and 53BP1 genes, which are implicated in cellular DNA repair mechanisms, as well as to inhibit the VDJ and VJ processes of heavy and light chain antibody gene rearrangements respectively. At the same time, the receptor binding domain of the spike glycoprotein forms a trimeric complex with the GRP78 chaperone, as well as with the ACE2 receptor, and it is the viral interaction with the GRP78 chaperone that further enhances infectivity and ultimately, virulence. Likewise, not only is it that the novel coronavirus utilises numerous methods to evade all essential areas of human immunity, but it was also discovered that the virus detects and utilises certain host proteins to increase its infective abilities (Carlos et al., 2021). It may be that a research focus that is primed upon the direct providence of the adaptive immune system with the genetic and proteic information of polymorphic viruses, like SARS-CoV-2, and ultimately not concentrated around the necessity of the training of first-line immune mechanisms to develop faster in front of the dilemma of first-line immune evasion, excessively increases the specificity of the host immune responses, which reaches a level that ultimately brings the pathogen the opportunity to evolve and escape previously developed mechanisms, as the developed immune memory does not cover mutated forms and novel antigens. Furthermore, given that early Interferon I and III-based immune signals are associated with overall high immuno-competency and in turn, to low extents of energy consumption due to low extents of induced disease, viral immune evasion could have been playing a major role in preventing a full increase of the human lifespan, particularly in world areas with higher incidences of hunger and poverty. Given that the “double-edged sword”-like immunological effects of Type I Interferons has shown visible signs of reaching areas as far as cellular metabolism and even brain ageing (via the choroid plexus), there are considerable reasons to believe that stimulating early Interferon I and possibly Interferon III-based immune signalling in large proportions of the world population by means of immunisation against infectious diseases and important forms of cancer will also play a major role in decreasing the average rates of oxidative stress, mutagenesis and metabolic acidification, leading overall to a better average quality and duration of life.

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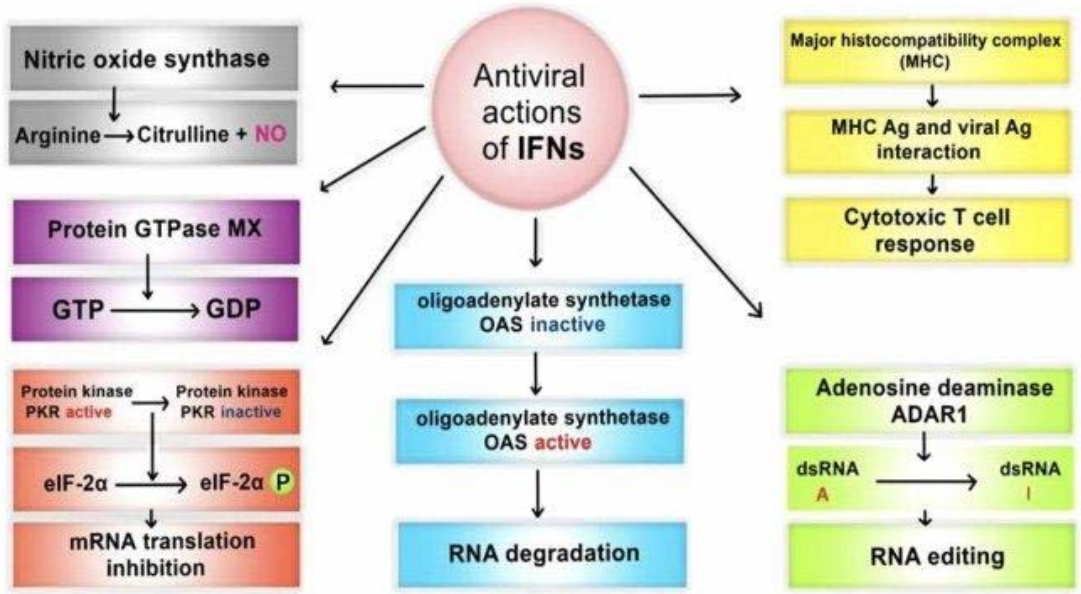

Figure 1: The molecular activities of Type I Interferons have implications upon key immune mechanisms, such as inhibition of viral replication, regulation of inflammatory responses, full training of lymphocytes and induced apoptosis of infected cells (Fatemeh S. et al, 2021)

The non-structural protein 1 (nsp1) activates the phosphatidylinositol 3-kinase (PI3K) pathway to inhibit the synthesis of Type I Interferons and activate cellular stress-response proteins, like heat-shock proteins, which inhibit apoptotic pathways of host cells at first, before they stimulate such inductions of host cell death (Ehrhardt et al., 2007). This initial inhibition of apoptosis stimulates a sharp increase of the viral load in the host organism. Moreover, the virus inhibits antigen presentation via the STAT1-IRF1-NLRC5 pathway and the first class of the Major Histocompatibility Complex, thereby affecting the specialisation of CD8+ T-lymphocytes (Yoo et al, 2021). Given that the antigen presentation process is affected as a result of the targeting of the same pathway as the one induced by Type I Interferon activation, we can determine that inhibited Interferon I activation is associated with a down-regulated endogenous antigen presentation, via Class I MHC. The downregulation of pattern recognition reception affects signalling from the TLR-3, TLR-4, TLR-7, RIG-1 and MDA5 receptors to the IFNA1, IFNA2 and IFNB1 genes. The non-structural protein 1 also lyses molecules of mRNA that encode Type I Interferons, whilst the non-structural protein 16 caps the 5′ end of the viral mRNA and makes the cell less capable of recognising the viral mRNA as pathogenic. Nsp1 was also found to impair the synthesis of Type III Interferon, potentially affecting the expression of IFNL1, IFNL2 and IFNL3 gene expression during infections with rotavirus and the porcine epidemic diarrhoea virus and, given that interferon-lambda was only discovered in 2003, we have reasons to believe that the synthesis rate of this sub-type of interferons could also affected during a SARS-CoV-2 infection. In other words, the production of non-structural protein 1 by the SARS-CoV-2 and Influenza A viral genomes

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represents a pathogenic evolutionary trait of viruses that is essential for pathogenic preservation in the human organism, as it represents a reaction against the hidden abilities of host organisms to lyse them efficiently from the moment of the first intracellular infection. Given that the synthesis rate of interferon-gamma, which is part of Type II interferons, partially depends upon the synthesis rate of interferon-beta, the impact of the listed non-structural proteins touches the normal synthesis rate of interferon-gamma, which is responsible with a normal signalling rate from the infected cells to neighbouring cells. And such signals in turn stimulate the neighbouring cells to produce and send antiviral signals to the immune system. Non-structural protein 16 requires activation by nsp10 and hence, nsp10 is known as the activator protein, whilst nsp16 is known as the effector protein. They then dimerize to form the 2'-O-Methyltransferase complex, and such nomenclature of the enzyme complex was established because nsp16 caps the 5' end of the mRNA molecule by attaching a methyl group to it. One study showed that SARS-CoV-2 did not induce interferon production and signalling in pHAE cell cultures. Namely, there was no detectable interferon-alpha of any subtype, and a low rate of synthesis and signalling of interferon-beta1 and interferon-lambda1, with normalised read counts that were lower than the value of 10. Furthermore, several genes involved in the pattern recognition reception and signalling cascade leading to Interferon I synthesis, including RIG-I, MDA5, TBK1, TRAF6, IRF-3 and IRF-7, displayed little to no transcription activities in response to the viral infection, which further indicates the impact of non-structural proteins 1 and 16 upon the sensitivity of the host cell to the virus (Abigail V. et al, 2020).

The methyl group is transported all the way from the S-Adenosyl-L-Methionine pocket, which is formed after joining of the S-Adenosyl molecule with the L-Methionine amino acid. The methyl group is transported to nsp13 and nsp14 before the nsp16 effector protein binds it. Non-structural protein 1 (nsp1) is the most problematic interferon antagonist because it significantly suppresses interferon-alpha and -beta synthesis, and because it was shown to suppresses interferon-lambda synthesis as well during rotavirus infection (Iaconis et al, 2021) and porcine epidemic diarrhoea virus (Zhang et al, 2018), thereby potentially amplifying the impairment of the formation of proper first and second-line immune defences. An impairment of such defences very likely have significant implications upon adaptive immune responses, and likewise, they can cause a higher incidence of moderate and severe disease. Given that Type III Interferon was only discovered in 2003, has the scientific community investigated the relationship between the viral non-structural protein 1 and interferon-lambda synthesis, and are there any odds that the SARS-CoV-2 nsp1 suppresses to any extent the synthesis of interferon-lambda, since one experiment involving a dosage of interferon-lambda2 in mice displayed positive results with regards to a mitigation of the disease (Chong et al, 2021)?

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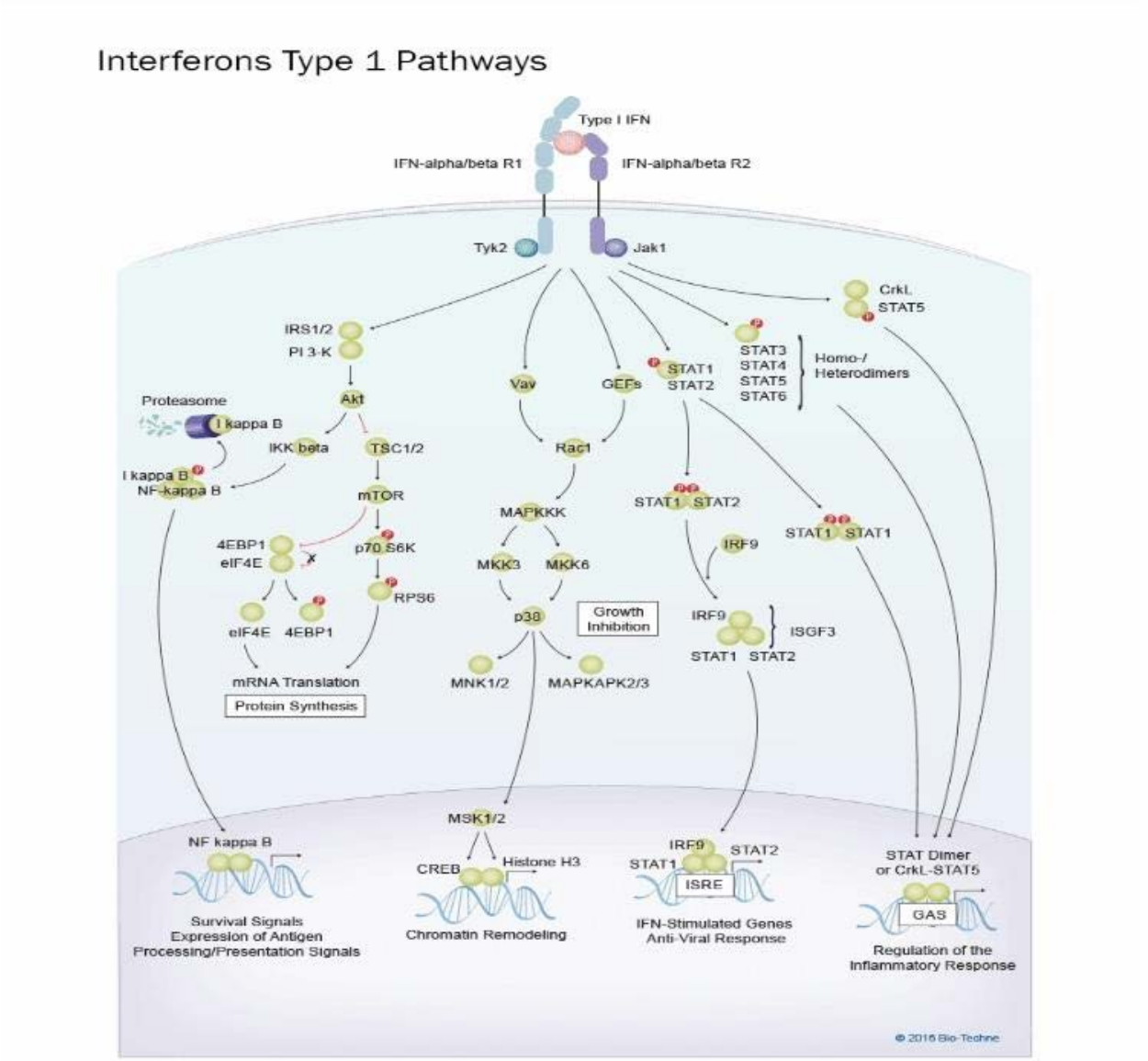

Figure 2: The four principal types of signalling cascades started by Type I Interferons (Bio-Techne, 2015)

Interferons represent soluble glycoproteins with a powerful antiviral activity, and they are produced mostly in dendritic cells, by means of tackling pathogenic viruses as soon as they infect such cells. There are three principal classes of interferons: Type I, Type II and Type III, and the first and the last have more specific antiviral activities, whilst the second class focuses more upon the development of pro-inflammatory responses as soon as an infectious event takes place. Recently, scientists discovered that a number of plants generate interferon-stimulating proteins, and we believe that specific dosages of such proteins could further empower the immunising and early therapeutic effects of the discussed interferons. The main focus in clinical research to tackle viral pandemics as the ongoing one is to regulate the ratio between the intensity of immune responses, their precision, as well as their timing according to the stage of viral

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infection and replication. The principal commonality between the majority of grave infectious diseases, numerous forms of cancer and several proteinopathies is that all of the disease categories generally involve a late and exaggerated development of Type I and Type III-Interferon-based immune responses, and this potentially means interferons of such kind could also play essential prophylactic, and sometimes, also early therapeutic roles in oncogenic, retroviral and neurodegenerative forms of disease as well, depending on the aetiology of the disease.

