

Review

Not peer-reviewed version

Turning Pathogens into Vaccines via Loss-of-Function Research and Interferon Gene Insertion: Trampling Death by Death?

[Theodor-Nicolae Carp](#) *

Posted Date: 23 January 2025

doi: 10.20944/preprints202501.1699.v1

Keywords: innate immunity; adaptive immunity; evolutionary microbiology; evolutionary immunology; interferon system; lymphocyte system; polymorphic microbes; single-nucleotide polymorphism; molecular self-camouflaging; loss-of-function research; gene editing; medical ethics; cytosol; gene expression; autocrine signalling; paracrine signalling



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Review

Turning Pathogens into Vaccines via Loss-Of-Function Research and Interferon Gene Insertion: Trampling Death by Death?

Theodor-Nicolae Carp

Independent Academic Researcher, Watford, Hertfordshire, England, United Kingdom of Great Britain;
theodore.nicholas100@gmail.com

Abstract: Throughout several centuries, infectious pathogenic agents have been used as models for the ongoing efforts of vaccine development, which saved hundreds of millions of lives from life-threatening infectious diseases worldwide. Nonetheless, there has been a missing gap that various polymorphic microbes have been taking advantage of in their evolutionary pathway: the interferon system, which often prevented the timely activation of second and third-line host immunity, leading to chaotic and mismatching immune responses. The phenomenon of increased incubation period of various infectious diseases may be a result of the increased abilities of such microbial agents to directly and indirectly undergo molecular self-camouflaging, which prevents the activation of Type I and Type III Interferon-encoding genes (INGs) in indirect and direct manners respectively, and cleaves the mRNA molecules encoding such interferon glycoproteins, often causing major delays in the process of autocrine and paracrine signalling of Type I and Type III Interferon glycoproteins, which in turn allows an unrestricted, exponential increase of the microbial load/count, giving rise to a statistical probability that the quality of the delayed immune response will be low and contributory to the processes of pathogenesis and pathophysiology. Apprehending the foundational layer of the current problems in evolutionary microbiology, epidemiology and public health studies is most likely crucial for the course of immunological, pharmaceutical and vaccine-related clinical research. In the current case, it is the complex set of molecular capabilities to suppress Type I and Type III Interferon-based signalling displayed by several polymorphic microbes of public health concern, and it may be that the rates of immunopathogenesis induced by such microbes are directly proportional with such pathogenic abilities of induced interferon suppression. Proportional medical responses could include the development of approaches involving low dosages of human recombinant Type I and Type III Interferon glycoprotein and perhaps also of protollin in the nasopharyngeal cavity, potentially bringing an example of putting a novel concept of a “United Immune System” into practice. Furthermore, similar dosages of such interferons could be administered into human immune cells including plasmacytoid dendritic cells, as well as natural and adaptive lymphocytes, to optimise their immune function and integrity against various environmental hazards. Ultimately, clinical researchers may isolate the pathogenic agents, attenuate them through the process of loss-of-function laboratory research, before performing gene editing to insert Type I and Type III Interferon-encoding genes into their genomic profile and releasing the genetically-modified pathogens back into the environment. Such a change may bring various pathogenic agents into a path of evolutionary self-destruction, as they would start producing and sending signals to the proximal, innate immune system as soon as they enter the first host cells, making their same processes of induced innate immune suppression ineffective. Processes of shrinkage of any level of limitations to potential efficacy would include the manual utilisation of inhalators, oral drops and/or injectable serums containing such modified microbes to ensure that such an immunising effect would be conferred simultaneously with exposure to the artificially-changed genetic version of the microbe. A set of clinical responses involving all such pathways may ultimately bring a promise of a health-related “Golden Age” throughout the world.

Keywords: innate immunity; adaptive immunity; evolutionary microbiology; evolutionary immunology; interferon system; lymphocyte system; polymorphic microbes; single-nucleotide polymorphism; molecular self-camouflaging; loss-of-function research; gene editing; medical ethics; cytosol; gene expression; autocrine signalling; paracrine signalling

