Infection-Simulator, Immunostimulatory and Immunomodulatory Effects of Interferons I and III in Biological Systems: A New Era in Vaccinology and Therapeutics Possible?

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Abstract: The severe acquired respiratory coronavirus–2 (SARS–CoV-2) infection has initiated both acute and chronic COVID–19 disease between 2020 and 2023, currently evolving with other homologous prior coronavirus strains of the Nidoviridae order, which encompasses other prevalent alpha/ beta coronaviruses, but also the Middle East Respiratory Syndrome (MERS-CoV) and SARS-CoV-1, with recent SARS–CoV–2 variants, increasing demands for effective immunogens and therapeutic approaches that will reduce global disease burden and further infection from SARS–CoV-2 affected individuals that may experience post acute sequelae (PASC) or "Long COVID". Following a worldwide programme of prophylactic vaccination, there is still a dilemma in the efforts to find prophylactic and early therapeutic approaches that would treat novel SARS-CoV-2 variants and prevent future epidemics or pandemics within host human and animal populations, where zoonotic or cross species transfer naturally occurs. Concerns about viral immune escape intersect at a specific point; a gained evolutionary ability of several viruses to co–infect and compete against previous scientific advances since 1796 that remain undetected or asymptomatic during the early stages of infection progressing to symptomatic and severe disease via the double methylation of the 5' end of eukaryotic DNA or RNA-based viral genomes, the $^{7\text{-Me}}GpppA_{2'\text{-O-Me}}$ cap, and its double methylation capping process is performed by the activated viral 2′ - O - Methyltransferase (MTase) enzyme, a complex of two viral non-structural proteins (NSPs) joined together through an activation process (NSP10/16) and by N7-Methyltransferase (N7-MTase/NSP14), respectively. Moreover, it was discovered that polymorphic viruses translate NSP1, which prevents the activation of various Pattern Recognition Receptors (PRRs), and consequently, detection of Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) alike. NSP1 also silences important interferon-encoding genes (INGs) and interferon-stimulated genes (ISGs), is signalled in a paracrine manner to neighbouring cells, and that induces the apoptosis of host cells, inducing an effect of "trace erase" effect and making the viral infection as immunologically "invisible" as possible during the initial, key stages of viral replication and distribution, all such mechanisms occurring independently of the viruses in cause. Another important viral NSP is NSP14, as it plays two functional roles that are independent of each other; to produce new viral genetic material for the purpose of maintaining the validity of the viral genome as well, and not just transfer a methyl group to the 5′ end of the viral genome. Other viral NSPs share a role with NSP1, 10, 14 and 16 in directly suppressing the activation of PRRs and ISGs, and all such viral proteins help the virus in its process of self-camouflaging against first- and second-line immunity, thereby often severely impacting the quality of the produced adaptive immune responses. The outcome of all such phenomena is the sharp decrease in the host Type I and Type III interferons' (IFNs) rate of synthesis by the host cells, that would usually occur and affect homeostatic cellular pathways, resulting in further viral replication and induced apoptosis. Nonetheless, effects of microbial immune evasion during the development of other viral or carcinogenic pathologies are not widely known. In short, polymorphic viruses developed a proportionate evolutionary response against developed adaptive immune responses, by currently relying on gaps mostly situated in the natural immune system in their process of molecular self-camouflaging. Scientists developed numerous approaches of early treatment that generally showed good success rates and fewer risks of adverse events, and the still early present stages of COVID-19 research should also be taken into consideration whilst filtering for the most appropriate solutions. For example, the administration of recombinant human interferons I and III into the nasal mucosa cellular layer, as key mediators of anti–viral

activity, can simulate intracellular infection and stimulate cellular activity in a timely manner, training the innate and adaptive immune system cells to develop and appropriately stimulate an adequate immune response through B and T cells. Another example could involve the treatment of natural and adaptive lymphocytes with a low dose of IFNs I and possibly III, prior to their insertion into the host lymphatic system, possibly alongside additional recruitment of plasmacytoid dendritic cells (pDCs) as further interferon "factories", all with the purpose of early infection management. 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 immune mechanisms. It is until the scientific community realises this potentially crucial aspect that large proportions of the world population will probably continue to face serious epidemics and pandemics of respiratory diseases over the coming several decades, evidenced with dengue fever and more recently, monkeypox and possibly avian flu. Of note, it has been indicated that IFN I and / or III display significant immunising, early therapeutic and clinical disease onset-attenuating effects for many other microbial evoked diseases, as well as for a number of oncological diseases.

Keywords: COVID-19; pandemic; immune evasion; first-line immunity; viral evolution; interferon; dendritic cells; cytokines; chemokines; natural lymphocytes; adaptive lymphocytes; innate immunity; adaptive immunity; vaccinology; therapeutics

Introduction

Interferons (IFN) are glycoproteins with antiviral activity that can be produced by dendritic cells (DCs), comparatively quicker upon infection that stimulate the immune system into its innate and adaptive compartments. WIthin these immune system compartments are IFN receptors located within not just DCs but also B-lymphocytes, monocytes, macrophages (Mϕ), and T-lymphocytes, as well as glial cells, neurons, and among others. These cellular receptors initiate both downstream and upstream effects that include initiating phagocytosing pathogenic viruses as soon as they infect such cells. There are three principal classes of IFN that are Type I, Type II and Type III with the first and the last that have more specific antiviral activities, whilst type II IFNs focus more upon the development of pro–inflammatory responses earlier in host infection. Interferons (IFNs) were originally characterised in 1957 by Isaacs and Lindemann (Stanifer M. L. et al., 2020), with comparatively recent differentiation of IFN subtypes further, as below. Recently, scientists further discovered that a number of plants also generate interferon–stimulating proteins, and we believe that by modifying dosages of such natural or synthetic proteins there could be a potential improvement of cellular effects of IFNs in various pathologies. The main focus in clinical research during viral pandemics like the recent COVID–19 is to balance the cellular immune responses precision and beneficial cellular effects, through ongoing IFN research, as timing of IFN release has been indicated to affect viral infection, propagation, replication and lysis in differential organ compartments and cell systems. The principal commonality between the majority of infectious diseases is that numerous forms of cancer and several proteinopathies is that all disease categories generally involve a late and exaggerated development of Type I and Type III IFN based immune responses, and this potentially means IFNs could play essential prophylactic, and sometimes also early therapeutic roles in oncogenic, retroviral and neurodegenerative forms of disease depending on disease aetiology. Therefore, we emphasised upon the search for safety data with regards to both clinical approaches and the physiology of each type of IFN signalling. The collected results and bibliographic references were then listed specifically, according to topic and degree of relevance to the title of the study. We present here projective analysis and clinical trials concerning the risks and efficacy of low-dose nasal recombinant human Type I and III IFN, with effects of subcutaneous dosing of Type I and III IFN that will require further research,.by means of gathering safety data and collateral evidence around the study's principal scope in order to fully elucidate the nature of IFN cellular responses and pathways for therapeutic benefit.

i) Overview to Interferon Cellular Types

Type I IFNs are synthesised and secreted by various types of human cells, with timing of nuclear transcription resulting in differential effects indicated as key in host cellular responses to pathogens and within cancer cellular proliferation. For example, early synthesis and release from plasmacytoid dendritic cells (pDCs)   that produce both Type I IFNs subtypes IFN–α and IFN–β can affect antiviral responses through innate and adaptive immune cell compartments initiating apoptosis in macrophages. Type I IFNs also include IFN–δ, IFN–ε, IFN–κ, IFN–τ, IFN–ω, and IFN–ζ subtypes, whilst Type III IFNs include IFN–λ and subtypes (Reizis B., 2019). There are more classifications of each subtype of such interferons that can vary between host species. To clarify further, human IFN–α presently consists of at least 18 subtypes, which include IFN–α1, IFN–α2, IFN–α5, IFN–α7 and IFN–α14, whilst IFN–λ consists of IFN–λ1, IFN-λ2,   IFN-λ3 and IFN-λ4, and among the listed examples of IFN-α subtypes, IFN-α2 and IFN-α14 are glycosylated (George J and Mattapallil JJ, 2018). The first IFN subtype is glycosylated on its Nitrogen-terminus (N-terminus, left hand-side), whilst the latter is glycosylated on its Oxygen-terminus (O-terminus, right hand-side). Recombinant human IFN-α2 has often been used during clinical trials for the purpose of safety and efficacy testing, with numerous trials indicating safety and potential in disease treatment. In addition, all subtypes of IFN-β are N-glycosylated. Furthermore, another clinical study showed that the addition of a glycosyl group on IFN-λ4 raised its level of anti-inflammatory and antiviral efficacy (Chung J. H. et al., 2020). It is important to note that glycosylated interferons have a greater stability and thereby display more powerful antimicrobial effects (Li S. et al., 2018). Glycosylated IFNs perform a molecular interaction with the carbohydrate molecules present on the plasma membrane of cells and they may have better binding affinities to the IFNAR1/2 and IFNLR1/IL10R2, and an easier overall access into their cells. On the other hand, Type II IFNs include IFN$-\gamma$. Whilst IFN-β and IFN-λ are produced by all kinds of human cells, IFN-α are generally produced by immune cells, including plasmacytoid Dendritic Cells (pDCs) (Kim Y. M. et al., 2021). It is important to note that research involving Type III IFNs is still in early stages, and much of the specific data about early therapy and immunisation is unknown although comparatively well documented in bacterial infection, but indications are that potential use could be at least as effective for as naturally produced Type II IFNs.