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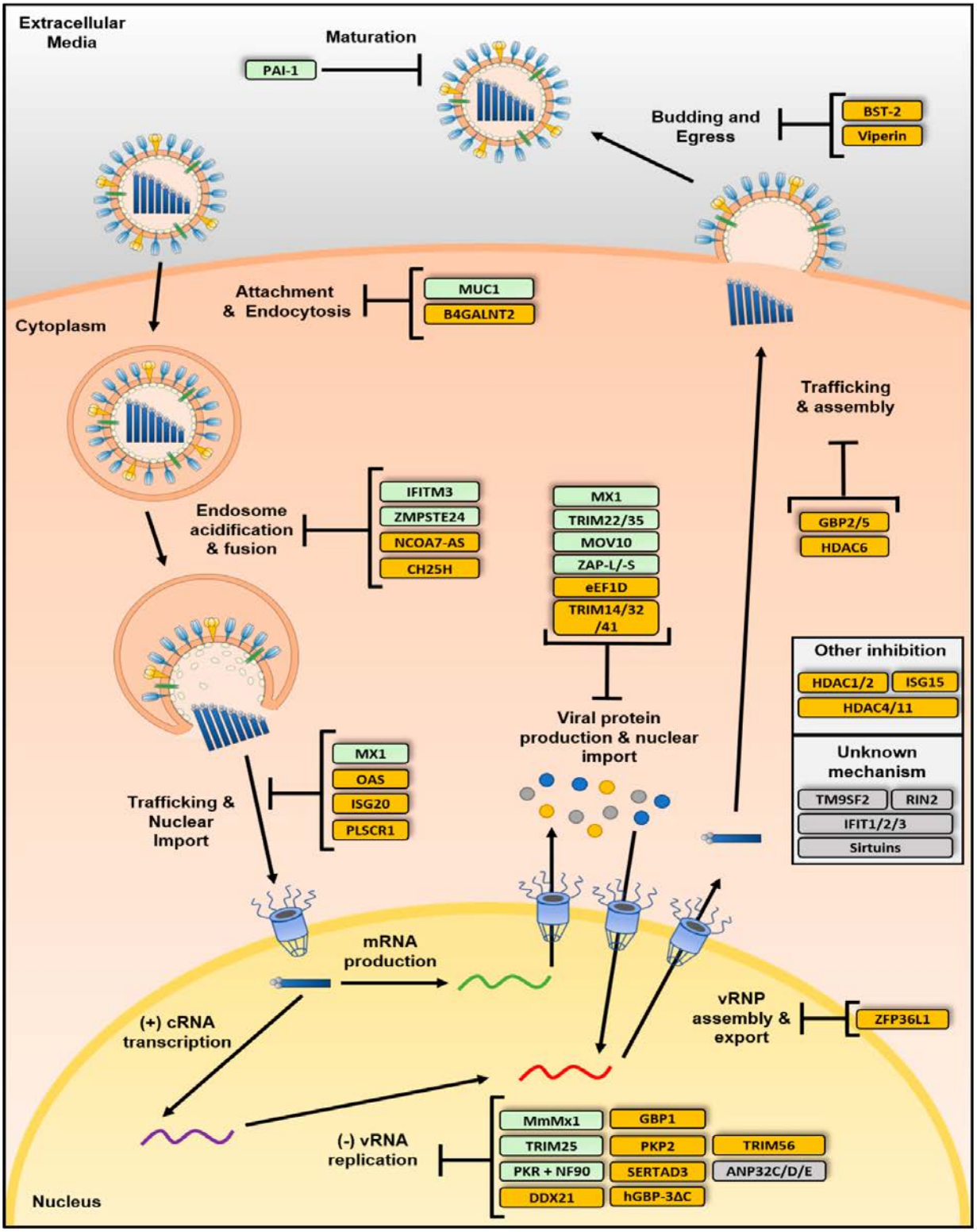

Figure 3: The ECM, cytoplasmic and nuclear proteins produced by interferon-stimulated genes, playing diverse important roles in restricting IAV infection (McKellar et al., 2021)

There can be three principal categories of Type I and III Interferon responses: early response, delayed response and an absent response. The first is followed by a firm restriction of viral load increase, enhanced regulation of pro-

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inflammatory responses and mild clinical forms of the disease. The second is followed by a dysregulated inflammatory monocyte-macrophage response, severe forms of pneumonia and lung tissue damage. A delayed and exaggerated Type I Interferon response will generally overstimulate pro-inflammatory mechanisms and stimulate the development of more severe forms of the disease. The third is followed by a high viral load, longer intensive care unit visits, invasive ventilation and a poor prognosis. Likewise, we can deduce that an administration of nasal sprays prophylactically might in turn be more important before the onset of the disease than after symptoms have occurred and our hypothesis is that patients would better receive the nasal spray either before they encounter any clinical forms of the disease, in the first stages of the clinical display, before the peak of the viral load has been reached, or in any other disease stages that do not involve serious symptoms and severe disease (Fatemeh S. et al, 2021). A delayed clearance of the viral load is likely a common consequence of Type I and III Interferon-based viral immune evasion.

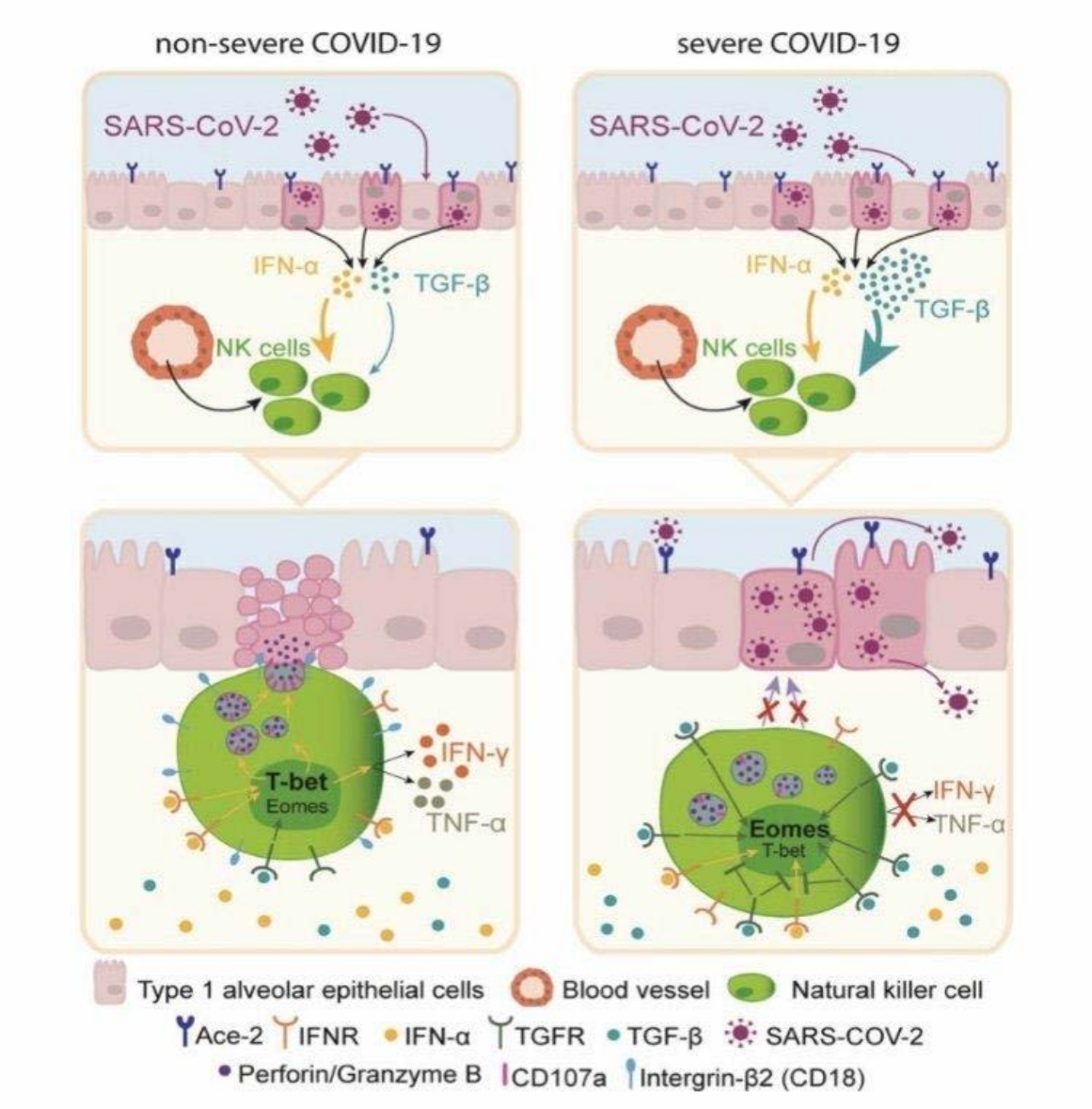

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Figure 4: Different signalling ratios between Interferon-alpha and Tumour Necrosis Factor-beta usually lead to different outcomes of COVID-19 (Barros-Martins et al, 2022)

Methods

Peer-reviewed scientific papers, journals and books concerning the effectiveness of early therapies using low-dose Type I and III Interferons were found using the [MeSH] algorithm on the Pubmed website. Data collected through numerous clinical trials implicating a low-dose interferon nasal sprays and high-dose intramuscular interferon doses was collected, and the kinds of clinical trials included preliminary, double-blind and meta-analysis. Evidential data was carefully analysed, from both sides of the scientific and clinical debate. We emphasised upon the search for safety data with regards to both clinical approaches and the physiology of each type of interferon signalling. The collected results and bibliographic references were then listed specifically, according to topic and degree of relevance to the title of the scientific paper. We then focused solely upon an analysis and accurate interpretation of evidence-based data as we reviewed scientific literature more profoundly. We aim to perform projective analysis and clinical trials concerning the risks and efficacy of low-dose nasal recombinant human interferon I and III, and to study the effects of high-dose intramuscular interferon I and III by means of gathering safety data and collateral evidence around the principal aim of the project. Our funding and resource availability projections involve insignificant expenditure and wide clinical resource availability, given the extensive, systemic production and secretion of the immunological proteins *in vivo*. During the study, we placed our emphasis upon the fact that accurate handling and interpretation of experimental clinical data represents an essential part of ethical research conduct.

Results

Following a thorough [MeSH]-based investigation on PubMed, we determined a pronouncedly higher number of detected papers highlighting the safety and effectiveness of early, low-dose Type I Interferon-based approaches than the number of papers warning about significant adverse events following late, high-dose Interferon I-based clinical approaches. The majority of the discovered papers emphasised upon safe early Interferon I and III-based immune signalling. At the same time, we detected peer-reviewed papers that highlighted evidence of significantly harmful effects of amplified, late Type I and III Interferon-based immune signalling upon important components of all systems of organs, including the central nervous system. The vast majority of the clinical trials performed in various areas of the world and run by numerous clinicians and scientists displayed an outstanding level of efficacy and mostly very insignificant risks for the development of adverse reactions. It is important to note that the high extent of success resulted mostly from the early stages of treatment and the low concentration of the administered human recombinant Interferon I and III respectively. Clinical trials that implicated latter stages of treatment and higher concentrations of recombinant interferon had considerably higher incidences of the development of significant adverse events, ranging from autoimmunity to a further aggravation of the disease. Surprisingly, the number of patients who experienced a pronounced recovery from the disease following latter treatment with a higher dosage of interferon remained considerable, highlighting the powerful antiviral effects of numerous proteins produced by the Interferon-Stimulated Genes (ISGs). Furthermore, clinical trials involving cancer therapy displayed a statistically significant value of success with regards to the administration of a low dose of such interferons, and recent research presented a considerable probability that applications of a therapy as such will prevent and sometimes even treat cases of important neurodegenerative diseases as well. The results reflect the core foundational nature of first and second-line immune defences and highlight the necessity of human immunity to build an evolutionary response and dominate the viral

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microbiota. Such results also indicate the existence of a new horizon of immunity against cancer and neurodegenerative disease, and propose a revolutionary set of updates in the sub-domains of vaccinology and early therapeutics. We aim to add updates with regards to collected clinical experiment data and significantly contribute to the development of the resolution of the detected patterns in the results of the overall study.

Discussion

Given the exponential nature of the increase of the viral load and the number of infected cells as the SARS-CoV-2 infection progresses, early Type I and III Interferon responses are much lower in abundance than delayed responses, given that early responses will only implicate the production and manufacture of the chemokines in the first few infected cells. Delayed responses will involve the activation of interferon-encoding genes in many more cells, resulting in the production of an amount of interferon that will rather contribute to pathogenesis and aggravation of inflammatory disease, given that the products of interferon-stimulated genes include important pro-inflammatory chemokines, such as CXCL10, CCL2 and CCL5. An increased synthesis rate of pro-inflammatory chemokines and cytokines is highly associated with a decreased quality of immune performance. Likewise, it is important to acknowledge the "double-edged sword"-like nature of Type I (i.e. IFN alpha-2b, beta-1, delta, epsilon, kappa, omega and tau) and Type III Interferons (i.e. IFN lambda1, 2 and 3) and hold fast to the criticality of robust first-line immune responses during SARS-CoV-2 infection. The most important sub-domains of interferons with regards to building important anti-viral and anti-inflammatory signals, alongside shaping important adaptive immunity pathways, represent interferons alpha-2b, epsilon, omega, lambda1, lambda2 and lambda3, although interferons beta1 also represent chemokines with interesting potential immunomodulatory and boosting characteristics.

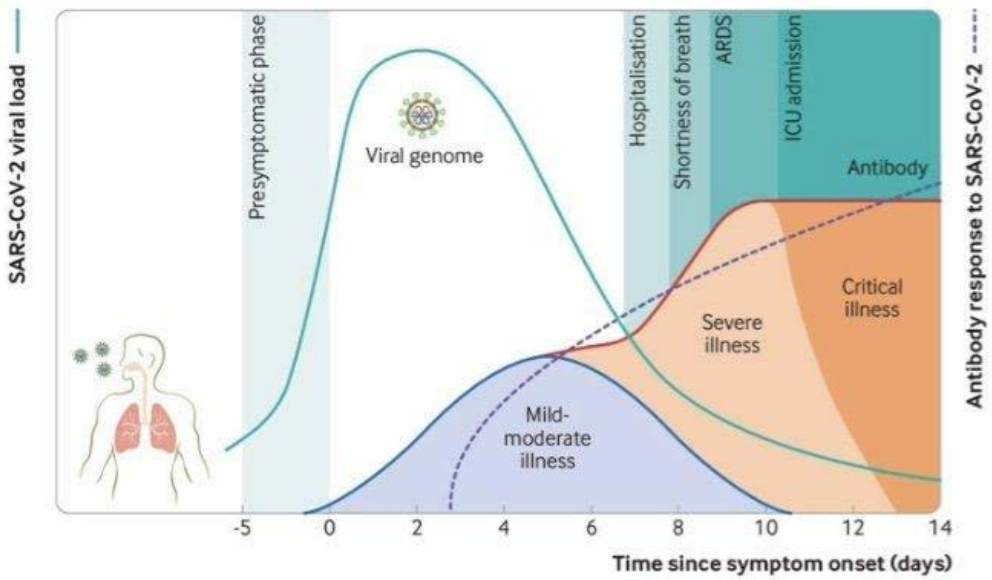

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Figure 5: The timeline of the SARS-CoV-2 infection and the onset of COVID-19, using the viral load, symptomatic intensity and antibody count as the principal parameters (Muge Cevik et al, 2020).