Introduction

Recently, several public health incidents have occurred and significantly impacted the health state of both animal and human host organisms. The highly diverse phenomena of molecular self-camouflaging displayed the causative microbial agents may represent a foundational factor for the induced severity of infectious clinical disease in both animal and human hosts, which seems to surpass the current version of vaccine-based clinical responses, despite their high rates of efficacy displayed throughout the past centuries. It may be that there is an existing gap of potential update in the domain of vaccinology - one that would directly antagonise such a foundational factor of induced severe infectious illness. Given the fact that natural immunity has recently been shown to exhibit traits of specificity and even its own, distinct “specific memory” as well makes it possible for the efforts of vaccinology to be updated through a wider inclusion of both first-line and second-line, natural immune elements. Such an aspect may only confirm the high rates of efficacy and safety displayed by recently-developed prophylactic and early therapeutic approaches involving low dosages of human recombinant Type I and Type III Interferon glycoproteins into the nasopharyngeal cavity. Interestingly, results indicate that such concentrations of Type I and Type III Interferon glycoprotein brought effects of immunostimulation, immunomodulation and even whole effects of immunisation against multiple diseases, including COVID-19, flu, AIDS and various oncological diseases. Moreover, it has been suggested that protollin brings similar immunostimulatory and immunomodulatory effects in the case of Alzheimer’s Disease, by the recruitment of adaptive lymphocytes to areas of the Central Nervous System, where they will in turn activate microglial cells and oligodendrocytes before misfolded alpha-synuclein and beta-amyloid toxins start causing clinical signs and symptoms (Frenkel D. et al., 2008). Scientists theorised that protollin brings an immunisation effect against the pathogenesis and early pathophysiology of Alzheimer’s Disease, potentially giving further rise to the probability that Type I and Type III Interferons bring similar effects (Frenkel D. et al., 2005). A similar outcome may occur for the case of Retinitis Pigmentosa, which is caused by misfolded Rhodopsin toxins in the process of a progressive destruction of retinal cells with rods, which is clinically manifested as a progressive loss of vision to the point of the patient reaching a state of complete blindness, often by mid-age adulthood. Furthermore, it is possible for plasmacytoid Dendritic Cells (pDCs), Natural Killer (NK) Cells, helper CD4+ T-Lymphocytes and cytotoxic CD8+ T-lymphocytes to be treated with a low dosage of Type I and Type III Interferons, perhaps alongside protollin, to improve both their efficacy and integrity against environmental hazards, and such an approach would effectively represent a form of “immunisation of immunising agents” and could potentially turn adaptive lymphocytes into “super-lymphocytes” in efforts to protect human immunity from the long-term and life-threatening danger of HIV-1-induced AIDS, essentially conferring a proportional “punch of immunological self-defence” against the virus (Carp T., 2024).

Given the fact that the interferon system may be calibrated likewise to help human immunity develop a proportional evolutionary response that would preserve human health over microbial self-camouflaging capabilities, it is possible for vaccine researchers and developers to include Type I and Type III Interferon-encoding genes into live-attenuated pathogens or pathogenic fragments. Furthermore, it is possible for researchers to perform similar gene editing procedures in isolated microbes to turn microbial agents into signalling facilities for the host innate immunity, which would essentially mean that pathogens as such would be effectively transformed into vaccines, as they would become unable to cause disease given the automatic microbial autocrine and paracrine

signalling of both Type I and Type III Interferon glycoproteins once it undergoes the first series of receptor-mediated endocytosis. Given the fact that the first and the third classes of the interferon system profoundly stimulate and modulate major immune responses, essentially representing the foundation for the adequate activation of the entire immune system following the first stages of infection, it may be that such a scenario may apply even for pathogenic agents causative of diseases of more significant public health concern. Likewise, with the unprecedented threats made by recent developments contained within the evolutionary path of pathogenic agents, there seems to be a small, but considerable window of opportunity that may bring unprecedented hope, with the possibility of artificially inducing genetic manipulation of newly-selected variants of microbial agents that constitute a concern for both human and animal public health, ultimately making it unnecessary for the pharmaceutical industry to develop nasopharyngeal spray or drop-based vaccine approaches, let alone traditional needle-based ones. In other words, the ultimate stage of vaccine evolution may involve a silent “infection” of human and animal hosts with attenuated microbes that contain active Type I and Type III Interferon-encoding genes, which produce a number of interferon glycoprotein that significantly crosses a threshold level characterised by the ability of the same pathogen to antagonise them. Poetically, just as advanced stages of microbial evolution hijacked and suppressed the quality of human immune responses via favouring the development of autoimmunity, so artificial interventions will lead to advanced stages of human and animal immune evolution by the induction of microbial activities that antagonise each other. If problems of inefficacy occur due to a lack of a threshold level of human-to-human and animal-to-animal transmission of such attenuated, interferon-encoding microbial agents, then inhalators or injectable serums containing low concentrations of such microbial copies may be administered to patients during the first weeks of the fall season to manually induce an immunising effect where gaps preventing the reach of herd immunity may exist.