ii) Pathological context

Immune system modulation and/or evasion could represent a serious immunological problem of the 21st century, and   is the result of less knowledge with a comparative shift in the evolutionary development between the human immune system and prior pathogens, like smallpox, human immunodeficiency virus (HIV), and *Streptococcus*, that took place throughout history. Respiratory viruses represent the pathological category of viruses whose mechanisms of immune evasion are among the most prevalent. It is likely that regular mutations also lead to the development of ongoing seasonal variants of the Influenza A positive-sense single-stranded RNA virus (+ssRNA virus) and the *Haemophilus Influenzae* bacterium (with 198 potential sub–type combinations for the latter). The avian Influenza A variant (H5N1) has undergone mutations of concern, with a few recent events of zoonotic spillover into humans, and severe forms of Influenza A may favour severe morbidity following secondary bacterial infection. *H. influenzae* is composed of haemagglutinin (HA) and neuraminidase (NA) protein antigens that co–exist alongside SARS–CoV–2 viral antigens that include spike (S), membrane (M), nucleocapsid (N) and envelope (E) proteins, and an effective restriction of an increased viral and pathogenic protein load is produced by the initial, sensitised ability of the immune system to react and lyse infectious viruses effectively during replication. Generally speaking, it seems that powerful microbes evade their host cell's immune mechanisms faster and develop trickier methods of direct and indirect molecular self-camouflaging than microbes causing routine infectious diseases. Four universal methods of microbial immune escape seem to comprise the phenomenon of pathogenic DNA or RNA 5′ capping, in which the microbe adds two methyl (CH3-) groups to the 5′ end of its genome to attempt significant evasion from Pattern Recognition Receptor (PRR)-mediated recognition of Pathogen-Associated Molecular Patterns (PAMPs), which are molecules specific of pathogenic agents, and Damage-Associated Molecular Patterns (DAMPs), which are molecules produced due to induced cellular damage and lysis, meaning

that recognition of microbe-induced damage and lysis of cells is also impaired; the direct inhibition of the activation and expression of interferon-encoding genes (INGs) to facilitate viral replication and distribution of its increasing load to neighbouring cells and tissues, the method of mitochondrial disruption via the increased production rate of reactive oxygen species (ROS), and the method of viral usage of inter-cellular channelling nanotubes between host cells, which are developed by many cells to facilitate paracrine signalling of important proteins between each other, and viruses utilise the same method of paracrine signalling for the purpose of facilitating the exocytosis and paracrine signalling of non-structural proteins that will prevent the activation and expression of interferon-encoding genes (INGs) in uninfected cells as well, which tremendously aids the virus in escaping recognition by such PRRs, which include Toll-Like Receptors (TLRs) and RIG-I-Like Receptors (RLRs) (Amarante-Mendes D. P. et al., 2018). Such a method of molecular self-camouflaging facilitates an exponential increase of the viral load whilst preventing much of the development of immune responses that normally induce clinical signs and symptoms characteristic of infectious disease (Sherer N. M. et al., 2008). The final evolutionary objective seems to be a prevention of Type I and possibly of Type III Interferon production by the infected cells. To specify, the non-structural proteins 1 (NSP1) produced by Dengue and Zika viruses were discovered to be packaged into exosomes, exocytosed and transmitted to neighbouring cells as soon as they were translated by the viral genome to prevent signalling of IFN I and III in them also (Safadi D. E. et al., 2022), and this molecular event likely indicates that oftentimes, the NSP1 produced by the novel coronavirus is also transmitted to neighbouring cells often faster than secreted interferons are. Moreover, it was discovered that the NSP1 produced by the H5N1 strain of Influenza A Virus (IAV) induces the caspase-induced apoptosis of their host cells, thereby seemingly bringing an effect of "trace erasing" to "ensure" that the "intelligence" of the virus is ahead of the "intelligence" of the host immunity (Zhang C. et al., 2010), and such phenomena may also widely apply to SARS-CoV-2 infection. A relationship of proportionality between disease mortality rate and extent of NSP1-induced apoptosis may be projected. Likewise, the extent of viral evolution over human and animal natural immunity seems to be a proportionate reaction to the developed adaptive immune responses and memory over past viruses and viral variants, ultimately according to the pattern behind Newton's Third Law in Motion, given the foundational role that physics plays in material sciences. The gap currently used by novel polymorphic viruses on their evolutionary path to gain advantage over the immune methodology of responses is very likely situated mostly in the natural immune system.

Other viruses of major concern, including the novel Monkeypox Virus (MPV), Ebola virus (EBOV), Marburg virus, the Human Immunodeficiency Viruses 1 and 2 (HIV-1 and HIV-2), as well as the Sendai, Hendra and Nipah viruses, displayed significant molecular activity that antagonises the synthesis and exocytosis of Type I and often Type III Interferons. One important common method of the majority of such viruses is the translation of viral proteins that cleave the interferon-encoding mRNA. For example, the EBOV viral genome translates the VP24 and VP35 proteins to substantially inhibit interferon production (Ilinykh et al., 2015), although the latter protein was not found to suppress IFN production in plasmacytoid dendritic cells (Leung et al., 2011). Sensitised Type I Interferon-mediated immune responses were found to considerably weaken the EBOV infection (Kuroda et al., 2020). Furthermore, scientists who induced a loss-of-function mutation in the EBOV gene encoding VP35 discovered that such a variant of the filovirus is not virulent and mounts a long-term immune memory against the regular Ebola viral variant (Woolsey et al., 2019). Moreover, one study showed the ability of HIV-1 to suppress Type I Interferon synthesis and transmission by producing the Viral infectivity factor nonstructural protein (Vif), which targets the cGAS-STING-related signalling cascades by interacting with the cellular Tyrosine (Tyr/Y) Phosphatase enzyme known as SHP-1, leading ultimately to the dephosphorylation of STING at the Y162 amino acid position (Wang Yu et al., 2022). Another study highlighted the ability of HIV-1 to evade TLR-8 detection via the translation and signalling of the snapin viral protein to neighbouring cells (Khatamzas et al., 2017).

Table 2. List of clinical trials involving the administration of Type I and Type III Interferons for both COVID-19 and non-COVID-19 purposes.