Given that children and young adults generally have first and second-line immune defences that are more robust in nature than old adults, and that the levels of interferon epsilon and interferon omega were found to be significantly higher during SARS-CoV-2 infections in young people than in old adults, and that SARS-CoV-2 was found to affect older people pronouncedly more disproportionately, it is likely that the two interferon sub-domains also play an outstanding role in maintaining a balance between anti- and pro-inflammatory immune factors whilst strongly stimulating the recruitment of NK cells, dendritic cells, as well as of B- and T-lymphocytes (Pierangeli et al., 2022). Nevertheless, the Omicron variant was found to affect younger people much more than the previous major variants, which possibly means that the new variant escaped interferon epsilon and omega signals significantly more. Likewise, the debate on whether interferon alpha-2b plays more relevant immunising and immunisation-adjuvant roles than interferons epsilon and omega remains strong, and further research is needed upon this matter. Moreover, a recently-developed SARS-CoV-2 variant that was named XBB, underwent natural selection and was discovered to significantly outcompete vaccine-induced IgM and IgG immunoglobulins, sparking fresh concerns with regards to the ability of the virus to perform immune evasion even if herd immunity had previously been reached, either by means of mass vaccination or by means of a mass exposure to the virus.

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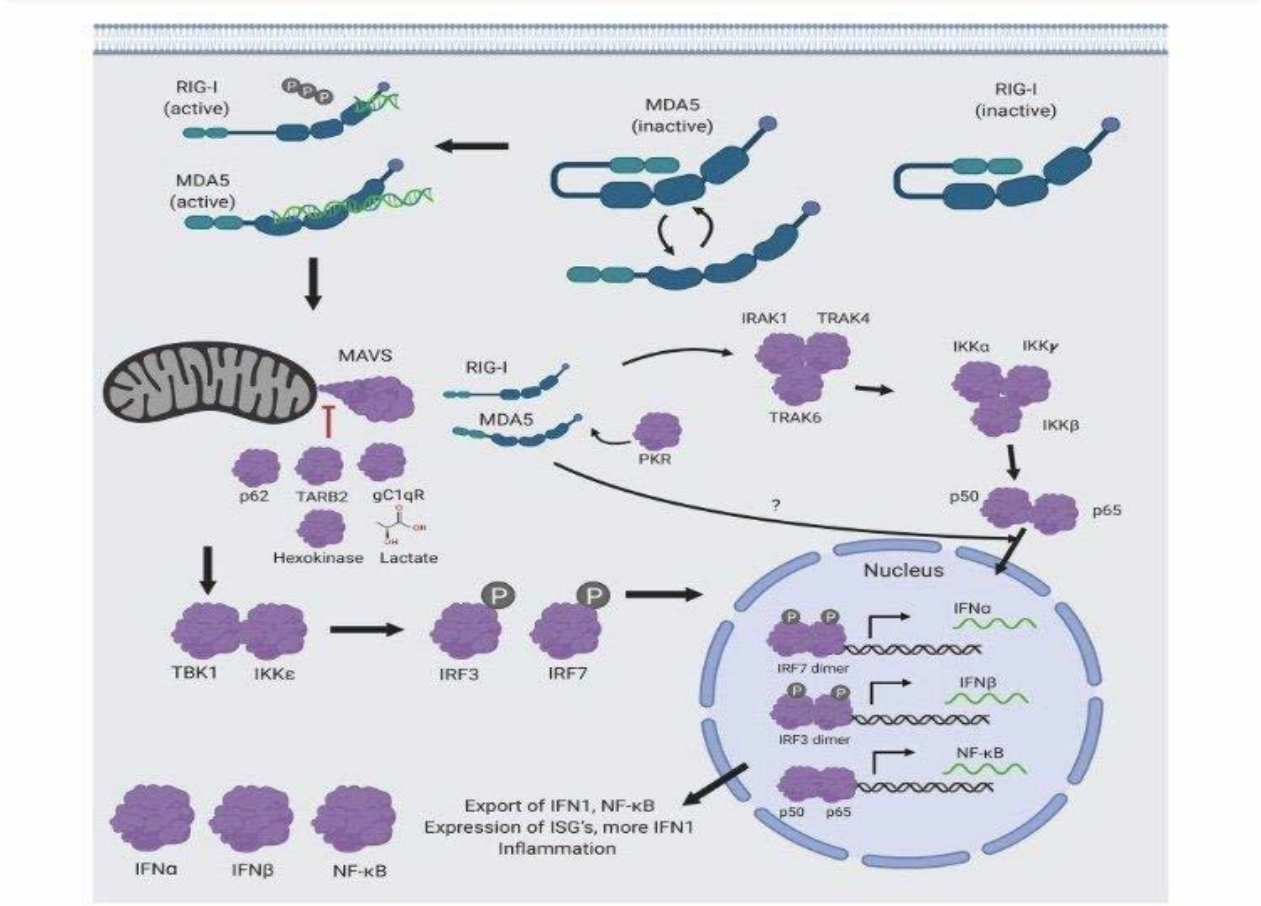

Figure 6: RIG-I and MDA5, which are cytoplasmic Pattern Recognition Receptors, detect Pathogen-Associated Molecular Patterns on the viral genome and then phosphorylate the IRF7 and IRF3 dimers, which in turn act as transcriptional factors of Type I Interferon-encoding genes (Front. Immunol., 2019). Both MDA5 and RIG-I require activation by a double-stranded RNA, but RIG-I requires activation by a triphosphate group as well, all before an interaction with MAVS, which will result in the phosphorylation of the TBK1 and IKK-epsilon dimer. In turn, the IRF7-IRF3 dimer is phosphorylate, which will then activate the Interferon I-encoding genes and result in the translation, folding, secretion, as well as the autocrine and paracrine signalling of the immunological messengers.

Once the +ssRNA of the novel coronavirus enters in the host cell via an endosome, toll-like receptors 7 and 8 become activated as a result of the detection of pathogen-associated molecular patterns, which are either found on the pathogen's genome or are generated during cellular infection. Following TLR7/8 activation, MyD88 binds to the pattern recognition receptor and becomes phosphorylated. As a result, three relay proteins are phosphorylated and will act as transcription factors for the synthesis of Type I and Type III interferons; AP1, IRF7 and NF-kB. Following the expression of the interferon-encoding genes in cause, the newly produced interferon proteins will undergo exocytosis and signalling, which will be autocrine and paracrine in nature. Once reaching neighbouring cells, Type I Interferons bind to the IFNAR1/2 receptor, whilst Type III Interferons bind to the IFNLR1/IL10R2 receptor. Following this event, the JAK1 and STAT2 molecules will become phosphorylated, leading to the phosphorylation of STAT1 and STAT2 and

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their dimerisation. IRF9 then binds to the STAT1-STAT2 phosphorylated dimer to form the STAT1-STAT2-IRF9 trimer before Interferon-Stimulated Genes will become activated. Following the signalling cascade, the ISGs will express anti-viral and anti-inflammatory signals that will be playing a critical role in shaping adaptive immune responses. Namely, the products of hundreds of activated ISGs seem to stimulate a desired level of antiviral immune responses by dendritic cells via antigenic presentation, as well as helper CD4+ and cytotoxic CD8+ T-lymphocytes via supporting plasma cells in the production of qualitative antibodies and inducing the lysis of infected cells respectively. Some of the ISG products, like the IFITM3, play major flexible roles in linking first and second-line immune responses to the adaptive immune system. Likewise, a significant impairment of Type I and Type III Interferon production and signalling result in severe implications for the adaptive immune response. The viral non-structural protein 1 (NS1 or nsp1) represents an important example of a viral component that is a result of an evolutionary response to impair first-line immune responses. Interestingly, human host cells developed anti-viral evolutionary responses to include the ability of such viruses to inhibit first-line immune responses. The 2',5' oligoadenylate synthase proteins 1,2 and 3, protein kinase R, nuclear factor 90 and interferon-stimulated gene product 15 represent proteins that restrict the ability of viruses like Influenza A and SARS-CoV-2 to replicate, and yet nsp1 was found to inhibit the activity of such proteins, alongside cleaving and lysing the mRNA encoding Type I Interferons. The binding capabilities of the viral RNA specifying nsp1 inhibits the activities of the 2',5' oligoadenylate synthase proteins and prevents RNaseL activation, leading to an inhibited process of viral RNA degradation. The viral RNA-inhibiting activities of protein kinase R and nuclear factor 90 shows how human host cells and the virus have co-evolved, and nsp1 has been helping the virus escape such proteins. Nuclear factor 90 is possibly not produced by Interferon-Stimulated Genes, which indicates that the evolutionary conflict between first-line immune defences and respiratory viruses of such nature has been more generalised than previously thought. Furthermore, interferon-stimulated gene product 15, which is produced by one of the most expressed interferon-stimulated genes, has been shown to target non-structural protein 1, as Isg15-deficient mice were shown to be more susceptible to Influenza A infection and that the pathogenic protein was recently displayed as a target of ISGylation. Moreover, Influenza A viruses also developed PB1-F2 and PA-X proteins to bypass innate immune responses, by inhibiting the process of viral RNA sensing and significantly downregulating the Type I and Type III Interferon-induced signalling cascades and the apoptotic process of infected cells (McKellar et al., 2021).

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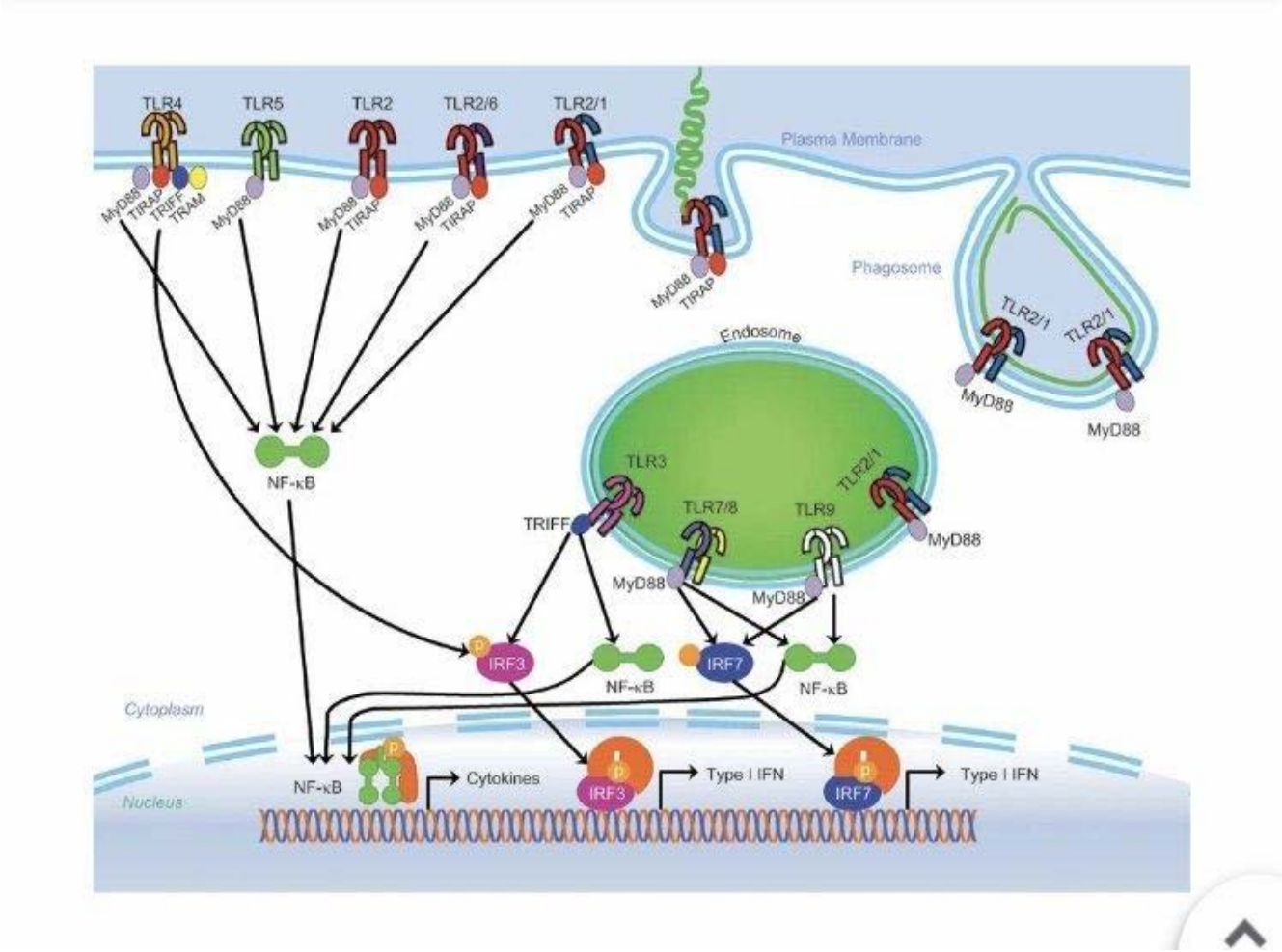

Figure 7: TLR-3, TLR-7, TLR-8 and TLR-9, which are endosomal Pattern Recognition Receptors, as well as TLR-4, which is a cytoplasmic Pattern Recognition Receptor, detect Pathogen-Associated Molecular Patterns (PAMPs) on the viral genome and phosphorylate the IRF3 and IRF7 dimers (Cell. Mol. Immunol., 2012). The activation of TLR-3 and TLR-4 results in the phosphorylation of TRIFF and then the IRF3 dimer, whilst the activation of TLR-7, TLR-8 and TLR-9 causes the phosphorylation of MyD88 and then the IRF7 dimer. Unlike the case of TLR-3, activating TLR-4 will also phosphorylate MyD88, TIRAP and TRAM before the activation of the IRF3 dimer. The final outcome is the same; the expression of Type I Interferon-encoding genes and the autocrine and paracrine signalling of the immunological messengers.