Discussion

Tackling the complex microbial machinery of induced immune evasion most likely represents the primary objective of public health and vaccine innovation-based pharmaceutical, scientific and clinical research. There is a highly diverse group of candidate clinical approaches that can help the human immune system outcompete the novel extents of induced immune evasion by several polymorphic microbes, and such approaches may be used even in combination to foster the production of utmost qualitative and long-lasting results for the human and animal immune systems alike. It may be that the ultimate solution to the dilemma of viral and bacterial immune evasion is the isolation, attenuation and genetic editing of epidemic microbes during their initial stages of distribution throughout human and animal populations respectively, which commonly occurs during the first weeks of the fall season. Despite the fact that microbial agents utilise highly diverse methods of inducing cellular and tissue-level pathogenesis and pathophysiology, there seems to be a Universal method of immune evasion utilised by the majority of such microbes in their preparation for inducing clinical disease. The machinery of induced immune escape generally consists of three distinct pathways, which all ultimately point to the common result of significantly suppressing the production and signalling of Type I and Type III Interferon glycoproteins. The first pathway constitutes a direct form of microbial self-camouflaging and involves the double methylation of the 5' end of the microbial genome by two viral non-structural protein complexes (NSP10/14 and NSP10/16 respectively, with NSP10 representing the activator protein and NSP14 and NSP16 representing the effector proteins), which leads to the prevention of Pattern Recognition Receptor (PRR)-based recognition of Pattern-Associated Molecular Patterns (PAMPs) on the microbial genome, as well as of Damage-Associated Molecular Patterns (DAMPs), which represent toxin proteins synthesised by the microbial genome once it has undergone receptor-mediated endocytosis without significant restriction. The second pathway represents an indirect form of microbial self-camouflaging, which however involves the direct antagonism of Type I and Type III Interferon-

encoding genes (INGs), as well as of Interferon-Stimulated Genes (ISGs) through various methodologies of mRNA cleaving and induced protein disposal - particularly by translated non-structural proteins (NSPs) 1 and 2. The third pathway involves the facilitation of the viral protein-based paracrine signalling through channeling nanotubes, which are produced by host cells with the original purpose of transmitting immune signals as soon as the first infection stages occur. Likewise, microbial agents of individual and public health concern have generally developed highly profound networks of immune evasion and even suppression, stimulating scientific and pharmaceutical researchers to develop unprecedented, world-class methodologies of clinical responses that “outsmart” such networks contained by the evolutionary machinery of viruses, bacteria and even yeasts.

Generally speaking, it is known that the cytokine system of the innate immune system constitutes the root of the entire process of adaptive immune activation and signalling that is proportional to the extent and severity of the microbial reproductive rates within the host organism. Nonetheless, it may be important to differentiate the first and the third classes of the interferon system from the second class, due to the fact that the production and signalling of Type II Interferons is directly dependent upon the production and signalling of Type I and Type III Interferons. Namely, it is known that Interferon-Stimulated Gene products, which are signalled as a direct result of adequate Type I and Type III Interferon signalling, are responsible for the recruitment of Natural Killer Cells, which constitute factories for Type II Interferons. Likewise, it may be more contextual for the research communities to deem Type I and Type III Interferon glycoprotein as pre-cytokine innate immune elements and potentially raise clinical awareness about the particularly high importance such particular interferon glycoprotein types brings in the activation process of the immune system, as they constitute a foundational factor for the adequate activation of the cytokine system itself. Moreover, the fact that the innate immune system displays considerable extents of “specific memory”, as well as considerable traits of specificity in their signalling processes, ultimately indicates the existence of adaptive immunity-like “purpose” even within its first line of defence, which comprises the PRR system, as well as the pre-cytokine networks of ING and ISG. Given the fact that innate immunity has shown to display considerable extents of “specific memory”, as well as specificity in their activation and signalling processes, Likewise, innate immunity may also be used significantly in the process of immune system-based vaccine innovation and development, despite the development of the initial theory that important elements of the innate immunity may only be used as vaccine adjuvants (Carp T., 2024). Such developments ultimately indicate that principal elements of first-line, innate immunity also play visible roles in whole processes of immunisation as well, and not solely the second line of natural immunity. Hence, infectious pathogens may be isolated, undergo loss-of-function research in various laboratory settings, have Type I and Type III Interferon glycoprotein-encoding genes inserted into their genome, prior to being released back into the surrounding environment as transformed, immunising agents that may be transmitted in an airborne manner. There are still some existing limitations in such a case, as there ought to be some form of transmission in order for herd immunity to be reached, and that may only occur if there is some extent of clinical symptoms occurring following such microbial exposures, and the interferon-encoding genes may prevent the development of symptoms, potentially making a significant number of the copies of the genetically-modified microbes unable to be transmitted. Perhaps, a low concentration of genetically modified microbial copies can be inhaled nasally by and/or administered via oral drops to a given number of human and animal recipients in order for herd immunity to be manually reached if necessary. In other cases, low concentrations of genetically modified microbial agents as such may be placed into an injectable serum, prior to being administered intramuscularly, in a similar fashion to traditional, intramuscular vaccination. The ultimate objective of such candidate vaccination approaches is to help both humans and animals outcompete the gained evolutionary capabilities of several microbial agents through direct and indirect methods of molecular self-camouflaging whilst keeping the extent of safety above the threshold level established by the Universal principles of medical ethics.