NCT Order	Disease status	NCT & Phase - Type I IFNs	NCT & Phase - Type III IFNs
I	COVID-19	NCT04469491, Phase 2 (Oral/Nasal)	NCT04354259, Phase 2 (Pegylated, subcutaneous)
II	COVID-19	NCT04469491, Phase 2 (Oral/Nasal)	NCT04967430, Phase 3 (Pegylated, subcutaneous)
III	COVID-19	NCT04732949, Completed (Oral/Nasal)	NCT04534673, Phase 2 (Pegylated, subcutaneous)
IV	COVID-19	NCT04350281, Phase 2 (Subcutaneous)	NCT04343976, Phase 2 (Pegylated, subcutaneous)
V	COVID-19	NCT05381363, Phase 1/2 (Oral/Nasal)	NCT04727424, Phase 3 (Pegylated, subcutaneous)
VI	IAV infection	NCT00895947, Completed (Oral/Nasal)	Not available yet
VII	Hepatitis B/C	NCT00917358, Completed	NCT01204762, Completed (Pegylated, subcutaneous)
VIII	HIV Infection	NCT01295515, Completed	NCT01866930, Completed (Pegylated, subcutaneous) - HCV patients co-infected with HIV
IX	Cancer	NCT01462773, Completed	NCT04469491, Unknown status
X	Cancer	NCT00278174, Completed	Not available yet
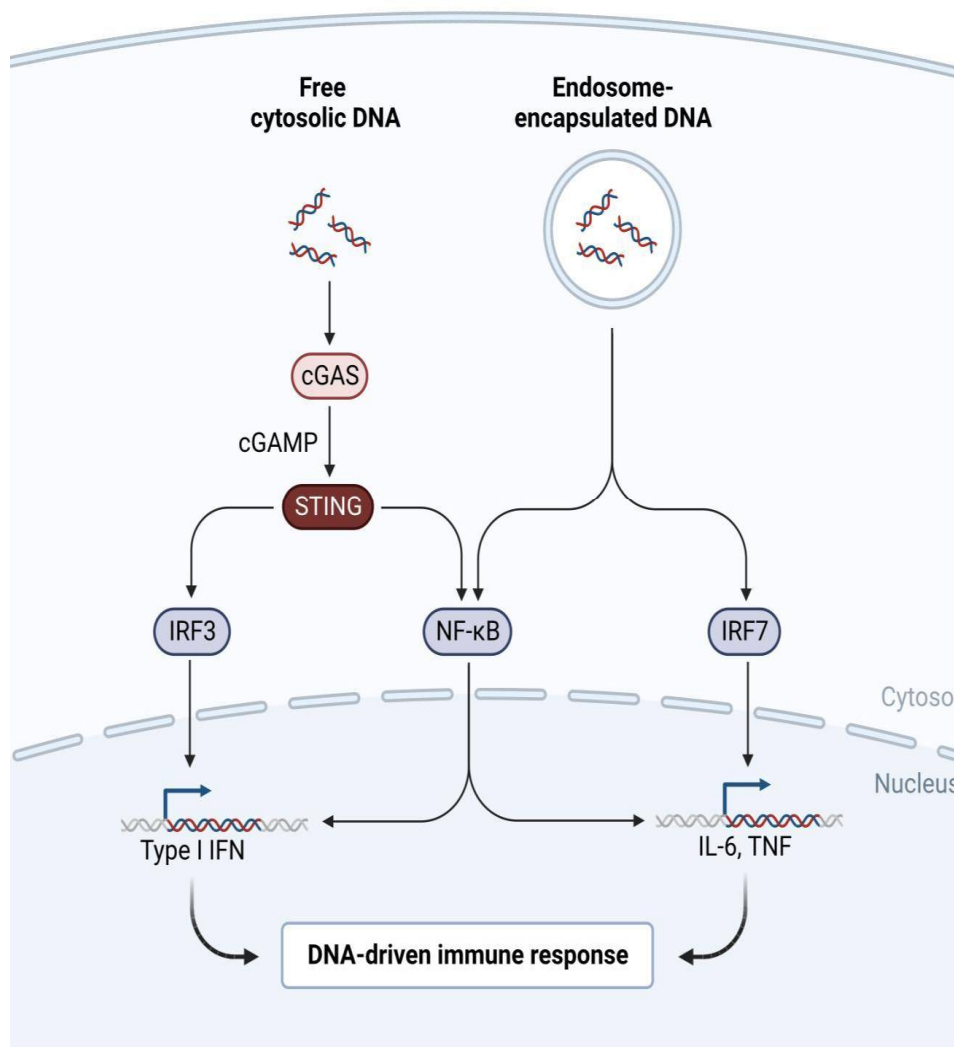
Figure 1. The cGAS-STING pathway inducing Type I Interferon, Interleukin-6 and Tumor Necrosis Factor expression and signalling (Created with BioRender.com under the IV2510F0GI License Number).

Overall, the evolutionary problem of viral antagonism against the depths of human immunity, the interferon system, may be more voluminous than previously believed. The increased ability of the novel coronavirus to evade recognition of cellular Toll-Like Receptors leads to a desensitised and delayed ability of the immune system to recognize, and let alone react against the virus, which explains the significant number of individuals that develop symptoms several days after an infection takes place, and the phenomenon is also known as a silent inflammation. Interestingly, a prolonged asymptomatic stage of the disease does not mark an immune preparation against an exponential increase of the viral load, but a lack of it. All infectious diseases begin with an asymptomatic stage, but the majority of such diseases include a far briefer stage that does not implicate the manifestation of clinical symptoms. The ability of microbes to evade first-line immunity could be proportional with the duration of asymptomatic disease.

iii) Limitations

It is important to note the difference of Type I and Type III IFNs with regards to the stage of research concerning their prophylactic and early therapeutic effects. Moreover, it is also essential to note a common problem that led to an interruption of some clinical trials; a lack of funding, which was often accompanied by insufficient participants. Likewise, in spite of the wide bioavailability of human recombinant interferons as such, as well as their significant impact upon the severity of

multiple diseases of concern, there seems to be a slight impediment of funding and human resource availability in a number of cases, particularly in areas of the world affected by precarious welfare and sanitary conditions, given that wider research involving IFNs as such began just after the mid-twentieth century. Despite such occurrences, which could be a result of barriers met commonly during research efforts that later prove to be successful, the novel discoveries of natural immune effectiveness and of its existent "memory" strongly encourage researchers to bring a much wider inclusion of natural immunity in their process of therapeutics and vaccine-based research. Adverse reaction-related limitations generally include the utilisation of larger dosages of human recombinant Type I and Type III IFNs, in latter stages of infectious diseases that display more concerning magnitudes of morbidity. In such cases, complications involved the onset of autoimmune diseases and increased rates of infectious disease pathophysiology. Moreover, more severe adverse events included the onset of systemic inflammation, as well as neurological diseases, including depression and anxiety-related pathologies. The "double-edged sword"-like nature of interferons of such classes with regards to quantity, type of disorders and their stages may explain why there are existing contexts in which interferons cause more harm to the host organism than benefit. Likewise, a significant extent of caution requires to be practised during the projection and development of such novel approaches in clinical research covering human immunity, regardless of the extent of efficacy interferons would display if administered within the appropriate medical context.

Methodology

Using MESH searches and/or the clinicaltrials.gov site, we used the keywords below and detected IFN NCT trials listed globally, without date restriction, which were listed as follows with 209 "type I IFN", 330 "type II IFN" but also 153 were classified as " type III IFN". Therefore, according to this a total of 692 NCTs were either entered or registered, awaiting, in progress, or completed prior to this analysis publication with or without results. However using keyword searches "IFN alpha" and/or "IFN beta" totalled 1845, but also "IFN gamma" totalled 2477 with 25 "IFN lambda", 3 "IFN epsilon", "1688 IFN delta", 21 "IFN kappa" and 21 "IFN omega". Therefore a total of 692 NCT are registered according to IFN type, however 6077 individual searches appear according to type of IFN. Only peer-reviewed scientific journals concerning the effectiveness of early therapies using low-dose Type I and III IFNs were analysed using the [MeSH] algorithm on PubMed. Data collected through numerous clinical trials (NCTs) implicating a low-dose IFN nasal spray and high-dose Type I, Type II or Type III IFN was collected, and the kinds of NCTs included preliminary, double-blind and meta-analyses, but also mainly in phase 2 and phase 3. We reviewed literature addressing similarities and differences between SARS-CoV-2, three other respiratory viruses, and a retrovirus, to determine other options open to clinical research or researchers for further investigation.

Discussion

1. Important highlights of innate immune evasion

Pathogenic microbes and the human organism have co–evolved since the natural selection of humans, and it is almost a matter of certainty that numerous microbes used the depths of first-line human immunity as a primary model for evolution. The novel SARS–CoV–2 impairs the IFN system in several methods. Initially, the virus aids the production of reactive oxygen species (ROS), which disrupts the activity of mitochondria and then, viral copies cross intracellular tunnelling nanotubes (TNTs), which were created for the purpose of cell-to-cell communication. Events as such prevent significant recognition by various pattern recognition receptors (PRRs), by translating open reading frames 6 and 8 (ORF 6 and 8), that downregulate the expression of major histocompatibility complex I (MHC–I) related genes and indirectly suppressing the immune stimulatory action of Type I and III IFNs by means of preventing the synthesis of ISGs proteins that have powerful anti–viral and anti–inflammatory molecular actions, and by translating 16 non-structural proteins (NSPs), that directly suppress the immune–stimulatory action of type I IFN and type   III IFNs by preventing translation, as well as the autocrine and paracrine secretion of IFN proteins (Rubio-Casillas A. et al., 2022), and