Type I Interferons have recently been found not to recruit NK cells directly, but through the activation of inflammatory chemokines and monocytes (CCL2, CCL5, CXCL10 and IMMs) (Lee AJ et al., 2019). Interferon-stimulated genes produce various inflammatory chemokines, such as CCL2 and CXCL10, which are responsible with the activation of inflammatory monocytes and dendritic cells, as well as with the recruitment of natural killer cells, which in turn activate macrophages and interferon-gamma, which belongs to the second domain of interferons, and induce the lysis of infected cells. Although interferon-gamma was found to have powerful preventive effects against important forms of respiratory,

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oncological and neurodegenerative diseases if produced and signalled in moderation (Aiman et al., 2022) and it was also found to share a similar bi-directional nature with Type I and III Interferons with regards to their effect upon pathogen integrity and immune competency respectively, according to the extent of its activation, it is the first and the third interferon domains that play the most foundational roles in shaping and balancing much of the immune response. The activation of antigen-presenting cells and the recruitment of natural killer cells will ultimately shape the processes of CD4+ and CD8+ T-lymphocyte recruitment, as well as the quality of antibody production and specification via the process of V(D)J antibody gene rearrangement in maturing B-Lymphocytes. A dysregulated synthesis rate of Type I and III Interferons result in an increased CXCL10 signalling extent, which in turn will inhibit the proliferation of myeloid progenitor cells (Khalil et al., 2021) and increase the level of p38-mediated primary T-lymphocyte apoptosis (Sidahmed et al., 2012). As a result, the risks for the development of deficiencies in myeloid cell (i.e. neutrophil and dendritic cell) and lymphoid cell (helper CD4+ and cytotoxic CD8+ T-lymphocyte) counts, thereby increasing the probability of significant adaptive immune consequences. CCL2 and CXCL2 were found to be capable of clearing tissues from the SARS-CoV viral load without the help of helper- and cytotoxic-T-lymphocytes, as well as of neutralizing antibodies, twelve days after the moment of first-cell-infection, and this finding indicates the high importance of activating antiviral innate immune responses by recruiting neutrophils, monocytes and macrophages toward the infected tissues. It was also shown that hyper-activated interleukin-6 and interferon-gamma-related pathways were associated with a higher severity of COVID-19 (Lagunas-Rangel et al., 2020), potentially meaning that delayed Type I and III Interferon responses are associated with higher signalling rates of IFN gamma and IL-6, as a significantly higher number of infected cells would almost simultaneously produce Type I and III interferons and likewise, their number would be much higher than in the cases when interferons are produced and undergo signalling early. The fact that the levels of inflammatory chemokines like CCL3, CCL5, CCL20 and CXCL10 were considerably higher than the levels of inflammatory chemokines secreted by CD14+CD16+ inflammatory chemokines in COVID-19 patients with developed acute respiratory distress syndrome (ARDS), unlike in the case of non-COVID-19 related viral and bacterial infections that resulted in the development of ARDS, when the chemokine levels were similar, represents a significant sign that the principle immunological problem caused by the novel coronavirus is not only related to, but based upon a disrupted timing and extent of Type I and III Interferon system activation. Moreover, in the case of the SARS epidemic, the virus is also capable of inhibiting Type I and III Interferon signalling and once interferon-stimulated genes are finally expressed, inflammatory chemokines, like CCL3, CCL7, CCL8 and CXCL10 are released and also contribute to the onset of the disease, which further suggests how several respiratory viruses have co-evolved with the interferon system. Although SARS-CoV and MERS-CoV display similar chemokine profiles, performed comparative studies showed that MERS-CoV infection results in higher activation rates of the CXCL10 inflammatory chemokine, and this may be an important reason why the systemic inflammatory extent and death rate of MERS are higher. CXCL10, CXCL8 and CCL2 represent potentially important markers of SARS, MERS and SARS-CoV-2 infection and onset of infectious disease, and

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the activation rate of CXCL10 is particularly analysed in COVID-19 patients. Such a chemokine binds to the CXCR3 receptor to become activated and stimulate the recruitment of natural killer cells, T-helper cells 1, cytotoxic CD8+ T-cells, as well as Th1-related immune responses, and its concentration is directly proportional with the severity of the infectious disease. It was found to be positively-regulated during early stages of the SARS-CoV-2 infection, which further indicates that its extent of synthesis is dependent on the timing of Type I and III Interferon synthesis, as well as autocrine and paracrine signalling.

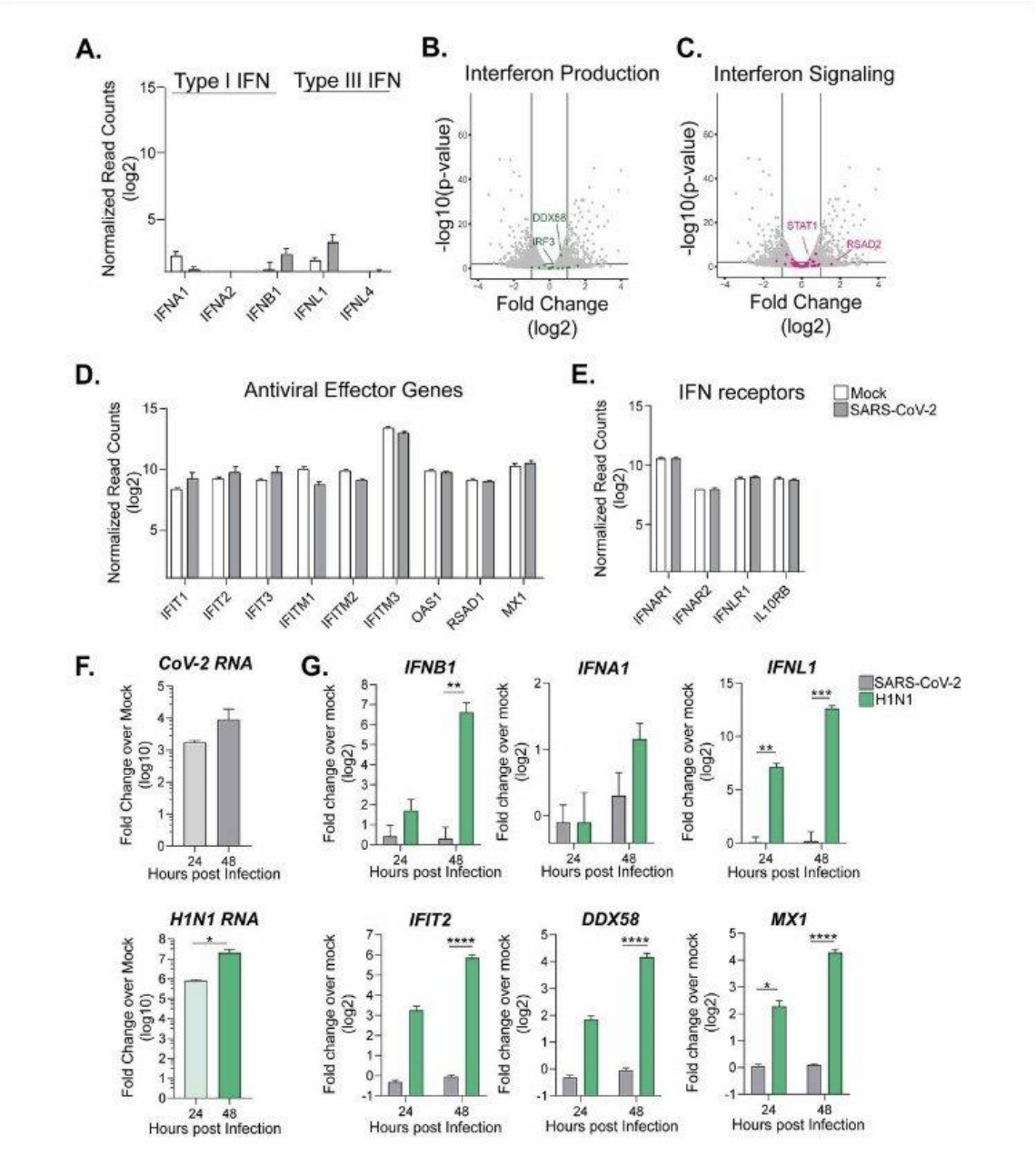

Figure 8: Interferon I and III production and signalling rates were much lower in pHAE cells infected with SARS-CoV-2 than in pHAE cells infected with the H1N1 variant of Influenza A (Abigail V. et al, 2021)

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The option of using a UV-attenuated SARS-CoV-2 specimen with a deletion in the genes encoding the non-structural proteins 1 and 16 could have been the best vaccination candidate, had the spike protein not acted as a superantigen, caused hyperinflammation via Toll-Like Receptor 4 signalling, weakened genes implicated in DNA repair and antibody gene rearrangement, entered the lymphatic system and caused damage to the endothelium, crossing the endothelial barrier and entering the bloodstream. We believe that the main problem is the great level of toxicity the spike protein has been displaying through severe cases of COVID-19. Furthermore, during the SARS epidemic, researchers developed the TP29 small peptide to separate the activator nsp10 from the effector nsp16 to prevent a large extent of 5' viral - ssRNA capping, as well as the oral methioninase enzyme to digest the S-Adenosyl-L-Methionine pocket of the virus in order to expose the concerned non-structural proteins to lytic factors and prevent the process of 5' viral mRNA capping. Almost two decades later, it was discovered that the novel coronavirus produce the same non-structural proteins and S-Adenosyl-L-Methionine pocket to camouflage itself and prevent the activation of the host cell's pattern recognition receptors. Likewise, the two early approaches could show significant efficacy and bring insignificant financial demands in the pharmaceutical market, and researchers showed that oral methoninase displays efficacy against COVID-19 as well (Hoffman et al., 2020). Moreover, there seems to be another method to evolutionarily combat the pathogen, by manually stimulating immunisation through the development of IgM super-antibodies to directly remove the viral camouflage, by tackling the non-structural proteins 1 and 16 inside the infected cells. The immune system could be trained in this way as well to build a better interferon-based defence against viruses that gained an evolutionary advantage of suppressing it. The problems with such an approach are the massive financial demands and a precision of the intervention that might be too elevated, which means it could overall bring an increased risk of adverse reactions. Boosting the mucosal immunity, on the other hand, represents an approach that has been tested numerous times, and many of the performed tests indicated outstanding positive results, despite a number of concerns of inefficacy and high financial demands from a number of critics. Concerns include a possible relatively weak connection between the development of qualitative IgA antibodies in the mucosal immune system and the development of qualitative IgG antibodies in the systemic immune system due to a high complexity of the local immunity. However, tests implicating the stimulation of IgA synthesis have shown outstanding prophylactic efficacy, with very few clinical trial participants experiencing infection or re-infection in the future. The COVID-19 pandemic was not exempt in this case, as attempts of intranasal prophylaxis and immunisation were associated with the development of long-term immune memory against the virus and the spike protein. Results have strongly indicated the importance of developing IgA-mediated mucosal immunity in the prevention of moderate and severe disease. Moreover, the fact that oral methioninase was shown to have significant efficacy in prophylaxis and early treatment further indicates the high potential of mucosal immunity in preventing the onset of severe infectious disease. One early therapeutic approach implicated the administration of inhalable IgA immunoglobulins that had previously been exposed to the spike protein of the Omicron variant, into the nasal cavity of K18-ACE2 transgenic members of the Mus. musculus species that were infected with the Omicron variant. The approach was shown to be more efficacious than an IgG Fc-based prophylaxis and treatment, and it used IgA antibodies that had been synthesised and secreted in Pichia pastoris for cost-effectiveness purposes (Qi Li et al., 2022).

Another method to stimulate Interferon I and III-based immune responses would be to gather proteins from diverse plants with the therapeutic effects, find the right quantity of each of them in order to bring robust effects, since plant medicine often brings slow effects and dosages usually require to be consistent over a longer period of time, and such methods represent applications of Translational Medicine. The ingredients of a natural compound based on plant medicine that stimulates interferon responses are as follow: Silybum marianum – a hydroalcoholic extract with 80%

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silymarin from fruit (200 mg); Astragalus membranaceus – 10: a hydroalcoholic extract from the roots (150 mg); Schisandra chinensis – a hydroalcoholic extract with 2% schizandra from fruit (150 mg); Agaricus blazei – a hydroalcoholic extract with 20% polysaccharides (100 mg); Ganoderma lucidum – a hydroalcoholic extract with 20% polysaccharides (100 mg); Morinda citrifolia – a hydroalcoholic extract with 40% polysaccharides from fruit (75 mg); Aloe vera – 20: a hydroalcoholic extract from the aerial parts (50 mg); Foeniculum vulgare (fennel essential oil) (0.11 mg); filler: microcrystalline cellulose; anti-caking agents: colloidal silicon dioxide and vegetable magnesium stearate. We are aware some ingredients are preservatives that probably have controversial traits, and there is no claim that this particular compound is certainly perfect. Perhaps, such preservatives could be replaced with alternative compounds if the situation imposes it. If required, we could create a medical drug containing a mixture of at least some of these plant-derived interferon-stimulating proteins and interferon-alpha, beta, delta, epsilon, kappa, omega and lambda, and we believe that such an approach would more likely be needed if more severe SARS-CoV-2 and Influenza A variants emerged and spread around the world.

With regards to the evolutionary advantage of the virus to suppress key mechanisms of natural immunity, a traditional vaccination approach using a pathogenic fragment might not help significantly on a long-term basis because the pathogen is highly polymorphic and, most importantly, because it will not directly support the development of a counter-evolutionary response to outcompete the ability of the virus to suppress such natural immunity mechanisms. This might represent a challenge even for dendritic cell-based vaccines, not because such antigen-presenting cells will bring accurate forms of antigen to lymphocytes and train them to target the most relevant variants, but because of the same gap created by the virus in key parts of the innate immunity (Saadeldin et al, 2021). As a result, the virus will use such gaps to adapt and become more capable of suppressing natural immunity. A sign that such events are already happening is the higher capability of the BA.1 variant of SARS-CoV-2 to suppress Interferon I responses, which explains why more children develop complications and become hospitalised (Lyudmila Shalamova et al, 2022). Moreover, the BA.2 variant of SARS-CoV-2 has recently been found to have an even higher ability to suppress such interferon-based responses, particularly in children and teenagers. A full and long-lasting immunisation against SARS-CoV-2 could only apply if the entire immune system is continuously covered. The dosage could involve a puff of the spray per day in each nostril, and the duration of the prophylactic or early therapeutic session could last from two weeks to a month. Likewise, we would consider this vaccine candidate of a long-term kind. Given that the classical vaccine, which involves sharpening immunity purely from an adaptive immunity perspective, does not seem to address the problem of viral camouflaging using its non-structural proteins, whose impact affects the innate immune system, we believe that an interferon I and III-based approach will make a greater difference and, possibly, even evolutionarily outcompete the virus and its skills of self-camouflage. This clinical approach could also include the administration of a TP29 small peptide, which separates the non-structural protein 16 from the non-structural protein 10 to deactivate it (Wang et al, 2015), and oral recombinant methioninase to disintegrate the S-Adenosyl-L-Methionine pocket of the virus and decrease the activity of RNA-dependent RNA Polymerase, which catalyses the replication of the virus (Hoffman et al, 2020).