There are multiple existing environmental approaches of weakening specific microbes, by physical, chemical, biological and/or genetic manners, to make them more tolerable by the host organisms, with the purpose of encouraging the production of a herd immunity level without the causation of individual, life-threatening forms of infectious disease in the process. Nonetheless, few would barely pass the bioethical screening procedures because the ultimate purpose of medicine is to first not cause any form of harm. Nonetheless, it has become possible to utilise such approaches in the specific context of added Type I and Type III Interferon-encoding genes into the genomic profile of the microbial agent, as there would be no harm induced any longer due to the fact that the pathogen would automatically produce the glycoprotein molecules that produce the adequate anti-microbial signals whilst maintaining the adequate balance between produced anti-inflammatory and pro-inflammatory signals. Such approaches would require due clinical testing if a direct, separate administration of Type I and Type III Interferon glycoproteins does not bring the required long-term effects of immunisation whilst keeping financial expenditure to a level as low as the case of the vaccination campaigns against various epidemic illnesses that have been occurring for the past century. Interestingly enough, it is such a missing “piece of puzzle” existent in research ideas concerning loss-of-function microbial research that seems to fill in a proportional gap in human and animal vaccinology, as the host interferon system represents the primary target of microbial adaptation via multiple single-nucleotide polymorphism events in various functional areas of their genome.

Conclusion

The evolutionary battle between human and animal immune systems and polymorphic pathogenic agents has reached a critical stage, with the current existence of highly profound and firm microbial networks that are evasive of first-line and second-line, natural immunity. It seems that the development of recent epidemic and pandemic diseases has heavily depended upon such evolutionary capabilities of direct and indirect molecular self-camouflaging of the causative pathogens in front of the host interferon system. The fact that there are existing therapeutic approaches designed to target microbial gene products directly or indirectly responsible for the suppression of the host interferon system displays an existing level of scientific awareness to the existing phenomenon of natural immune evasion by numerous microbes. According to the latest stages of scientific, pharmaceutical and clinical research of the human immunity and microbial evolution, there is a paradoxical existence of both unprecedented threats to the integrity of human and animal public health, as well as of novel horizons of hope, as there is a possibility for clinical researchers in almost any geographical area of the world to turn threatening pathogenic agents into immunising factories for foundational, innate immune signals that will automatically activate the adaptive immune system in a manner that is proportionate to the microbial count or load. An update of the current course of therapeutic and vaccine-based research and innovation may likewise involve a proportional inclusion of first-line and perhaps also second-line, natural immunity, to merge a considerable extent of such immune departments with the central, adaptive immune elements, with the overall purpose of naturally stimulating the human immune system to outcompete the highly developed interferon-suppressive evolutionary responses developed by polymorphic microbial agents through numerous rounds of single-nucleotide polymorphism (SNP) in diverse important genes. Such an approach may illustrate the concept of “United Immune System” put in clinical practice. Loss-of-function microbial research may represent a controversial form of research if it is not accompanied by viable methods to turn microbial agents into immunising agents whilst causing no harm in the process, and gene editing via the insertion of active Type I and Type III Interferon-encoding genes may represent the accompanying factor that may turn such a research procedure into a thoroughly ethical one for both the medical and the biological domains. And the current context of advanced microbial evolution may be causing the production of sentiments of urgency within major research communities regarding the development of innovative solutions to proportionately