that effect lysis of ISG products that play a major role in antiviral defence (McKellar et al., 2021). As above, the SARS-CoV-2 ORF3a, ORF9b and ORF10 proteins also play a role in evading Type I and Type III IFN mediated immune responses by inhibiting nuclear transport of IRF3, NF-kB and STAT polymers, leading to an overall down-regulated expression of interferon-induced genes (*IFI*) (Rashid F. et al., 2022). Interestingly, prompt and robust translation and exocytosis of IFN–α (Glennon-Alty L. et al., 2021) and IFN–λ (Zanoni I. et al., 2017), as is historically though to occur by DCs, inhibits the production and degranulation of ROS quicker, thereby tending to secure further robust IFN–λ signalling from neighbouring cells, and both IFNs play a significant role in regulating the activation and recruitment of neutrophils. The SARS–CoV–2 genome produces a number of non-structural proteins (NSP) that significantly decrease the amount of cellular secreted IFN, either by viral self-camouflage or by cleaving IFN–producing mRNA and downregulating the activation of cellular transcription factors (TFs) that translate interferon inducible proteins (*IFI*). Similar events occur in the cases of respiratory syncytial virus (RSV) (Bossert et al., 2002, Hijano et al., 2019, *H. influenza* and subsequent variant infections (Ma D. Y et al., 2015), as both viruses synthesise NSP1 that inhibit the translation of type I and type III interferon-encoding genes leading to stimulation or inhibition of IFN receptor activity (e.g., IFNAR2), whilst RSV translates NSP2 to suppress responses as such (Munir S. et al., 2011). Respiratory syncytial virus (RSV) particularly activates Rab5a host cell proteins to downregulate the activation of type III IFN based signalling cascades (Mo S. et al., 2021). Furthermore, it was discovered that the NSP1 protein, translated by the avian H5N1 strain of the Influenza A virus, induces the caspase-induced apoptosis of the host cell, before it is independently exocytosed and signalled in a paracrine manner, undergoing receptor-induced endocytosis into neighbouring cells. In such a manner, polymorphic viruses like (A)H5N1 Influenza, and very likely SARS-CoV-2 as well, seem to also induce a "trace erasing" effect in order to prevent the buildup of natural and adaptive immune memory during the initial, most critical stages of the viral replication and distribution of the viral load to multiple, distinct types of host tissues (Zhang et al., 2010). This aspect seems to reflect a pattern of developed "counter-intelligence" of viruses as such, by means of imitating the "intelligence" of human natural and adaptive immunity. Despite the fact that scientists first generally observed a lack of specificity behind natural immune mechanisms, it was recently discovered that natural immunity develops "memory" against pathogens after all and likewise, the concept of "trained immunity" now covers the principal mechanisms of natural immune activation, with its quality first covering timing of action and then physical extent (Dagenais A. et al., 2023). Furthermore, there has recently been a collection of scientific data displaying unexpected results with regards to pathogen-derived vaccination of poultry against the H5N1 strain of IAV. Namely, it has been discovered that live attenuated H5N1 IAV-based poultry vaccination resulted in a faster evolutionary process of the viral haemagglutinin (HA) gene, involving thereby an accelerated process of viral zoonosis, with rates of transmission and intensity of virulence increasing as a result. Likewise, efforts of poultry vaccination against H5N1 IAV infection resulted in an accelerated viral evolutionary process, and such a case may further highlight the evolutionary stronghold polymorphic viruses as such have gained upon human first-line and second-line immune defences (Li B. et al., 2023).

With regards to SARS–CoV–2 induced COVID–19 disease, it is important to note methods used to escape animal host immune systems by means of replication and spread to host tissues. Namely, once the virus enters the host, modulation of the activities of cellular pattern recognition receptors occurs, such as Toll-like receptors (TLR) (e.g. TLR3, TLR7 and TLR8), but also others like pathogen-associated molecular patterns (PAMPs) found within host genomes generated through gene transcription and translation that   occurs via diverse transcription factors (TFs). Therefore as IFNs generate anti-viral immunity through systemic, organ, tissue and cellular pathways, it is essential to consider the synthesis and expression rate of Type I and III Interferon-encoding genes and proteins (Kim You-Me and Eui-Cheol Shim, 2021). The cellular source and nature of IFN remains unclear. However, recent indications in 2021 indicate that type I IFNs are not produced or at a lesser rate by certain cells during SARS–CoV–2 infection that consist of either innate or adaptive immune cells and

others, like macrophages (Mϕ), dendritic cells (DCs) or epithelial cells that could potentially affect immune systemic responses during pathological disease (Niles et al., 2021).

See Diagram 1 (IFN Receptors)
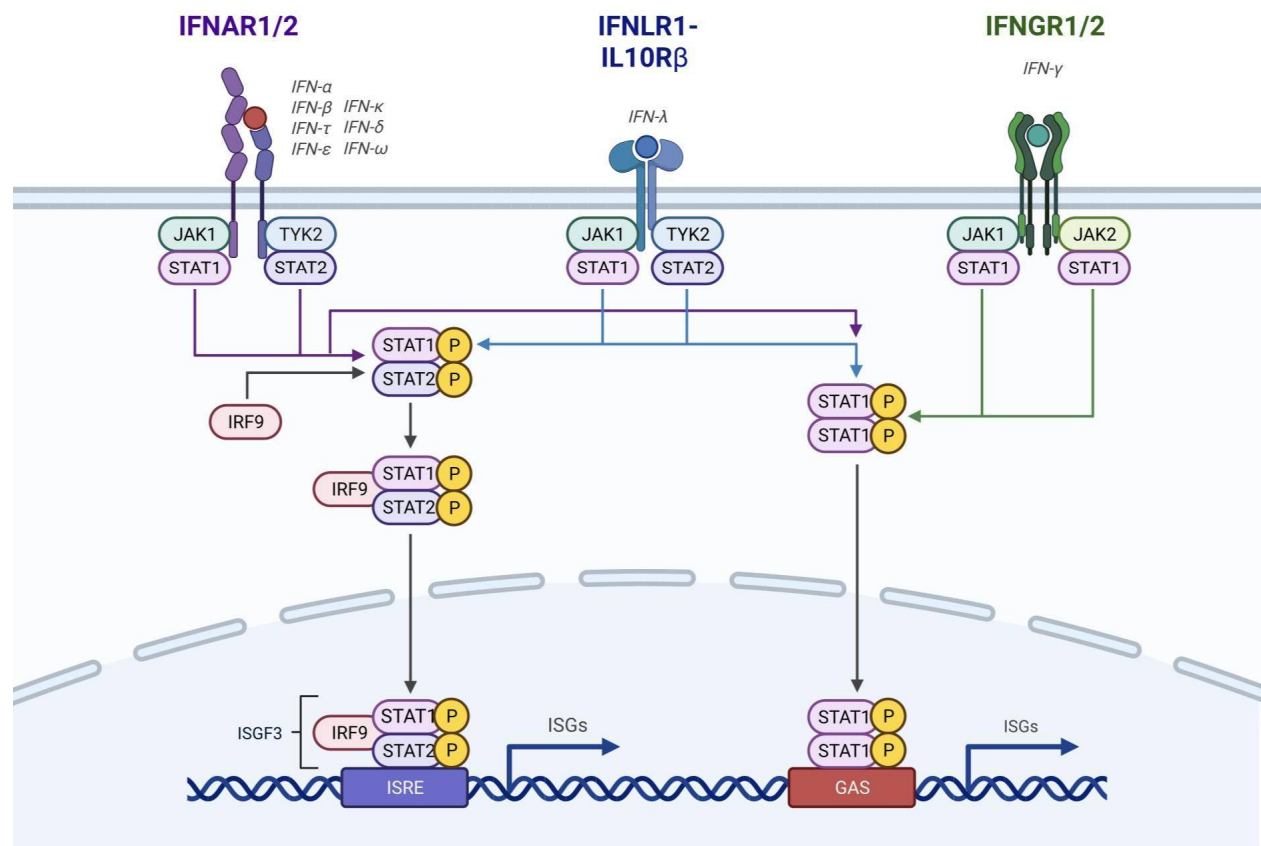
Figure 2. The interferon proteins present on the surface of plasmacytoid Dendritic Cells (pDCs) as a gateway for the activation and secretion of Interferon-Stimulated Gene (ISG) products with major antiviral activities (Created with BioRender.com with the permission of publication under the XA2510ANAU licence code).

2. SARS-CoV-2 Mechanism of Cellular Action in Disease

Many of the NSPs that SARS-CoV-2 is composed of are defined as follows and include NSP1 responsible for cellular mRNA degradation, NSP2 - arresting cell cycle, NSP3 - 7 propagation, formation of replication complexes, and code for enzyme proteases but also others including NSP8/9/10/13/14/16 – that encode primase/helicases, polymerases, binding proteins and exonucleases and endonucleases. These end with NSP16 2'-O-MTase, an enzyme that caps mRNA, conserved in a viral pocket known as the S-Adenosyl-L-Methionine pocket affecting the enzyme NSP16, which is ultimately activated by joining with NSP10 to form the 2′-O-Methyltransferase enzyme complex. NSP10 is known as an activator protein with NSP16 as an effector protein, and NSP16 transfers a methyl group (-CH3) to the 5′ end of the positive sense (+ss) RNA viral protein once activated. This viral genome 5′ methylation facilitates evasion and recognition of both extracellular and intracellular sensors TLR3, TLR7 but also an extracellular cellular receptor TLR4 expressed differentially and also cellular interferon-encoding genes that have differential and variable activation that facilitating compartmental cellular delay of Type I and III IFN signalling. Oral methioninase had been developed to degrade the S-Adenosyl-L-Methionine viral pocket and lower the ability of NSP13, NSP14 and NSP16 to be conserved (Hoffman et al., 2020), six natural drug-like compounds, including quercetin, oxopowelline and deacetylbowdensine (Saliu T. L. et al., 2021), were developed to prevent the interaction of NSP10 and NSP16, and ultimately, the formation of the NSP10/NSP16 methyltransferase complex. It is known that NSP14 and NSP16 are responsible for the final step of