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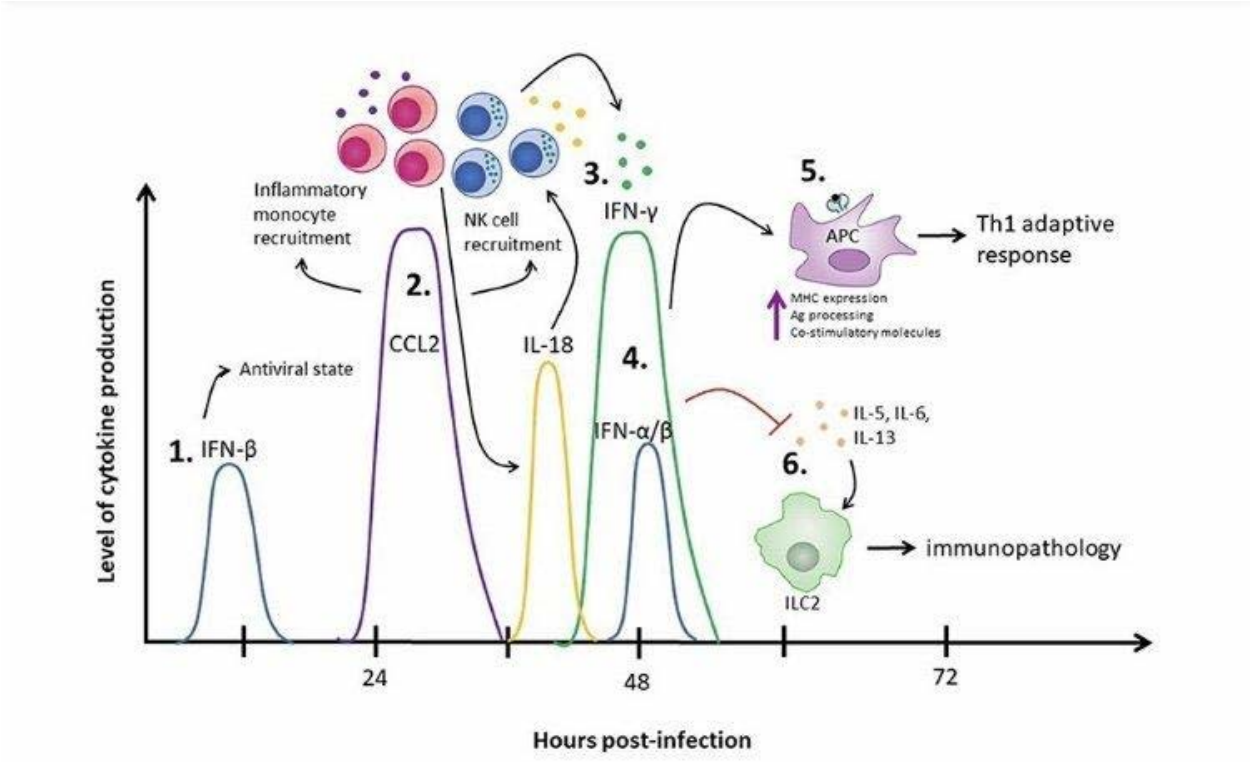

Figure 9: A more specific timeline of Interferon-alpha and Interferon-beta synthesis in the early stages of Herpes Simplex Virus 2 (HSV-2) infection (Amanda J. Lee and Ali A. Ashkar, 2018)

There is a considerable probability that interferon-beta will first be produced to signal to the immune system that the cell has just been infected, around 12 hours after the first HSV-2 virus entered its host cell. Interferon-alpha will be produced around 40 hours after the synthesis of interferon-beta and just over 48 hours after the first host cell becomes infected. Interferon-beta can be produced again at the time when the production of interferon-alpha commences. This Type I Interferon synthesis timeline may be similar in the case of a SARS-CoV-2 infection. Given that it usually takes significantly more time than 40 hours for the coronavirus to infect more cells and cause symptoms, a sole interferon-alpha-based prophylaxis and therapy will probably not be substantially different from a therapy consisting of a combination with interferon-beta. Nevertheless, the synthesis of interferon-gamma depends on the extent of the Natural Killer Cell recruitment, which itself depends, to a certain degree, on the extent of interferon-beta synthesis. Importantly, Natural Killer Cells also form an immune memory against pathogens and differentiate into memory cells, despite being part of the innate immune system (Lena Müller et al, 2017). One clinical study involving the administration of a nasal spray containing interferon-beta and serine residues to check the prophylactic effects against rhinovirus showed a higher degree of effectiveness than interferon-alpha-2b based nasal sprays, and likewise, trialling a nasal spray using a combination of interferon-alpha and interferon-beta could be worthwhile (Sperber et al, 1988).

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The results of a pharmacokinetic *in-vitro* study displayed a high effectiveness of recombinant interferon-alpha-2b therapy for the respiratory syncytial virus (RSV), parainfluenza virus (HPIV) and coronavirus strains causing common cold (i.e. HCoV-OC43 and HCoV-229E). The therapy had particularly immune-sharpening effects for the parainfluenza virus and the common cold coronavirus infections, and results were better than the drug control section for certain Influenza A variants as well. Overall, the *in-vitro* experiment involving interferon-alpha residues showed broad antiviral effects, a high therapeutic index and a low toxicity (Hui Qiang Wang et al, 2014). Moreover, a preliminary *in-vivo* study was performed in Beijing, China, in order to verify whether a low-dose interferon-alpha-2b-based nasal spray is effective in preventing the rubella and measles infectious diseases, and the results showed that such a nasal spray can be used for preventing these diseases as well. In this context, a low dosage is in nanograms (ng) and a high dosage is in milligrams (mg), and only a low dosage of interferon-alpha is generally required to prevent and treat infectious diseases ranging from the flu and COVID-19, to the Acquired Immunodeficiency Syndrome (Joseph Cummings, 2020). An *in-vitro* research study of human cell cultures, performed at the University of Texas in 2020 as part of the Journal of Antiviral Resistance, displayed clear evidence that SARS-CoV-2 is highly influenced by the presence of interferon-alpha and interferon-beta, and has indicated a considerably possible link between the proportion of 80% of infected people who develop mild symptoms and the fact that in many cases, infected cells manage to robustly send Interferon I signals and stimulate immune responses rapidly and proportionally (E. Mantlo et al, 2020).

In June 2020, the University of West Australia published an article stating that Type I Interferon nasal and oral sprays, as well as lozenges, may play an important role in preventing COVID-19. They referenced a clinical trial that included 2,944 participants from the infectious diseases' hospital departments in China involved the prophylactic administration of a low-dose of recombinant interferon-alpha-2b as a way of protecting frontline healthcare workers in areas of COVID-19 outbreaks, and the results were promising. No participant developed pneumonia afterward (M. Zhongji et al, 2021). Moreover, about 750 army soldiers in China participated in the experimental group of a clinical trial in 2005 involving the administration of a low dose of interferon-alpha, and the results were successful on a similar scale. There was no significant side effect reported in neither of the trials, and I believe this was so because the dosage was accurate and used within the right context; the quantity of the administered interferon-alpha matched the quantity of the deficient Type I Interferons (Gao et al, 2010). Furthermore, during the Hong Kong influenza outbreak in January and February 1969, there was a clinical trial conducted by Dr. V. Soloviev in the former USSR, who tested the efficacy of a nasal spray based on a small concentration of human leukocyte-produced interferons on a treatment group of 14,000 participants, and the calculated efficacy rate was between 56.3% and 69.2%, with variations according to the age group. Around 128 units of interferons were used in the nasal sprays, the treatment session lasted for five days and it was determined that the interferon-based treatment significantly reduced the number of influenza cases ($p < 0.01$). Furthermore, it had been suggested that the Hong Kong strains of influenza virus could have been divided into interferon-positive and

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interferon-negative variants. It was reported that the approach was harmless and that it should be applied in cases of threats of immediate infections, which means it should be regarded as an emergency prophylaxis (V D Solov'ev, 1969). With regards to the exact mechanisms that a recombinant interferon alpha-2b-based therapy resulted in, a clinical trial indicated the ability of the human interferon alpha to decrease the duration of viral transmission and consequently, to reduce the markers of acute inflammation, such as Interleukin-6 and C-Reactive Protein. Namely, by testing human interferon alpha in COVID-19 patients, it was determined that a longer viral transmission from the host can be associated with stronger markers of acute inflammation and likewise, that an impaired interferon-alpha response causes the viral infection to become a more common factor of pathogenesis and severe illness. The results encouraged scientists to recommend interferon-alpha-2b therapy as a method to combat the pandemic (Q. Zhong et al, 2020). Also, interferon alpha-2b therapy also resulted in a shorter duration of time the viral load was detected in the upper respiratory tract (Qiong Zhou et al, 2020). Another clinical trial in Iran implicated an injectable dose of interferon-alpha of 12 million IU, and the study had encouraging results, despite the exceptionally higher dosage used. Specifically, the mortality rate from COVID-19 in the cohort was reduced by more than 50%, and early interventions sharply reduced the death rate (E. D. Monfared et al, 2020). We share the thoughts of Dr. Joseph Cummings that a low-dose interferon-alpha therapy would likely have further decreased, not only the mortality rate of the disease, but also the ability of the virus to increase its load and the probability of morbidity following infection in that cohort. One important aspect to add is that clarithromycin-based early therapy against COVID-19, which showed a high rate of efficacy and very low risks of adverse events, was associated with a decreased circulation of the C-reactive protein, tumour necrosis factor-alpha and interleukin-6, as well as an increased rate of Th1 and Th2 mononuclear responses and a clear restriction against the increase of the viral load. The effects of normal Interferon I signalling rates and early therapy result in an almost identical outcome as clarithromycin-based early therapy (Konstantinos Tsiakos et al, 2021).

The majority of the immune cells produce Type I Interferons, meaning that the glycoprotein cytokine is widely bioavailable (De Maeyer, E. et al., 1998). Plasmacytoid dendritic cells (pDCs) produce Type I Interferons most commonly, and they are also known as antigen presenting cells. Given that SARS-CoV-2 is known to decrease the ability of such cells to capture and present pathogenic antigens, that means the viral inhibition of Type I Interferon production automatically decreases the ability of pDCs to present captured viral antigens. As a result of the interferon inhibition, natural killer cells are also relatively absent. The absence of natural killer cells and interferon-dependent killer dendritic cells (IKDCs) leads to a poor production of Type I Interferons (mainly by plasmacytoid dendritic cells, or pDCs). Plasmacytoid dendritic cells are also known as conventional dendritic cells (cDCs) (David Vremec et al., 2007). In other words, a robust production of Type I Interferons during viral infection plays a central role in stimulating NK cell recruitment and antigenic presentation by pDCs, which produce the interferons in the first place. Likewise, even if the SARS-CoV-2 spike protein were barely affecting the development of B-lymphocytes, the viral non-structural proteins

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causative of first-line immune inhibition would still significantly affect the development of necessary adaptive immune responses. Viral apoptotic inhibition facilitates viral replication and spread to more kinds of tissues, particularly during the first few days of infection. Overall, this results in a lower recruitment rate of B and T-Lymphocytes, which in turn results in the development of poorer natural and adaptive antibodies. Furthermore, this facilitation of viral replication and spread, on top of the viral inhibition of first-line immune responses, further contributes to the problem of a compromised collective immune privilege against novel infectious viruses. Also, it is rather possible that this impairment of the immune system to effectively reduce the replication rate of the virus and tackle its pathogenicity in the end is an important factor of the dilemma of induced autoimmune diseases (i.e. long COVID post SARS-CoV-2 infection) as well. Such an induction of autoimmune disease is voluminously favoured by a disrupted anti-inflammatory to pro-inflammatory mediator ratio, as the probability of induced autoimmune disease is proportional to the intensity of the antiviral and pro-inflammatory immune responses.

With regards to the relationship between immunocompetency and the severity of COVID-19; it is essential to note that immunosuppression does not always lead to a severe outcome of the disease due to the complexity of the nature of the immune responses that are resulted from the viral infection. Namely, the clear innate immune suppression is the number one cause for a disrupted set of adaptive immune responses, which in turn can lead to the onset of severe symptoms and post-COVID autoimmune diseases. Immunosuppressed patients in this case often develop milder symptoms because the intensity of their immune responses is considerably lower. As a result, the risk of immune-derived tissue damage is actually lower, and this also explains the heated debate about whether certain immunosuppressants are actually effective in reducing the intensity of COVID-19 symptoms. Therefore, the outstanding level of the initial induced first-line immune suppression by SARS-CoV-2 brings higher risks of the onset of disruptive pro-inflammatory immune responses, meaning that the extent of viral self-camouflage, suppression of interferon production, inhibition of antigenic presentation and temporary suspension of induced host cell apoptosis is directly or even exponentially proportional with the intensity of the induced symptomatologic immune responses afterward.