counteract such microbial genetic “intelligence”. Utilising a set of combined approaches, particularly in groups of patients where prophylactic immune support is needed more, may bring the utmost effect of immunisation and long-term immunity. The ultimate objective of such hypothesised and proposed updates in the known methods of immunisation, prophylaxis and early therapeutic approaches is to at least gradually decrease the probabilities of occurring limitations toward the point of zero. Currently, it is the responsibility of the scientific communities to assess and distribute any existing piece of scientific evidence that is relevant to such hypotheses and novel developments into clinical research, with the ultimate purpose of encouraging clinical researchers to assess novel candidate approaches that cross the initial threshold levels of safety and efficacy that are necessary for initial clinical trials to occur.

References

1. Daffis, S., Szretter, K. J., Schriewer, J., Li, J., Youn, S., Errett, J., Lin, T. Y., Schneller, S., Zust, R., Dong, H., Thiel, V., Sen, G. C., Fensterl, V., Klimstra, W. B., Pierson, T. C., Buller, R. M., Gale, M., Jr, Shi, P. Y., & Diamond, M. S. (2010). 2'-O methylation of the viral mRNA cap evades host restriction by IFIT family members. *Nature*, 468(7322), 452–456. <https://doi.org/10.1038/nature09489>
2. Szretter, K. J., Daniels, B. P., Cho, H., Gaaney, M. D., Yokoyama, W. M., Gale, M., Jr, Virgin, H. W., Klein, R. S., Sen, G. C., & Diamond, M. S. (2012). 2'-O methylation of the viral mRNA cap by West Nile virus evades ifit1-dependent and -independent mechanisms of host restriction in vivo. *PLoS pathogens*, 8(5), e1002698. <https://doi.org/10.1371/journal.ppat.1002698>
3. Diamond M. S. (2014). IFIT1: A dual sensor and effector molecule that detects non-2'-O methylated viral RNA and inhibits its translation. *Cytokine & growth factor reviews*, 25(5), 543–550. <https://doi.org/10.1016/j.cytogfr.2014.05.002>
4. Menachery, V. D., Debbink, K., & Baric, R. S. (2014). Coronavirus non-structural protein 16: evasion, attenuation, and possible treatments. *Virus research*, 194, 191–199. <https://doi.org/10.1016/j.virusres.2014.09.009>
5. Menachery, V. D., Gralinski, L. E., Mitchell, H. D., Dinno, K. H., 3rd, Leist, S. R., Yount, B. L., Jr, Graham, R. L., McAnarney, E. T., Stratton, K. G., Cockrell, A. S., Debbink, K., Sims, A. C., Waters, K. M., & Baric, R. S. (2017). Middle East Respiratory Syndrome Coronavirus Nonstructural Protein 16 Is Necessary for Interferon Resistance and Viral Pathogenesis. *mSphere*, 2(6), e00346-17. <https://doi.org/10.1128/mSphere.00346-17>
6. Schindewolf, C., & Menachery, V. D. (2023). Coronavirus 2'-O-methyltransferase: A promising therapeutic target. *Virus research*, 336, 199211. <https://doi.org/10.1016/j.virusres.2023.199211>
7. Schindewolf, C., Lokugamage, K., Vu, M. N., Johnson, B. A., Scharton, D., Plante, J. A., Kalveram, B., Crocquet-Valdes, P. A., Sotcheff, S., Jaworski, E., Alvarado, R. E., Debbink, K., Daugherty, M. D., Weaver, S. C., Routh, A. L., Walker, D. H., Plante, K. S., & Menachery, V. D. (2023). SARS-CoV-2 Uses Nonstructural Protein 16 To Evade Restriction by IFIT1 and IFIT3. *Journal of virology*, 97(2), e0153222. <https://doi.org/10.1128/jvi.01532-22>
8. Menachery, V. D., Yount, B. L., Jr, Josset, L., Gralinski, L. E., Scobey, T., Agnihothram, S., Katze, M. G., & Baric, R. S. (2014). Attenuation and restoration of severe acute respiratory syndrome coronavirus mutant lacking 2'-o-methyltransferase activity. *Journal of virology*, 88(8), 4251–4264. <https://doi.org/10.1128/JVI.03571-13>
9. Lazear, H. M., Schoggins, J. W., & Diamond, M. S. (2019). Shared and Distinct Functions of Type I and Type III Interferons. *Immunity*, 50(4), 907–923. <https://doi.org/10.1016/j.immuni.2019.03.025>
10. Dowling, J. W., & Forero, A. (2022). Beyond Good and Evil: Molecular Mechanisms of Type I and III IFN Functions. *Journal of immunology* (Baltimore, Md.: 1950), 208(2), 247–256. <https://doi.org/10.4049/jimmunol.2100707>
11. Chiale, C., Greene, T. T., & Zuniga, E. I. (2022). Interferon induction, evasion, and paradoxical roles during SARS-CoV-2 infection. *Immunological reviews*, 309(1), 12–24. <https://doi.org/10.1111/imr.13113>