the methyl (-CH3) group transfer to the 5' end of the viral genome. Whilst NSP14 does not require activation by NSP10 whilst acting as the C-terminal N7 Methyltransferase (N7-MTase) enzyme to place the 7Methyl (7Me) group to the 5' $^{7Me}GpppA_{2'-O-Me}$ end of the viral genome, NSP16 does require molecular interaction with and activation by NSP10 to transfer the 2'-O-Methyl (2'-O-Me) group to the 5' $^{7Me}GpppA_{2'-O-Me}$ end of the viral mRNA, in order to make it less recognisable as a particle foreign to the host cell (Park G. J. et al., 2022). Nonetheless, NSP14 also acts as an N-terminal 3'-5' exonuclease (ExoN) enzyme, which requires activation by NSP10 through the formation of the NSP10/NSP14 enzyme complex to become an effector protein, playing a role in producing new viral RNA to maintain a threshold level of viral genomic validity. Even though the process of the viral 5' end modification is not profoundly understood, it is presently known that a molecular self-camouflaging process of viruses implicates the modification of their 5' end, which can fully occur if two methyl groups are added to it. One such group is added by the C-terminal N7-MTase enzyme, which does not require activation by NSP10, whilst the other methyl group is added by the NSP16 effector protein, which can only function if it is joined and activated by NSP10 beforehand, to form the 2' - O-MTase complex. Likewise, NSP14 also likely represents a particularly important target for the development of antiviral drug-like molecules (Samarago M. et al., 2021). Furthermore, several years after the SARS outbreak in 2003, researchers developed a small drug-like peptide called TP29 to prevent an interaction between NSP10 and NSP16 (Wang Y. et al., 2015), and we also hypothesise that the peptide could show a similar extent of efficacy in COVID-19 cases. Furthermore, it is important to note that there is a particularly high binding affinity of sinefungin (SFG) to NSP16 effector methyltransferase component, and S-Adenosyl-L-Homocysteine (SAH) also displayed a lower, but still considerable affinity to NSP16, and both components have the potential of inhibiting NSP16, though more evidence needs to be collected to confirm such data (Mahalapbutr P. et al., 2020). Consequently, SARS–CoV–2 downregulates both autocrine/paracrine signalling and synthesis of Type I and Type III IFNs during critical early stages of infection and replication. Some viral NSPs also inhibit other products of inflammatory gene signatures (IGS) that lyse the viral genome. Therefore, SARS–CoV–2 has an ability to affect the innate and adaptive immune system that usually ensures quicker phagocytosis or stimulates viral cell apoptosis by activation of B cells, T cells and antigen-presenting cells (APCs) that could be considered antagonised by the mechanisms that Type I and Type III IFNs that usually robustly induces clearance of infected cells once released by the newly infected host cells to prevent further viral replication and spread. Moreover, by downregulating IFN synthesis, pathogens and viruses like SARS–CoV–2 gained an advantage over the ability of the immune system to create important antiviral Protein Kinase R (PKR) and anti-inflammatory signals, which are crucial for the development of effective immune responses. Protein Kinase R represents a molecule that plays a major role in the regulation of the ageing process and the mount of cellular antiviral defences, and it also has key functions in regulating intracellular transcription, mRNA translation, rates of apoptosis and cell proliferation (Gal-Ben-Ari et al., 2019). Moreover, the receptor binding domain (RBD) of the SARS–CoV–2 S glycoprotein forms a trimeric complex with a GRP78 chaperone, as well as with the ACE2 receptor, and it is the viral interaction with GRP78 that further enhances infectivity and ultimately, virulence.

GRP78 represents a protein that normally targets and degrades misfolded proteins, and it also plays an important role in preventing the onset of autoimmunity (Quinones Q. J. et al., 2008), and likewise, a viral interaction with the chaperone was shown to amplify its activity and favour the development of autoantibodies (Sabirli R. et al., 2021), ultimately resulting in a decrease of the quality of the overall antiviral immune response. Likewise, not only is it the novel SARS–CoV–2 that utilises numerous methods to delay or evade essential areas of human immunity, but it was also discovered that the virus detects and utilises other 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 type I IFN and type III IFN based immune signalling pathways systems are associated with higher immuno-competency and in turn, to low extents of energy consumption due to lower viral loads and resulting 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 IFNs has shown visible signs of affecting cellular metabolism and even brain ageing, via the choroid plexus, there are considerable reasons to believe that stimulating early type I IFN and possibly type III IFN 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.

3. Cellular Mechanism of IFN Action in Disease

The molecular activities of Type I IFN have implications upon cellular mechanisms. These include inhibition of viral replication, activation of nitric oxide synthase (NOS), inactivation of PKR, activation of oligoadenylate synthetase (OAS), regulation of inflammatory responses, peptide presentation by the class I/II major histocompatibility complexes (MHC-/III), activation of adenosine deaminase 1 (ADAR1), maturation and development of leukocytes alongside apoptosis of infected cells. Activation of Protein Kinase R (PKR) leads to downregulated translation of viral RNA encoding pathogenic proteins, whilst the activation of OAS results in the degradation and lysing of RNA and the activation of ADAR1 enables RNA editing (Fatemeh S. et al, 2021). NSP1 activates the phosphatidylinositol 3-kinase (PI3K) pathway that inhibits type I IFN synthesis and activate cellular stress-response proteins, such as heat-shock proteins (HSPs), which inhibit apoptotic pathways of host cells at first, before they stimulate such inductions of host cell death (Ehrhardt et al., 2007). This selective inhibition of apoptosis stimulates a temporal increase of viral load in the host organism. Moreover, the virus further inhibits antigen presentation via the STAT1-IRF1-NLRC5 pathway and the MHC class I complexes present within the majority of nucleated cells but also MHC class II molecules expressed at higher levels on DCs, thereby affecting the specialisation of CD8+ T-lymphocytes (Yoo et al, 2021). Given that the antigen presentation process is affected by targeting of the same pathway as the one induced by Type I IFN activation, we can ascertain that inhibited type I IFN activation could be associated with down-regulated endogenous antigen presentation of peptides, via MHC class II molecules. The downregulation of pattern recognition reception affects signalling from TLR–3, TLR–4, TLR–7, RIG–1 and MDA5 receptors to the *IFNA1*, *IFNA2* and *IFNB1* genes. NSP1 lyses molecules of mRNA that encode Type IFNs, whilst NSP16 caps the 5' end of viral RNA and makes the cell less capable of recognising the viral RNA as pathogenic.

NSP1 was also found to impair the synthesis of Type III IFN, potentially affecting the expression of *IFNL1*, *IFNL2* and *IFNL3* gene expression during infections with rotavirus and the porcine epidemic diarrhoea virus and, given that IFN–λ was only discovered in 2003, we have reasons to believe that the synthesis rate of this sub-type of IFN could also be affected during a SARS–CoV–2 infection. In other words, the production of NSP1 by SARS–CoV–2 and Influenza A viral genomes represents a pathogenic evolutionary trait of viruses that is essential for preservation in animal hosts that also includes the avian influenza virus (H5N1 IAV), as these comprise a reaction against the hidden abilities of host organisms to lyse them efficiently from comparative recent research discovery. Given that the rate of interferon-gamma, which is part of Type II IFNs, 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 expression 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. SARS–CoV–2 NSP16 requires activation by NSP10 and hence, NSP10 is known as the activator protein, whilst NSP16 is known as the effector protein. These 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 IFN production and distribution in pHAE cell cultures. Namely, there was no detectable interferon-alpha of any subtype, and a low rate of synthesis and transmission 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 type I IFN 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 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/or NSP14, before the NSP16 effector protein binds it. NSP1 represents a problematic IFN antagonist because it significantly suppresses IFN–α and IFN–β synthesis, and was shown to suppress IFN–λ synthesis during rotavirus infection (Iaconis et al, 2021) and porcine epidemic diarrhoea virus (Zhang et al, 2018), thereby potentially amplifying the impairment of innate immune responses. An impairment of such responses can have significant implications upon adaptive immune responses, and likewise, can cause a higher incidence of moderate and severe disease. Given that Type III IFN was only discovered in 2003, has the scientific community investigated the relationship between the viral NSP1 and IFN-λ synthesis, and are there any odds that the SARS-CoV-2 NSP1 suppresses to any extent the synthesis of IFN-λ, since one experiment involving a dosage of IFN-λ2 in mice displayed positive results with regards to a mitigation of the disease (Chong et al, 2021)? Moreover, ORF6 was found to prevent the polymerization of STAT1-STAT2-IRF9 trimer with the ISG3 protein, thereby preventing the expression of important antiviral cytokines (Setaro A. C. et al., 2021). ORF9b was also found to impair Type I IFN and Type III IFN based responses, by targeting important elements of the RIG-I, MDA-5, MAVS, Toll-Like Receptor 3 and cGAS-STING pathways, which normally result in a robust expression of such interferons (Han L. et al., 2021), and such an event further highlights the importance of early Interferon III signals in the prevention of severe forms of COVID-19.

The extracellular matrix (ECM), cytoplasmic and nuclear proteins produced by ISGs, play diverse important roles in restricting IAV infection as well (McKellar et al., 2021), meaning that advanced methods of viral immune evasion may substantially impair diverse intracellular and intercellular mechanisms of antiviral first-line immunity, which include the restriction of viral replication, the inhibition of viral packaging and even the lysing of non-structural proteins, which restrict the expression of Type I and Type III IFNs. Likewise, viral co-infection and evolution   with host cells may allow viruses to develop counter-mechanisms unknown to the host that directly inhibit the ability of viruses to replicate, translate their pathogenic proteins and spread to neighbouring cells.