An Interferon I response should be early and prompt, otherwise infected people can develop serious forms of the disease. The ability of the virus to camouflage itself and limit the amount of synthesised Type I Interferons likely has caused millions of unnecessary deaths and put further tens of millions of lives at risk all around the world since the first outbreak took place. There are three scenarios with regards to the timing and extent of Type I Interferon synthesis. The first scenario implicates the prompt synthesis and secretion of the right amount of Interferon I, and this leads to the development of a strong and intelligent response, to the development of mild or no symptoms and a quick recovery. The second situation implicates a delayed Interferon I response, which often can become exaggerated as well because

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of the increased viral load, and this scenario is associated with moderate to severe clinical symptoms, the development of pneumonia, as well as hospital admission, which sometimes can lead to a further admission into the Intensive Care Unit. The third situation implicates a completely absent Type I Interferon response, which is followed by a severe form of the disease, admission into the Intensive Care Unit, intubation, a systemic inflammation caused by a high viral load and the spread of the virus from the lungs to other important organs through the blood and often death. A delayed administration of prepared interferons not only does not improve symptoms or help the patient recover more quickly, but can worsen the disease, since because this delay allows a sharper increase of the viral load, this intervention would only contribute to an over-sensitised and exaggerated interferon signalling. In turn, there could also be a number of instances when a proper interferon-gamma production and signalling rate will be delayed, and when the rate of response will finally increase, it could become exaggerated as well due to the higher viral load, which will lead to a higher immunological demand. As a result, a delayed increase of interferon-gamma response could also contribute to a worse disease form. In other words, timing is critical for a virus with a high replicative rate. Furthermore, around 10% of the cases when there is a delayed and exaggerated Interferon I-based response, patients develop autoantibodies and consequently, diverse forms of autoimmunity. Long COVID is most of the time caused by autoimmunity and it could be treated with the BC007 drug, which consists of a DNA sequence that lyses autoantibodies. Moreover, specific immunosuppressants could also decrease the extent of induced autoimmunity and significantly shorten the duration of long COVID. Likewise, interferon-induced autoimmunity may be treated with the BC007 drug and with adequate immunosuppressants.

An Interferon-based therapeutic approach generally requires to be taken even before an infected person requires hospitalisation. The fact that the approach did help save lives brings hope that the approach is useful even in slightly more advanced stages of the disease. One important aspect to mention is that severe symptoms would likely represent a marker for a delayed and exaggerated interferon response, which means that only infected people with milder symptoms should be eligible for interferon-based therapies. In the Cuban study of interferon efficacy for COVID-19 hospital patients, 95.1% of the patients in the cohort who received the interferon-based therapy were discharged, compared to 21% of those who did not receive this therapy. The case-fatality ratio of the patients in the placebo group was 32.1%, compared to the 0.9% case-fatality ratio of the patients in the treatment group, and the case-fatality ratio for the patients with severe disease who did not the therapy (48.6%) was more than double the number of patients with severe disease who did (21.9%) (Ricardo Pereda et al, 2020). Likewise, it is possible that, the earlier and less severe the stage of the disease is, the more effective interferon-based therapy is, and it is likely that a prophylactic approach will almost always prevent the onset of the disease. Such events show the power of specific innate immune mechanisms in front of a virus that can cause significant morbidity and an unprecedented number of deaths.

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Furthermore, a recent study published in January 2022 indicates that the Omicron variant of SARS-CoV-2 is more capable of silencing pathways involved in interferon-alpha and interferon-beta signalling and, as a result, there may be increased risks of delayed or impaired antiviral and anti-inflammatory responses, leading to a higher susceptibility to the development of chaotic adaptive immune responses. This phenomenon is tricky because the Omicron variant has been proven to generally be ten-fold less morbid and deadly than the Delta variant (Lyudmila et al, 2022). Given that children generally have a stronger innate immune system and likewise, their interferon I signalling is generally robust and in greater amounts, the higher ability of the Omicron variant to delay and impair Interferon I-based responses is the reason why more children are affected by the Omicron variant-induced disease than the Delta variant-induced disease. Likewise, we believe that there should be a greater awareness of the need for sharpening interferon I-based immunity, given that increases in the Tumour Necrosis Factor and IL-6 production rates, as well as NF-kB-based inflammatory processes were not enough to significantly restrict the increase of the viral load and the inflammatory responses (Lee et al, 2020). We believe that, if it will be proven necessary, around 125-150 IU of interferon-beta can be combined with around 175-200 IU of interferon-alpha residues and form a combined prophylaxis and therapy, which could be even more effective against COVID-19 and flu diseases induced by Influenza A variants of concern.

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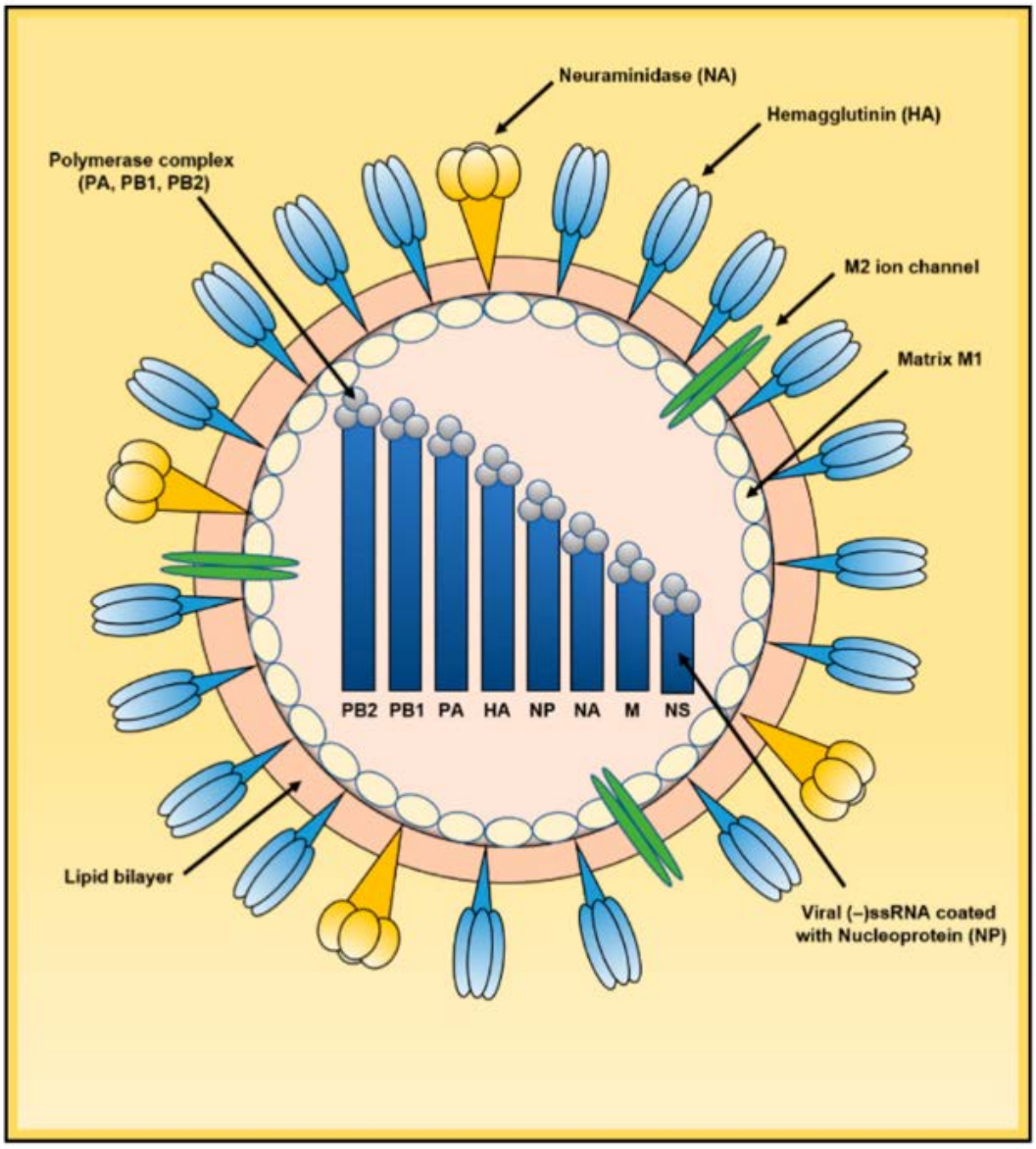

Figure 10: The biochemical structure of the Influenza A virion, a negative-sense single-stranded RNA (McKellar et al., 2021)

Due to the fact that interferon-gamma also plays an important role in sharpening antiviral immunity and restricting unnecessary inflammation, we believe that combining interferon-alpha with interferon-beta and interferon-gamma and forming a triple-interferon-based prophylaxis and therapy could also be a suitable candidate, although we believe that a combination of interferon-alpha and interferon-beta would be enough to reach the maximum potential of the interferon candidate. The candidate would have a maximum total interferon amount of 500 IU (i.e. 200 IU of IFN-alpha and 300 IU of IFN-beta). Given that the peak of the viral load is usually reached around two days after the symptomatic onset, a nasal recombinant interferon alpha-2b-based spray should be administered up to two days after the first symptoms of COVID-19 have occurred for the desired therapeutic outcome. In other words, scientists could bring an

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emphasis upon this potential vaccine candidate in stages of local outbreaks and in people who have mild or no symptoms and have just received a positive polymerase chain reaction or rapid antigen test result. The product could be administered either just via the nasopharynx or both via the nasopharynx and the oropharynx to bring about a more extended mucosal immunity activation. The candidate should not be recommended to anyone with COVID-19 that has received a positive antibody test result, since the viral peak had most likely already been reached by then. The right kind of Interferon I therapy involves a low-dose administration before the viral peak has been reached, and according to the timeline presented above, the viral peak is reached around 48-55 hours after the onset of the first symptoms. Likewise, we believe that the dosage should take place only for prophylactic and early therapeutic purposes, and this includes people who do not display symptoms, are tested negative and happen to be in an area of outbreak and infected people who have just received a positive real-time polymerase chain reaction or rapid antigen test, and developed the first symptoms. Infected people who receive a positive antibody test should not receive any dosage of interferons, since the stage where antibodies are formed and more widely present in their system indicates that the viral peak has already been reached, and the patients would only risk aggravating their disease. A higher quantity of administered Interferon I can raise the risks of developing unwanted adverse reactions and sometimes autoimmune responses as well.

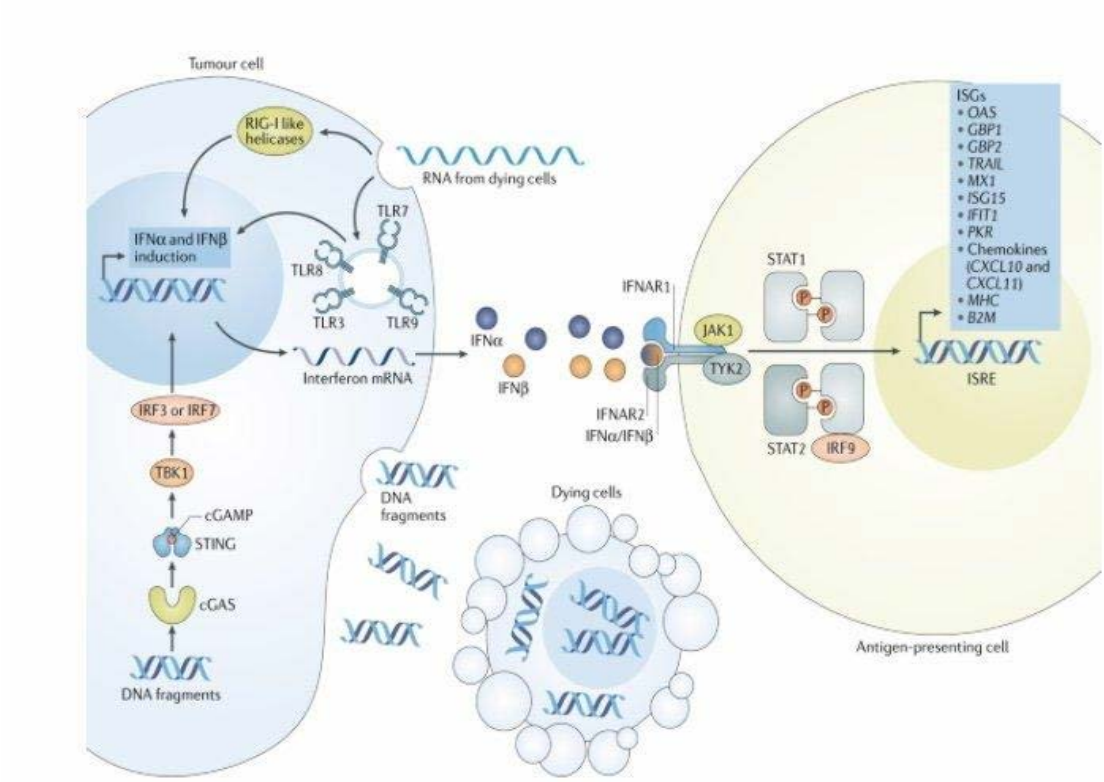

Figure 11: Type I Interferon synthesis and exocytosis from tumour cells represent an essential step in a correct signalling of tumour cells to immune components implicated in tackling cancerous formations (Ernest C. Burden, 2019)

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A disrupted balance between Interferon-alpha, which is an anti-inflammatory cytokine, and Tumour Necrosis Factor-beta, which is a pro-inflammatory cytokine, is highly associated with severe COVID-19, as in the case where there is a significantly higher number of TNF-beta residues than IFN-alpha residues, there will be much weaker restrictions against inflammation. Moreover, a lower amount of IFN-alpha will lead to weaker restrictions against viral replication and spread. These two issues combined can make a huge negative difference with regards to disease outcome. Moreover, an excess of Tumour-Necrosis Factor-beta had a dysregulatory effect upon many Natural Killer Cells, which as a result failed to attach and induce the apoptosis of cells infected with the virus. With the impairment of interferon-alpha synthesis, there will already be a disrupted interferon-alpha to tumour necrosis factor-beta ratio, which will make the immune system more prone to excessive inflammatory responses and impeded antiviral responses. Other clinical studies implicated an injectable amount of recombinant interferons of 3 to 6 million International Units for severe diseases, like malignant tumours and polycythaemia and, although the risks there were higher, the majority of the participants experienced recovery from their disorders and likewise, the clinical trials were deemed successful. People were often put into two main categories in order to differentiate dosage based on the underlying health condition, since a much higher quantity of interferon-alpha poses a higher risk of moderate and disruptive adverse reactions. Given that the majority of the participants did not experience visible adverse events and experienced a significant improvement of the clinical display of their disorder, we believe that the administration of recombinant interferon-alpha-2b represents a likely pivotal approach in immunology, microbiology and pathology restriction, and will potentially result in a scientific progress that would not have a precedent.