With regards to the chronology of the extent of interferon signalling post-cellular infection, there are three principal categories of Type I and III IFN 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-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 IFN 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 administration of nasal sprays prophylactically might in turn be more important before or at the onset of the disease than after symptoms occur and our hypothesis is that individuals would 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). If the nasal spray was administered prophylactically, the sensitivity of the viral +ssRNA sensors will probably increase substantially, which will facilitate a larger extent of early type I IFN and type III IFN translation and exocytosis, alongside a more abundant secretion of the necessary anti-viral and anti-inflammatory ISG products. If the nasal spray is administered at a time that just precedes the moment of first-cell infection, there

will already be an immune activity by the time the virus will have attempted evasion of first-line immune signals, and an event as such will make the virus likely much more detectable and vulnerable in the host cells. A delayed clearance of the viral load is likely a common consequence of Type I IFN and III IFN viral immune evasion. Different signalling ratios between Interferon-alpha and Tumour Necrosis Factor-beta usually lead to different outcomes of COVID-19. Mild and moderate forms of the disease involve a balanced ratio between produced interferon-alpha (IFN-alpha) and produced Tumour Growth Factor-beta (TGF-beta), whilst severe forms of the disease involve a far greater extent of Tumour Growth Factor-beta production and signalling. Moreover, severe COVID-19 also involves the inhibition of interferon-gamma (IFN-gamma) and Tumour-Growth Factor-alpha (TFG-alpha), and there is a significant inhibition of the expression of CD18 molecules on the surface of Natural Killer Cells (NK Cells) (Barros-Martins et al, 2022).

Dendritic cells constitute a type of immune cells that play a critical role in the development of responses to viral infectious diseases, such as COVID-19. Dendritic cells are able to recognize and capture viral antigens, process them, and present them to other immune cells, such as T- and B-lymphocytes. This process is known as antigen presentation and is essential for the activation of the adaptive immune response. There are several different subtypes of dendritic cells, each with different functions and surface markers. One important subtype of dendritic cells represents the plasmacytoid dendritic cells (pDCs), which are known for their ability to produce large amounts of interferon I (IFN-I) in response to viral infections. IFN-I is a key component of the innate immune response to viral infections and it is produced by a variety of cells, including dendritic cells, in response to viral infection. IFN-I has a range of antiviral effects, including the inhibition of viral replication, the activation of innate immune cells, and the enhancement of antigen presentation. Impaired first-line immune responses are visibly associated with the recruitment of immature dendritic cells and the development of weakened T-lymphocyte-mediated adaptive immune responses (Niles et al., 2021). CD123 represents a relevant marker for Dendritic Cell activation (Matic S. et al., 2020), meaning that a decreased CD123 expression on the surface of DCs could be an important marker of a delayed interferon-based expression and transmission that is predominantly anti-inflammatory in nature.

A low-dose Type I and Type III Interferon-based nasal spray administered to a patient with COVID-19 could activate the dendritic cells, leading to the subsequent activation of M1 and M2 macrophages. The activation of dendritic cells is mediated by the binding of IFN-I to the IFNAR1/2 receptor on the surface of the dendritic cell. Once activated, dendritic cells are able to produce a range of cytokines and chemokines that can recruit other immune cells to the site of infection, including M1 and M2 macrophages. The activation of M1 macrophages is mediated by the production of pro-inflammatory cytokines, such as Tumour Necrosis Factor (TNF)-α and interleukin (IL)-12. M1 macrophages are involved in the initial immune response to the virus and are able to kill infected cells via apoptosis, necroptosis and pyroptosis, through the production of reactive oxygen and nitrogen species, as well as of diverse caspase enzymes, including caspases 1 and 8. Severe inflammatory responses favour the onset of pyroptosis, which implicates the programmed death of macrophages (Shan C. et al., 2021). The activation of M2 macrophages is also important for the immune response to COVID-19. M2 macrophages are involved in tissue repair and the resolution of inflammation. They produce anti-inflammatory cytokines, such as Interleukin 10 (IL-10) and Transforming Growth Factor (TGF)-β, and help to limit tissue damage caused by the immune response. In COVID-19, M1 and M2 macrophage-mediated immune responses are unbalanced and often polarised, and this leads to an uncontrolled development of inflammation (Mortezaee K. et al., 2022). The activation of dendritic cells and M1 and M2 macrophages is mediated by a variety of surface markers, including CD markers. CD markers are cell surface antigens that are used to identify and characterise different cell types. Different subsets of dendritic cells express different CD markers, which can influence their function and activation. For example, pDCs express CD123 and CD303, which are used to identify and isolate these cells. CD40 is another important CD marker that is expressed on the surface of dendritic cells. CD40 is a co-stimulatory molecule that is involved in the activation of T-lymphocytes and the production of cytokines by dendritic cells. The use of a low-dose interferon I and III-based nasal spray may also influence the expression of CD markers on dendritic

cells. For example, one study found that treatment with IFN-I increased the expression of CD80 and CD86 on the surface of dendritic cells, which are important co-stimulatory molecules that are involved in the activation of T-lymphocytes (Alculumbre S. et al., 2019).

Given the exponential nature of the increase of the viral load and the number of infected cells as SARS-CoV-2 infection progresses, early Type I and III IFN responses are less than delayed responses, given that early responses will only implicate the production and manufacture of better understood cytokines i infected cells. Delayed responses will involve the activation of interferon-encoding genes in many more cells, resulting in the production of an amount of IFN that will rather contribute to pathogenesis and aggravation of inflammatory disease, given that the products of ISGs include important pro-inflammatory cytokines, such as CXCL10, CCL2 and CCL5. An increased synthesis rate of pro-inflammatory cytokines is associated with a decreased quality of immune system performance. Likewise, it is important to acknowledge the "double-edged sword"-like nature of Type I (i.e. IFN-α2b, IFN-β1, IFN-δ, IFN-ε, IFN-κ, IFN-ω and IFN-τ) and Type III Interferons (i.e. IFN-λ1, IFN-λ2 and IFN-λ3) and hold fast to the criticality of robust first-line immune responses during SARS-CoV-2 infection. The most important sub-domains of IFNs with regards to building important antiviral and anti-inflammatory signals, alongside shaping important adaptive immunity pathways, represent IFN-α2b, IFN-ε, IFN-ω, IFN-λ1, IFN-λ2 and IFN-λ3, although   IFN-β1 also represent glycoproteins with interesting potential immunomodulatory and boosting characteristics.

The timeline of SARS-CoV-2 infection and the onset of COVID-19 disease, using the viral load, symptomatic intensity and antibody count as the principal parameters, was studied in more detail. Generally speaking, COVID-19 symptoms begin when the viral load is approaching its peak and the peak of the intensity in symptomatology for patients experiencing moderate disease occurs when the viral load has already started decreasing. Severe disease generally occurs when the viral peak reaches the level where the disease has not started its clinical manifestations (Muge Cevik et al, 2020), and this could imply the increased abilities of the novel coronavirus to escape host immune sensing can often impair the immune system by resulting in the development of autoantibodies and/or the suppression of the quality and wellbeing of the immune system as a whole. 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.

RIG-I and MDA5, which are cytoplasmic pattern recognition receptors, detect pathogen-associated molecular patterns (PAMPs)   on the viral genome and phosphorylate the IRF7 and IRF3 dimers, which in turn act as transcriptional factors of Type I IFN -encoding genes. Both MDA5 and RIG-I require activation by   dsRNA, but RIG-I requires activation by a triphosphate group,   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 phosphorylated, which will then activate the type I IFN encoding genes and result in the translation, folding, secretion, as well as the autocrine and paracrine signalling of the immunological messengers (Brisse M. and Ly H., 2019). Once the +ssRNA of the novel coronavirus enters in the host cell, TLR3 and TLR7 become activated as a result of the detection

of PAMPs, that are either found on the pathogen surface or synthesised by its genome or are generated during cellular infection. TLR4 activation also occurs, but not inside the host cell, whilst TLR8 is located on endosomes and becomes activated generally due to bacterial infection. Following TLR3/7 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 transmission, 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 their dimerisation. IRF9 then binds to the STAT1-STAT2 phosphorylated dimer to form the STAT1-STAT2-IRF9 trimer before Interferon-Stimulated Genes 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 antigen 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 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. Namely, NSP1 has been shown to cleave and lyse the mRNA encoding Type I Interferons, alongside NSP2 (Xu et al., 2022). 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 synthetase 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 synthetase 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).

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. 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. (Cervantes J. L. and Weinerman B., 2012). 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 A. J. 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, oncological and neurodegenerative diseases if produced, exocytosed and transmitted 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 neutralising 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 transmission 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 transmission 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 expression and once interferon-stimulated genes are finally expressed, inflammatory chemokines, including CCL7 and CCL8 as well, are released and further 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 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.

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), which suggests that the novel coronavirus is significantly more capable of escaping detection by PRRs, of capping the 5' end of the +ssRNA viral genome and of lysing interferon and ISG proteins than the Influenza A +ssRNA virus. 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, 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, often resulting in the formation of sub-optimal antibodies and significant autoimmune implications. 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 produces 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. It is suggested that the IgG1 to IgA1 antibody secretion ratio and the extent of neutrophil activation are proportional with disease severity (LaSalle T. J., 2021), meaning that a delayed, systemic Type I and III Interferon signalling and a widespread secretion of IgA antibodies may likely become markers of severe COVID-19 disease. The duration of the pre-clinical stage of COVID-19 is very likely also proportional with the probability that the COVID-19 disease will be severe. 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 could involve the gathering of proteins from diverse plants that stimulate a more robust production and exocytosis of Type I and possibly of Type III Interferons, 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% 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 (Dacia Plant, 2021). 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. Perhaps, such an approach could be combined with approaches of immune system-based prophylactic and early therapeutic vaccines involving human recombinant plasmacytoid dendritic cells as factories of interferon glycoproteins and/or natural and adaptive lymphocytes treated themselves with a fairly low dose of interferon glycoproteins beforehand, particularly in the context of preventing or attenuating the effects of disease in the early stages of HIV-induced AIDS (Carp T., 2024).

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).

A more specific timeline of Interferon-alpha and Interferon-beta synthesis in the early stages of Herpes Simplex Virus 2 (HSV-2) infection has been studied. 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 (Amanda J. Lee and Ali A. Ashkar, 2018). 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 (NK) Cell recruitment, which itself depends, to a certain degree, on the extent of interferon-beta synthesis. Importantly, NK Cells also form and develop 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).

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 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 (IL-6) and C-Reactive Protein (CRP). 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. 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 and III-based 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 and Type III 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 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 and Type III 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 expression. 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, approximately 10% of the cases when there is a delayed and exaggerated Interferon I-based response, patients develop autoantibodies and consequently, diverse forms of autoimmunity.

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.

Several clinical studies suggested that lozenges and nasal sprays containing a low dose of Type I Interferons show prophylactic and even early therapeutic efficacy against HIV-induced AIDS as well. For example, one interim clinical trial involved the recruitment of forty adults tested positive for the HIV-1 infection and they were offered daily lozenges containing an amount of IFN-alpha ranging from 75 to 600 IU. Eighteen other patients infected with HIV-1 were recruited but were not offered the interferon lozenges. From the total number of patients, eighteen patients received long-term treatment and five of them died. Among those patients, two of them had suffered from Kaposi's Sarcoma and two others died because of HIV-1 related factors (Babiuch et al., 1993). Another clinical study involved the administration of Pegylated Interferon-alpha-based treatment (Peg-Intron A), in combination with antiretroviral treatment that involved the administration of Highly-Active Antiretroviral Therapeutics (HAART), Nelfinavir, Stavudine and Didanosine. From the total number of 168 injections with the Pegylated Interferons, only six were not administered at a maximum dose due to safety concerns. The IFN therapy was found to be tolerated well, to significantly restrict HIV replication , protein assembly, packaging and distribution, as well as to ultimately induce a robust reduction of the viral road during the early stages of infection, and to visibly prolong the lifespan of the infected CD4+ T-Lymphocytes (Emilie et al., 2001).

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 expression 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 hypothesise that around 125-150 IU of interferon-beta may 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.

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, interferon-beta and interferon-lambda 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 could be most suitable for administration 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 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.

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). A disrupted balance between Interferon-alpha, which is an anti-inflammatory cytokine, and Tumour Necrosis Factor-beta, which is a proinflammatory 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 to have significant negative social 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 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 probably 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. Both viral infection (Zhang et al., 2020) and the administration of the spike protein-encoding mRNA vaccines (Aldén M. et al., 2022) led to the activation of a number of LINE-1 Reverse Transcriptases and the reverse transcription and integration of around 1% of the viral genome and of the spike protein-encoding mRNA into the DNA of diverse host cells, such as hepatocytes. This phenomenon is rather novel for non-retroviral RNA particle-like pathogens. Furthermore, the novel coronavirus 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.

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 neuronal protection and maintenance, and likewise, causing risks of protein misfolding and the onset of neurodegenerative disease.

It is important to note that the spike glycoprotein (S protein), which represents the principal viral protein of pathophysiological induction, 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 S protein has been shown to function as a superantigen, 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, the S1 subunit and the active trimer of the viral glycoprotein are also capable of disrupting the activity of mitochondria in brain endothelial cells and likewise, have implications upon metabolism (Eun Seon Kim et al, 2021) and the 674-685 amino acid 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 S 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 S 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 vaccinal full length spike is very similar to the viral full length spike. The S protein produced by the vaccinal mRNA is very 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 S protein in a pre-fusion conformation, but it is not fully certain that the stabilised S protein will keep its initial conformation (Timothy P. Riley et al, 2021). Likewise, there is currently still no evidence determining that the vaccinal S 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 thereby, 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, risks of harmful intracellular interference may sadly not be significantly decreased 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 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, intracellular signaling cascades can become visibly disrupted and likewise, the spike protein can still cause significant intracellular damage. Likewise, risks may not be substantially decreased, 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 following SARS-CoV-2 infection were inducible pluripotent STEM cells (iPSCs) located in the myocardium and the alveoli (Zhang L. et al., 2020). 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 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. 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 one to two weeks. 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, 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.

As time went by and the disease became visibly endemic, the mass vaccination campaign displayed poorer long-term results than it was desired and initially projected by the scientific community, despite the unprecedented intellectual and clinical efforts to create life-saving vaccines against COVID-19, and despite the successful induction of variant-specific IgM and IgG immunoglobulin production, as new viral variants often evaded the recognition of immunoglobulins developed after the reception of the spike glycoprotein-based vaccine(s). In the process, an unprecedented number of people also developed serious adverse reactions, and the frequency and severity of both short- and long-term reactions as such were particularly higher in people who either received the adenoviral vector 5/26-based, the mRNA-1273 mRNA-based or at least two or three doses of the BNT162b2 mRNA-based vaccine, depending also on other variables, like health status and age. Numerous people who received even three or four doses of the BNT162b2 mRNA vaccine eventually developed COVID-19 again, many people even repeatedly, and the extent of symptoms was numerous times nearly the same as the symptoms developed by unvaccinated people who contracted the illness from the time it started becoming endemic. During the recent couple of years, vaccinated people became even more susceptible to infection than unvaccinated people, likewise pointing toward the significantly important role trained immunity played in turning the pandemic

disease into an endemic one, despite the paradox that the aid for reaching a threshold level of timing and quality with regards to adaptive immune activation plays a critical role in combating complex epidemics and pandemics. The overall events that occurred during the past few years may in fact expose an unintentional negligence of the critical role that natural immunity plays in protecting the human body against polymorphic viruses like SARS-CoV-2, and such a negligence occurred whilst an unprecedented extent of financial investment occurred in the effort to find effective approaches of clinical response against the disease. 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, 10, 14 and 16?

Could interferons also contribute as a potential cancer therapeutic? Given that early Interferon I and III-based immune responses are associated with significant levels of prophylactic anti-cancer cellular mechanisms (Yu *et al.*, 2022), it is probable that low dose interferon I and III-based nasal sprays will also upregulate the activity of important proto-oncogenes and tumour suppressor genes, thereby partially restoring the ability of cells to perform the necessary DNA repair mechanisms and potentially preventing numerous incidences of mutagenesis and genome toxicity over the next several decades. Furthermore, 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. 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 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. Anthony Fauci 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 publication of secret contracts between Pfizer and world governments that occurred at the beginning of 2022, 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 comorbidities 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.

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 type IFN I and LINE-1 retro-transposons regulate each other, and that an exaggerated type I IFN expression 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 autocrine and paracrine 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. 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. Furthermore, the activity of LINE-1 Reverse Transcription upon roughly 1% of the SARS-CoV-2 genome is new, given that all members of the Betacoronavirus genus are widely different and unrelated to the members of the Betaretrovirus genus. SARS-CoV-2 has outstanding evolutionary abilities of suppressing Type I Interferon-based transmission, 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 distribution 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, 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 "sensationalization" 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 hemophagocytic lymphohistiocytosis, 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 often accompanied by an exaggerated Complement C3a and C5a-related immune response, which may indicate that the quality of the complement system's activation process is not fully autonomous of the quality of the activated interferon system. Clinical research involving the search for methods to prevent exaggerated activations in this part of the complement system could also support the development of an early Interferon I and perhaps Interferon III-based antiviral and anti-inflammatory signals, although it is clear that more evidence needs to be found to confirm that the interferon system also displays a degree of dependency upon the complement system, and not solely the other way around (Shibabaw T., 2020). 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 antiviral immune responses, and the focus on antiviral action will become much higher than the focus on synthesising qualitative antibodies. Consequently, the onset of hemophagocytic lymphohistiocytosis will be much more likely, particularly in patients with underlying health conditions, which predispose their immune system to overreact.