There is a circulating theory that the Fukushima disaster in 2011 has already started to cause forms of Acute Radiation Syndrome (ARS) around the world. The theory is based on the evidence that the Fukushima disaster is worse than the Chernobyl one, that it will be affecting the Earth for potentially 100 years, and that it has significant negative impacts upon animals and the fauna. It was mentioned numerous times that certain effects of the disaster will be irreversible. Likewise, it is very possible that some kind of radiation-induced disease or set of diseases will be circulating around the world, maybe even for decades. Symptoms of Acute Radiation Syndrome include inflammation of upper and lower respiratory tracts, shortness of breath, fever, loss of smell and taste happening regardless of whether the nose becomes blocked or not, headaches and dizziness. More severe cases involve the onset of pneumonia, cytokine storm and multi-systemic inflammation. In other words, the symptomatology is often very similar to the one of COVID-19, and we are wondering whether cases of Acute Radiation Syndrome perhaps infiltrated the SARS-CoV-2 pandemic (Rios et al, 2021), given that a number of patients who developed COVID-19 around the world experienced a more significant loss of hair as well, for example. The trickiest commonality between COVID-19 and Acute Radiation Syndrome is that the lung injury morbidity caused by both disorders can be significantly mitigated using inhibitors of the Angiotensin Converting Enzyme (ACE) (L. Cerezo and M. M. i Garau, 2012). Likewise, because of the visible commonalities between COVID-19

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and ARS, we believe that certain methods of treatment developed for ARS could apply for COVID-19, and vice versa. Given the evidence that the future does not look bright with regards to respiratory illnesses and the projected general state of health of the planet, we are urging scientists and clinical researchers to create a nasal spray consisting of either interferon-alpha and interferon-beta, or rather likely even a combination of interferon-alpha, interferon-beta and interferon-lambda, and determine whether the immune-stimulating agents can be regarded as a vaccine for not only the current pandemic, but also for other serious respiratory illnesses that are significantly probably to emerge over the next decades. With regards to the lost sense of smell and taste as a result of radiation poisoning, we could perhaps apply important principles by Nikola Tesla into electricity-based therapies to repair the damaged ophthalmological nerves, and if SARS-CoV-2 also damages such nerves, then this therapeutic approach could be applied for COVID-19 as well. Furthermore, all pathogenic agents seem to have their own sound frequency, and perhaps there could be the development of a frequency-based therapy to target and neutralise the virus during diverse stages of infection and tissular spread. An interesting intervention for intubated COVID-19 could be the transport of Ultraviolet A (Ali Rezaie et al, 2021) and Ultraviolet C rays through the tracheal tube by means of reduction of the viral load in the trachea and the bronchi, and a general mitigation of the hyper-inflammatory processes (Stanislaw P Stawicki, 2020).

SARS-CoV-2 represents a pathogenic agent with a high degree of complexity with regards to developed evolution against human immunity. It produces diverse non-structural proteins to inhibit first-line immune signals, it inhibits the activity of specific chaperones and consequently, the development of some important antibodies, and it produces the spike glycoprotein to further stimulate an already exaggerated, late interferon-based signalling and activation of Interferon-Stimulated Genes. The spike glycoprotein often showed problematic mechanisms even when it was used for immuno-stimulatory purposes, which displays the degree of severity in the evolutionary and immunological matter as such. This further indicates the super-antigenic nature of the spike protein, and likewise, this also highlights the ability of SARS-CoV-2 to eventually mutate into variant forms that escape the majority of vaccine-induced antibodies. We are possibly situated at a dead-end with regards to the current inability of immunology to solve the puzzle of preventing the onset of diseases caused by pathogens with mechanisms of immune evasion, upon which viral mutation and polymorphism is usually dependent upon. A continuation of viral mutations based upon interferon I and III-suppressive models could eventually result in the natural selection of pathogenic super-powers. Overall, the novel coronavirus has acquired evolutionary abilities to suppress all essential areas of human immunity. Likewise, the scientific community is being under an increasing pressure to shift the overall approach in order to include the direct stimulation of first-line immune responses whilst developing prophylactic, therapeutic and immunising agents to tackle epidemics of concern. The matter represents direct evidence of a degree of error and failure in past immunological research to tackle infectious pathogens of concern and treat significant forms and stages of induced diseases.

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Given the significantly damaging effects of the spike protein upon endothelial cells, it was proposed that COVID-19 is mainly a blood-borne disease, although infection first occurs in the cells of the pharyngeal wall (Salk Institute, 2021). Likewise, it is more likely that important blood vessels (i.e. the venae cavae and the aorta) will be affected in people with more severe forms of COVID-19, as the number of tissues infected by the virus is generally proportional with the intensity of the symptoms. It is important to note that the spike protein is often capable of damaging the endothelial cell barrier and entering the bloodstream (Raghavan et al., 2021), and that the way the novel SARS-CoV-2 vaccines have been designed can often allow the pathogenic protein to reach the endothelial cells and then important blood vessels. For example, the mRNA from the BNT162b2 vaccine is nucleoside-modified, as it contains nucleosides with pseudouridine, rather than wild-type uridine, and is protected by an outer layer of lipid nanoparticles, which allow the molecule to last from a few days to a few weeks, thereby entering numerous cells and producing more copies of the spike protein. Given the peculiar nature and origins of the spike protein, there is a real likelihood that there will be a spread of the spike protein and induced collateral damages in a significant number of cases worldwide. Furthermore, not only the spike protein was demonstrated via 2D static and 3D microfluidic in vitro models to be capable of crossing the blood-brain barrier and damaging neurons, but also excessive inflammatory responses induced by the spike protein can prolong the activity of monocytes, which in turn will create leaks in the blood-brain barrier and make it easier for the pathogenic protein to cross it. Namely, whilst the spike protein upregulates genes expressing a number of metalloproteinases, including MMP3, MMP9 and MMP12, which then cause leaks in the blood-brain barrier, the S1 subunit of the spike protein interacts with the Toll-Like Receptor 4 (TLR-4) on macrophages in the alveoli and monocytes in mainstream blood vessels, and induces pro-inflammatory signalling, which in turn can cause further leaks in the blood-brain barrier. In addition to this, the receptor binding domain of the same pathogenic protein was shown to at least sometimes be capable of interacting with developing central nervous system proteins involved in neuro-sustainability and causing risks of protein misfolding and the onset of neurodegenerative disease.

Some studies do not rule out a form of recombination on a small scale with fragments from the HIV-1 virus following the accidental lab-leak of a virus with natural origins that underwent gain-of-function research to examine the extent of immune responses in infected bats (Segreto et al., 2021). The reverse transcription of a visible number of nucleotides from both the SARS-CoV-2 and the HIV-1 genomes led to their integration into the coding DNA of host cells and this is abnormal, given that nucleotides from viral RNAs are very rarely reverse transcribed and integrated into the host cell's DNA, and when this happens, they are almost always inserted into the non-coding DNA. This would explain why a study performed by two Harvard University scientists determined that a small proportion of the spike protein-encoding mRNA is reverse transcribed via the catalysis of LINE-1/HIV-1 Reverse Transcriptases and then the new DNA nucleotides are inserted into diverse areas of the functional and non-functional genome via the catalysis of DNA Integrases (Zhang L. et al, 2020). The fact that about 1% of the spike protein's mRNA nucleotides was shown to become

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reverse transcribed via HIV-1/LINE-1 Reverse Transcriptases and integrated into various parts of the genome show the difficulty to demonstrate the existence of HIV-1 inserts into the spike protein's mRNA, given the small amount. People with weaker immune systems could be at a higher risk of complications because the spike protein and its mRNA may enter multiple kinds of cells, and therefore increase the chance that the reading frame of various important genes will be altered. Recently, it has been discovered that up to approximately 1% of the mRNA in the BNT162b2 vaccine was received into hepatic cells quickly and then reverse transcribed via the catalysis of LINE-1 Reverse Transcriptases, giving rise to risks of integration into coding DNA and consequently, genomic toxicity, mutation and tumourigenesis (Aldén M. et al, 2022). Such a discovery brings a number of concerns with regards to the general approach of using the spike protein and its genetic information as a method of mass vaccination.

There are a number of commonalities in pathophysiology and therapy between COVID-19 and AIDS, and the latter disease could also be regarded as an immunological hurricane, particularly in people with one or more significant comorbidities. An example is the repurposing of the lopinavir, ritonavir and darunavir antiretroviral drugs for COVID-19 therapy. Another example is the interaction of both SARS-CoV-2 and HIV-1 with the AIP4 protein, which is implicated in inflammation, and both interactions led to lower signalling rates of interferons. Interestingly, people with significant comorbidities are pronouncedly more likely to develop complications due to cytokine depletion and the development of a cytokine storm in the case of infection by SARS-CoV-2 and HIV-1 (Olga Tarasova et al, 2020). It is important to note that the spike protein is deemed as cytotoxic, not only for several tissues in the human body, but also for the marine environment (Ives Charlie-Silva et al., 2021). The spike protein has been shown to function as a super-antigen, reaching a magnitude of an immunological impact similar to the staphylococcal enterotoxin B super-antigen when COVID-19 patients developed complications, such as a multi-systemic inflammation (Mary H. Cheng et al, 2020). Moreover, it has recently been discovered that the spike protein can have implications upon the optimal activity of certain genes, such as the ones implicated in DNA repair mechanisms and antibody gene rearrangement (Jiang H and Mei Y-F., 2021). Specifically, the spike protein was discovered to inhibit the processes of VDJ gene rearrangement in the heavy chain of antibodies and the VJ gene rearrangement in the light chain of antibodies respectively, which in turn will cause produced antibodies to have a poorer quality of structure and function. Also, the viral protein was found to downregulate the BRCA1 and 53BP1 genes, which means that important processes of DNA repair are also inhibited, leaving some essential parts of the host cells' functional DNA potentially more vulnerable in front of mutagenesis and genome toxicity. Because the spike protein is capable of weakening the activity of such genes, we believe that a threshold of concern has been crossed with regards to long term risks of vulnerability to mutations, as well as production and secretion of suboptimal antibodies. Moreover, the S1 subunit and the active trimer of the spike protein are also capable of disrupting the activity of mitochondria in brain endothelial cells and likewise, have implications upon metabolism

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(Eun Seon Kim et al, 2021) and the 674-685 fragment of the protein was shown to prevent mitochondria from synthesising cytochrome c, which is responsible for inducing apoptosis of infected cells (Olena Kalashnik, 2021).

The spike protein likely causes a significant number of host cells not to undergo apoptosis if the virus and the spike protein spread to tissues in various sites of the host organism. Likewise, the spike protein displays a level of toxicity significantly greater than previously thought and, although we fully support the concept of immunisation, we believe the scientific community should reconsider the spike protein-based mass vaccination approach. The spike protein produced by the vaccinal mRNA is most likely not less toxic, but only more immunogenic, meaning that there is a higher immune sensitivity against it than against the viral spike protein, and researchers induced two Proline amino acid substitutions in the S2 subunit of the spike protein so that it became more immunogenic. The amino acid substitutions were induced to keep the spike protein in a pre-fusion conformation, but it is not fully certain that the stabilised spike protein will keep its initial conformation (Timothy P. Riley et al, 2021). The receptor-binding domain of the vaccinal spike protein is intact, meaning that it is as capable of binding to the ACE2 receptors of host cells as the viral spike protein, and as a result, intracellular signalling cascades can become visibly disrupted and likewise, the spike protein can still cause significant intracellular damage. With regards to the affected rates of B-lymphocyte development due to inhibited V(D)J immunoglobulin gene rearrangement, the vaccinal spike glycoprotein can still produce significant disruptions to such B-lymphocyte developmental rates by means of disrupted intracellular signalling cascades. It is possible that DNA repair mechanisms are not as much affected by the vaccinal spike glycoprotein, although there is currently still no evidence determining that the vaccinal glycoprotein is not at all capable of entering host cells after synthesis and exocytosis, given the emergency state of the COVID-19 vaccine clinical trials in 2020 and likewise, of the limited production of conclusive data. It may be necessary to consider that the scientific community probably still has not fully apprehended the complex nature, origins and pathological flexibility of the virus and, implicitly, of the spike glycoprotein. Importantly, the translation of mRNA into a protein is only possible within the intracellular matrix, in the cytoplasm, meaning that the spike glycoprotein can only be produced, fold and be manufactured inside of a host cell. Hence, the risks of intracellular and even intranuclear interference, which include the inhibition of important DNA repair and immunoglobulin gene rearrangement processes, sadly do not significantly decrease in the case of the mass administration of spike protein-based vaccines, and an increased immune sensitivity could mean a higher susceptibility for hyper-inflammatory immune responses, especially in people with one or more comorbidities.

The cell types that were among the most affected by the HIV-1/LINE-1 Reverse Transcription phenomenon were inducible pluripotent STEM cells (iPSCs) located in the myocardium and the alveoli. Likewise, it is possible that the spike protein affects those cells the most, and it is known that children and young people generally have a higher

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number of STEM cells in their organism. From this information and the fact that children and young people generally have a very low risk of developing morbidity and dying from COVID-19, we deduced the likelihood that children are at a significantly higher risk of developing disease and dying as a result of vaccine adverse reactions than in the case of natural infection, given that their natural immune system is also generally more prepared to build their first and second-line defences than the one of adults (L. Zhang et al, 2020). Likewise, with regards to the administration of spike protein-based vaccines in children and teenagers; the following affirmation ought to be addressed; just because health authorities will be recommending only a single dose of the mRNA vaccines, which will be around a third of the dose used in adults, it does not mean risks of significant adverse reactions for this age group will visibly drop. There likely will still be a significant amount of spike protein produced, since the mRNA is nucleoside-modified and protected by lipid nanoparticles, making it potentially immune against RNA-degrading factors for up to a week or two. To exemplify, instead of 27,000 produced spike protein copies overall, there will be around 3,000 copies (~27,000 / 3 / 3) in the case of the administration of a single dose, or 6,000 copies (~27,000 / 3 / 1.5) in the case of the administration of two doses, both of which still being significant numbers for a pathogenic protein with cytotoxic effects for multiple kinds of tissues, including the endothelial ones, and with toxic effects for the aquatic environment as well. Moreover, children have a significantly lower body mass index than adults and likewise, a third of the dose for children is often equivalent to a whole dose for adults (3,000 spike proteins in a 20 kg-weight organism ~ 9,000 spike proteins in a 60 kg-weight organism). Hence, the risks likely still remain outstandingly high and are probably even higher than in the case of young adults aged 18-25. It is likely much safer for children and teenagers to receive low-dose Interferon I-based nasal sprays instead. Would it not be much more efficient, less time consuming and financially demanding to create such sprays, support the mucosal immune system more directly and eventually outcompete the virus evolutionarily by filling in the gaps in the cellular immune system created mainly by the viral non-structural proteins 1 and 16?