Likewise, IFNs can be deemed as a double-edged sword in immunology and cancer biology, and herein lies the importance of ensuring that such chemokine-based signaling 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 increased demand for energy consumption implicates an increased speed of cellular and tissular ageing, despite the recent advancements in scientific and medical research. For example, there is a correlation between an

activated hexosamine process and an activated interferon pathway during hyperinflammation (Hugo et al., 2020), meaning that a more sensitised interferon system could prevent exaggerated hexosamine-related metabolic processes, which would play a considerable part in lowering the overall metabolic consumption rate, lower cellular stress and prolong cellular and tissular life expectancy long-term. Furthermore, one mathematical model-based study suggests that early interferon activation via the organisation of the cell cycle and of the mTOR pathway results in the post-transcriptional inhibition of Sox2 and the induction of quiescence, ultimately leading to a decrease of the maturation rate of neuronal cells of substantial importance, which was shown to have good effects for young people and decaying effects for the elderly. Interferons were shown to be major regulators of neuronal STEM cell homeostasis, which could explain the lack of efficacy and rather increased process of ageing for the aged brain due to the generally decreased quality of the immune system, the highly solicited metabolic processes and the overall resulted contribution to neuronal ageing (Ibanez et al., 2023). Likewise, early and local interferon production and activation may be associated with a slower neuronal ageing process in young and middle aged people. 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 over the following several decades. Interferon I and III will not only increase the wisdom of the immune system, so to speak, 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 microbes, and 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. Recently, researchers have also suggested the utilisation of recombinant NK and T-lymphocytes, alongside dendritic cells, altogether treated with a fairly low dosage of Type I and possibly Type III Interferons beforehand to possibly increase their state of integrity and ability of immune performance, in the efforts to develop natural immune system-based vaccines and therapeutics against future public health crises, given also the context in which the human immunodeficiency virus (HIV) is known to directly infect and kill major subtypes of T-lymphocytes. In such a particular case, the prior treatment of CD4+ and CD8+ T-lymphocytes with Type I and Type III IFNs could bring the most proportionate extent of evolutionary self-defence against pathogenic agents like HIV (Carp T. et al., 2024). The addition of dendritic cells into the equation would be due to the fact that they represent main "factories" of Type I and Type III IFNs. Given the context of heavy innate immune evasion by polymorphic viruses, it would not be recommended for the research community to focus upon developing adaptive and pathogen-based immunisation candidates, given the risk of immune defences becoming too specific for such particular viruses, and only for their current variants. The objective for vaccine development should

include the reach of a balance between innate and adaptive immune methodology as the main objective. Not to mention that the yet not fully known origins of SARS-CoV-2 and of the multi-dimensionally pathological extent of the spike glycoprotein, does not allow the scientific community to rely on claims that the spike glycoprotein-based vaccines are safe and effective for the entire world population, despite the colossal efforts of researchers and clinical scientists to rapidly resolve the problem of health system overload caused by the high rate of viral transmission and by the life-altering symptoms of the disease, more prevalently in the people of an advanced age, with one or more significant comorbidities. Polymorphic viruses in general also discourage clinicians from developing pathogen-based vaccines, and sometimes even vaccines based on adaptive immunity, at least without a major aid of natural immune elements, because the developed antibodies would be specific for certain viral variants and future mutations would likely result in the virus evading the previously developed antibodies, alongside its newly developed methods of quickly evading first- and second-line immune signals. In other words, situations of "going back to square one" would often be reached if specificity would be solely relied upon by therapeutics and vaccine developers, with major research and public health funds proving to be wasted in the process. Likewise, updating and revolutionising human vaccinology in the manner described 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 extent of scientific and medical progress.

Conclusion

Given results from NCT data, there is a high number of reasons to believe that   low-dose type IFN I and III IFN based nasal sprays could match the definition of a therapeutic vaccine with beneficial effects than prophylactic ones.Therefore, whilst potential vaccine candidates can prevent severe cases of COVID-19 disease, it would have the highest impact when administered in varying populations of vulnerable people potentially with or without comorbidities who became infected and developed symptoms that would be noticeable . Examining further the administration of   type I IFN from NCTs clarifies that IFN alpha-2b, epsilon, omega and perhaps IFN beta1, (BAI et al., 2022) and type III (IFN lambda1, lambda2 and lambda3) may act as mimitics of cellular infection and stimulate a robust and natural immune response against either viral or neoplastic pathologies, and likewise, such an intervention fits the definition of a traditional vaccine. Because this likely requires further research into 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 type I in the tissue would be caused. The quantity of administered IFN differs based on the disease. For example, a higher amount of IFNs would generally be needed for COVID-19 than the general flu, and for people experiencing significant immunosuppression. Administered interferons could, on the other hand, contribute to pathology induced by autoimmunity, meaning that caution is likely needed nevertheless. Compared to the dosage of experimental injectable interferons, which generally ranges from 3 to 6 million International Units, which is measured in milligrams, the nasal sprays generally contained an interferon concentration ranging from 200 to 500 International Units when used in past clinical trials, 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 hypothesising 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, given their lower BMI, as well as for 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. Given their widespread and trans-species immune modulatory and stimulatory effects, we hypothesise that low-dose interferon-containing substances could be administered to live birds to prevent the spread of the present avian Influenza A viral variants in chicken, which would in turn save animal lives and plenty of alimentary resources for the human society during the present financial and resource availability crises. Overall, the present scientific paper does not mention medical statements, but scientific hypotheses encouraging clinical researchers to further investigate the matter and collect pieces of evidence that would eventually reach conclusive stages. The dosages measured during clinical trials involving Type I and Type III Interferons only constitute part of preliminary research reports, which implies that further clinical research is required to be performed, by medical doctors, pharmaceutical clinicians and research scientists, to determine more exact amounts of interferons that could be used, depending on factors such as age, health status and type of disease to be prevented or attenuated in the early stages of onset. We strongly encourage further testing of such interferon substances and propose that they will play a major part in improving immunological, metabolic and systemic wellbeing in the human body, as well as in animals.

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List of Abbreviations

SARS-CoV-2 - Severe Acute Respiratory Syndrome-Coronavirus 2

COVID-19 - Coronavirus Infectious Disease 2019

ECM - Extracellular Matrix

ACE2 - Angiotensin Convertase Enzyme 2

IAV - Influenza A Virus

RSV - Respiratory Syncytial Virus

ICM - Intracellular Matrix

ORF - Open Reading Frame

NSP - Non-Structural Protein

IFN - Interferon

PAMP - Pathogen-Associated Molecular Pattern

PRR - Pattern Recognition Receptor

TLR - Toll-Like Receptor

MDA-5 - Melanoma-Differentiation Associated protein 5

RIG-I - Retinoic acid-Inducible Gene I

ADAR - Adenosine Deaminase Acting on RNA / RNA-specific Adenosine Deaminase

ADAR1 - Adenosine Deaminase 1

MyD88 - Myeloid-Differentiation primary response 88

IKK - IkB Kinase

IFNAR - Interferon alpha/beta Receptor

IFNLR1 - Interferon lambda Receptor 1

IL10R1 - Interleukin-10 Receptor 1

STAT - Signal Transducer and Activator of Transcription

IRF - Interferon Regulatory Factor

NLRC - Nucleotide-binding oligomerization domain-Like Receptor C

NF-kB - Nuclear Factor-kappa-light-chain-enhancer of B-Lymphocytes

ISG - Interferon-Stimulated Gene

NK Cell - Natural Killer Cell

IFITM3 - Interferon-Induced Transmembrane Protein 3

cGAS-STING - cyclic AMP-GMP Synthase - Stimulator of Interferon Genes

N7-MTase - C-terminal N7 Methyltransferase

ExoN - N-terminal 3′-5′ Exoribonuclease

IL - Interleukin

TNF - Tumour Necrosis Factor

TGF-α - Tumour Growth Factor-alpha

TGF-β - Transforming Growth Factor-beta

CRP - C-Reactive Protein

CCL - Chemokine (C-C motif) Ligand

CXCL - Chemokine (C-X-C motif) Ligand

CCR - Chemokine (C-C motif) Receptor

CXCR - Chemokine (C-X-C motif) Receptor

NK Cell - Natural Killer Cell

IMM - Inflammatory Monocyte and Macrophage

pDC - plasmacytoid Dendritic Cell

HLA - Human Leukocyte Antigen

MHC - Major Histocompatibility Complex

Th Lymphocyte - T-helper Lymphocyte

CTL - Cytotoxic T-Lymphocyte

CD - Cluster of Differentiation

LINE-1 - Long Interspersed Nuclear Element 1

AIDS - Acute Immunodeficiency Syndrome

Ab - Antibody

Ig - Immunoglobulin

C5a - Complement component 5a

GRP78 - 78 kDa-Glucose-Regulated Protein

HSP - Heat-Shock Protein

ARS - Acute Radiation Syndrome

+ssRNA - positive-sense single-stranded Ribonucleic Acid

BMI - Body-Mass Index

IU - International Unit

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