Could interferons even cancel cancer? Given that early Interferon I and III-based immune responses are associated with significant levels of prophylactic anti-cancer cellular mechanisms, it is probable that low dose interferon I and III-based nasal sprays will also upregulate the activity of the BRCA1 and 53BP1 genes, thereby partially restoring the ability of cells to perform the necessary DNA repair mechanisms and prevent mutagenesis and genome toxicity. In other words, such nasal sprays could display a number of immunising effects against SARS-CoV-2 and spike protein-induced cancer. Performing thorough studies on the links between a virally hijacked host immune system and the onset of cancer is likely the next important step in understanding the relationship between cellular immunology and cancer aetiology. Also, there is likely an extent of prevention from the inhibition of antibody gene rearrangement following an interferon-based immunisation approach, given that the projected viral peak will be significantly lower. Nevertheless, the highest impact of the antiviral proteins will be upon the ability of the virus to self-camouflage, to significantly downregulate interferon synthesis and signalling, and to inhibit antigen presentation. Furthermore, it has recently been discovered

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that fungi often grow in and around cancerous cells, and this finding further indicates that cancer is an immunological problem as well (Dohlman et al., 2022). Likewise, interferons may prevent the formation of tumours because they often sharpen first-line immune responses to the point of stimulating a rapid induction of apoptosis of the affected cells, as well as the spread of toxins that may be developing inside and around them.

Around the time the AIDS pandemic started, the TIME magazine came with two important suggestions: that interferon-alpha drops can significantly impact cancer and that it can treat the common cold. Moreover, Dr. Fauci himself acknowledged once the growing evidence that low dose Interferon I-based drops are effective against AIDS and yet, during the current pandemic, the same governmental scientist first insisted there was no cure or significant method of treatment against COVID-19, and now that the only way to pull civilisation out of the pandemic is to introduce another significant amount of spike proteins intramuscularly, according to classical methods of immunisation, which we have well-founded reasons to believe they do not quite apply in this context, especially for groups of lower risk. Withholding information from or refusing to testify to the public about critical past research represents one of the greatest bioethical issues that the world has been facing, and financial interests and institutional corruption may represent two important factors of this issue, and the recent publication of secret contracts between Pfizer and world governments containing information about serious adverse reactions that are probable to occur after the administration of BNT162b2 vaccines in a significant number of people represents a relevant example of such corruption, and this example also marks a failure of reaching informed consent in a significant number of cases, which is an unprecedented situation. Overall, we believe that trialling the prophylactic and therapeutic effects of Type I and Type III Interferons, and testing their position in relation to vaccinology are two steps of prime importance and may contribute to the greatest clinical research in modern history.

The foundational factors of malignant tumours and neurodegenerative disease are immunological in nature, and the problem of immune escape represents an important stronghold of the worldwide epidemic of cancer and neurodegeneration. Immune escape not only facilitates pathogens to infect kinds of tissues that are vulnerable to mutagenesis and genome toxicity, but also prevents the apoptosis of cells that have already undergone tumour-related mutagenesis. Understanding the key mechanisms of cellular signalling resulting in the phenomenon known as "wise immune sharpening" represents the number one objective of cancer research. Weakened first and second-line immune responses are not only caused by active pathogens, but by a series of genetic factors that likely emerged as a result of a repeated exposure of ancestors with diverse immune co-morbidities to pathogens of more significant concerns. Understanding the spectrum of genetic-epigenetic factors that favour a specific outcome in offspring is also important in increasing the resolution of the details collected during applied immunological research in cancer biology.

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Recent in-vitro and in-vivo research has indicated the presence of a link between Type I Interferon-based signalling and LINE-1 retro-transposition. Namely, the study suggests that IFN I and LINE-1 retro-transposons regulate each other, and that an exaggerated IFN I signalling is linked to a higher incidence of autoimmune disease. With regards to SARS-CoV-2 and the spike protein, it was previously indicated that small regions of the viral genome undergo LINE-1 reverse transcription and integration into various parts of the junk and functional DNA of the host cell and, given that long COVID is a result of a delayed and exaggerated extent of IFN I signalling, it is possible that the viral infection results in a less regulated propagation of LINE-1 retro-transposons. According to evidence collected from genetic studies, it is possible that substantially small, but still concerning, parts of the viral genome have laboratory origins. Namely, it is possible that up to 0.5-1% of the overall viral genome (including about 1% of the spike protein-encoding +ssRNA) was extracted from a retroviral kind of pathogenic genome, and there are various circulating theories, including that the virus having had natural origins beforehand underwent gain-of-function research to test the way the immune system of bats would react to it. The novel coronavirus has outstanding evolutionary abilities of suppressing Type I Interferon-based signalling, which is outstandingly concerning, no matter whether it has fully natural origins or a number of inserts from other pathogens. Furthermore, given the likelihood that the timing and extent of IFN I production influence the spread of LINE-1 retrotransposons, it is statistically probable that, the more capable a virus is of suppressing IFN I production and signalling to neighbouring cells, the more capable such a virus is of inserting fragments of its genome into the DNA of the host cell, given that the LINE-1 retrotransposon-encoding DNA represents around 17% of the human genome. Likewise, the more capable a virus is of suppressing first-line immune responses, the higher the risks are that such viral infections will ultimately result in the formation of cancers.

As a result, the research is approaching the conclusion that facilitated early and regulated IFN I responses are paramount not only in maintaining anti-viral immunity and preventing the onset of various autoimmune diseases, but also in preventing an exaggerated spread of LINE-1 retro-transposons and maintaining genomic integrity. The research has also started to directly challenge the safety and long-term effectiveness of spike protein-based mRNA and adenoviral vaccines that had been developed during the midst of the COVID-19 pandemic. We are therefore requesting immediate study and clinical trials involving the efficacy of low-dose Interferon I and III-based nasal sprays in human and animal vaccinology, particularly for viruses and bacteria of significant concern. Additionally, we are proposing that such nasal sprays will play a major role in a collective prophylactic and early therapeutic fight against retroviral infection and also in the prolongation of the host cellular and systemic lifespan.

Given the powerful effects of the combination of restricted C5a complement activation and a robust activation of Type I and III Interferon signalling, updating vaccinology accordingly may slowly reduce the intensity and morbidity of numerous diseases from "incurable" to " flu and common cold-like" as decades and centuries pass. In a number of cases,

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such an approach could be merged with other discovered approaches to ensure long-term effectiveness (i.e. the protollin-based potential nasal vaccine against Alzheimer's disease). Hence, this may be the case given the central role of immunology in facilitating general human and animal wellbeing. COVID-19 may represent a very important opportunity to discover the hidden power of human natural immunity and to facilitate the inclusion of sharpening natural immunity into the efforts of vaccinology-related medical research. To note, for scientific and academic research, the term "sensationalisation" represents one of the most important antagonistic terms, and big words have often been disproven in front of the committee. Likewise, it is of an essence for scientists and academicians to perform their due diligence before making any scientific observation, and this study is not exempt from the obligation to perform prior due diligence.

Numerous kinds of significant infectious diseases implicate a latter hyper-activated interferon set of responses, alongside a severe complement-mediated set of immune signals, which often result in the onset of haemophagocytic lymphohistocytosis, which is in short known as cytokine storm. The truth is that a desired extent of complement system activation also stimulates an early development of interferon signalling, which means that eventual updates in vaccinology could require the inclusion of approaches sharpening complement system-related immunity. A delayed Type I Interferon-based immune response is accompanied by an exaggerated Complement C5a-related immune response, which means that finding methods to prevent exaggerated activations in this part of the complement system will also support the development of an early Interferon I and perhaps Interferon III-based antiviral and anti-inflammatory signals. The reason why the discrepancy in timing is significantly elevated is that the production of interferon-alpha, -beta, -delta, -epsilon, -kappa, -omega and lambda takes place as a result of viral sensing, and when the sensing process is temporarily inhibited, then a sudden process of viral sensing will take place in a pronouncedly higher number of host cells, leading to a much higher number of synthesised interferons, which will only contribute to hyper-apoptotic and hyper-inflammatory processes, leading to a large extent of tissue damage and demand for a replacement of the cells that underwent programmed death. In numerous cases, delayed first and second-line immune signalling will have allowed the virus to replicate and spread to tissues in the lower respiratory tract, which in turn will significantly raise the likelihood of the development of severe inflammatory responses, particularly if viral copies have reached bronchioles and alveoli. There will be a much higher extent of natural killer and dendritic cell recruitment, alongside the activation and specification of significantly more lymphocytes. Pro-inflammatory cytokines will become more active than anti-inflammatory chemokines, often leading to a severely disrupted set of anti-viral immune responses, and the focus on anti-viral action will become much higher than the focus on synthesising qualitative antibodies. Consequently, the onset of haemophagocytic lymphohistocytosis will be much more likely, particularly in patients with underlying health conditions, which predispose their immune system to overreact.

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Likewise, interferons can be deemed as a double-edged sword in immunology and cancer biology, and herein lies the importance of ensuring that such chemokine-based signalling takes place significantly during the early stages of the disease, and that prevention methods against the pathogenesis of cancer implicate the stimulation of a solid interferon-based response during such a critical stage, before the disease can advance. Moreover, certain approaches could be merged with this immunological method to bring broader positive changes in the fight against cancer, and certain immunosuppressive methods could be temporarily applied for latter stages of cancers and infectious diseases in order to restrict the extent of induced inflammatory responses.Sharpening interferon-based immune responses on an evolutionary scale is likely still enough to improve general human immunity against pathogens with tricky mechanisms of pathogenesis. Nevertheless, a prophylactic approach against a hyperactive complement system will possibly bring a further shift against pathogens with abilities of immune evasion.

Furthermore, given that correct Interferon I and III-based immune signalling has a central importance in maintaining a fortified and wise immune system, it is possible that developing Interferon I and III-based vaccines will reach areas of efficacy as far as the prolongation of the average human lifespan. Moreover, a high energy metabolism, which is associated with high levels of stress and general poor alimentation, leads to a shorter lifespan, as the higher demand to consume energy implicates a higher speed of cellular and tissular ageing. A general re-establishment of human lifestyle to a nature-friendly point may involve a lower energy metabolism, as the general levels of stress and energy consumption will significantly decrease. There is a wide availability of resources due to the high number and wide areas of nature-friendly areas worldwide; it is the increase of human and societal corruption that allowed for a progressive development of a general crisis of lifestyle. Non-qualitative food and beverages are epigenetically and ultimately genetically predisposing human metabolism to switch to high-energy consumption, thereby accelerating the process of ageing. It is possible that a repeated set of developed early, regulated interferon-based responses over a longer time reduce the rate of cellular ageing, whilst a repeated set of developed late, exaggerated interferon-based responses increase the speed of cellular ageing.

If the interferon-based approach is proven to be successful as a prophylactic, immunising and early therapeutic method against important pathogenic agents and the onset of cancers, then it will constitute a significant step in prolonging the lifespan of humanity, with an estimated increase of the average human lifespan of at least 10 to 20 years. Interferon I and III will not only wisen the immune system up, but it will significantly strengthen important DNA repair mechanisms and ultimately repair many of the past damages done upon human metabolism as well. A process of immune wisening will not only involve better first and second-line responses due to a combined approach to regulate C5a complement activation and stimulate IFN I and III may result in a decreased sensitivity of complement system activation and an increased sensitivity for Type I and III-based signalling and immune sensing of many problematic

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microbes, but will also stimulate a better process of V(D)J antibody gene rearrangement in developing B-Lymphocytes via the upregulation of the activity of certain genes, including BRCA1 and 53BP1, which in turn will lead to the production of more qualitative IgM and IgG antibodies during challenging infections. Research has shown that the administration of interferon-alpha to pregnant mothers is safe for the foetuses and that it increases the probability that the future baby will be immunologically healthy. This possibly means the effectiveness of such interferons will cross the umbilical cord and reach the health state of the foetus as well. Likewise, updating and revolutionising human vaccinology in such manner may bring a level of breakthrough the great minds in the past centuries only dreamt about, and believing in a positive outcome and paying close attention to new, conclusive evidence, represents a major step toward a desired scientific and medical progress.

Conclusion

Given the overall results from the researched clinical data, there is a high number of solid reasons to believe that such a low-dose Interferon I and III-based nasal spray could match the definition of a vaccine with a few more therapeutic traits than prophylactic ones. This means that, whilst the potential vaccine candidate could prevent numerous cases of COVID-19, it would have the highest impact when administered in people who became infected and developed the first symptoms. Administered Type I (IFN alpha-2b, epsilon, omega and perhaps IFN beta1, delta, kappa and tau) (BAI et al., 2022) and III Interferons (IFN lambda 1, lambda2 and lambda3) mimic cellular infection and stimulate a detailed, robust and intelligent immune response against the virus and likewise, such an intervention fits the definition of a vaccine. Because this likely requires numerous dosages, we might refer to the potential immunisation process as a long-term one.

Hence, there is a probability that the medical community does not need to insert any viral fragments to stimulate a desired immune response and ultimately gain immune memory. It is essential to mention that an excess of administered interferon-alpha could give rise to the probability of developing adverse reactions, like epistaxis, headaches and dizziness in this case, since an excess amount of Interferon I in the tissue would be caused. The needed quantity of administered interferon differs based on the disease. For example, a higher amount of interferons would generally be needed for COVID-19 than the general flu. Compared to the dosage of injectable interferons, which ranges from 3 to 6 million International Units, which is measured in milligrams, the nasal sprays can only have an interferon concentration from 200 to 500 International Units, which is measured in nanograms. The best part of this discovery is that a matching dosage of Interferon I might bring us a few steps forward with regards to the preparation for a future potential avian influenza pandemic, but in that case, it would be slightly more useful and safer for the compound to be administered only as soon as symptoms develop or when certain tests indicate the presence of the virus in the organism. With regards to the dosage based on age and health condition groups, we are proposing a session of vaccination of two to four weeks, with a daily dosage of 350-375 International Units for almost all adults, and 200-225 International Units for children and

adults with blood and autoimmune conditions due to slightly increased risks of epistaxis in children and the aggravation of the autoimmune conditions in the affected adults.

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