12. Garcia-Del-Barco, D., Risco-Acevedo, D., Berlanga-Acosta, J., Martos-Benítez, F. D., & Guillén-Nieto, G. (2021). Revisiting Pleiotropic Effects of Type I Interferons: Rationale for Its Prophylactic and Therapeutic Use Against SARS-CoV-2. *Frontiers in immunology*, 12, 655528. <https://doi.org/10.3389/fimmu.2021.655528>
13. Felgenhauer, U., Schoen, A., Gad, H. H., Hartmann, R., Schaubmar, A. R., Failing, K., Drosten, C., & Weber, F. (2020). Inhibition of SARS-CoV-2 by type I and type III interferons. *The Journal of biological chemistry*, 295(41), 13958–13964. <https://doi.org/10.1074/jbc.AC120.013788>
14. Lokugamage, K. G., Hage, A., de Vries, M., Valero-Jimenez, A. M., Schindewolf, C., Dittmann, M., Rajsbaum, R., & Menachery, V. D. (2020). Type I Interferon Susceptibility Distinguishes SARS-CoV-2 from SARS-CoV. *Journal of virology*, 94(23), e01410-20. <https://doi.org/10.1128/JVI.01410-20>
15. Shimizu, J., Sasaki, T., Ong, G. H., Koketsu, R., Samune, Y., Nakayama, E. E., Nagamoto, T., Yamamoto, Y., Miyazaki, K., & Shioda, T. (2024). IFN- γ derived from activated human CD4+ T cells inhibits the replication of SARS-CoV-2 depending on cell-type and viral strain. *Scientific reports*, 14(1), 26660. <https://doi.org/10.1038/s41598-024-77969-4>
16. Vallejo, A., Vizcarra, P., Quereda, C., Moreno, A., Casado, J. L., & CoVEX study group (2021). IFN- γ cell response and IFN- γ release concordance after in vitro SARS-CoV-2 stimulation. *European journal of clinical investigation*, 51(12), e13636. <https://doi.org/10.1111/eci.13636>
17. Chen, J., Liu, J., Chen, Z., Peng, H., Zhu, C., Feng, D., Zhang, S., Zhao, P., Zhang, X., & Xu, J. (2022). Angiotensin-Converting Enzyme 2 Potentiates SARS-CoV-2 Infection by Antagonizing Type I Interferon Induction and Its Down-Stream Signaling Pathway. *mSphere*, 7(4), e0021122. <https://doi.org/10.1128/msphere.00211-22>
18. Busnadiego, I., Fernbach, S., Pohl, M. O., Karakus, U., Huber, M., Trkola, A., Stertz, S., & Hale, B. G. (2020). Antiviral Activity of Type I, II, and III Interferons Counterbalances ACE2 Inducibility and Restricts SARS-CoV-2. *mBio*, 11(5), e01928-20. <https://doi.org/10.1128/mBio.01928-20>
19. Goletti, D., Petrone, L., Manissero, D., Bertoletti, A., Rao, S., Ndunda, N., Sette, A., & Nikolayevskyy, V. (2021). The potential clinical utility of measuring severe acute respiratory syndrome coronavirus 2-specific T-cell responses. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 27(12), 1784–1789. <https://doi.org/10.1016/j.cmi.2021.07.005>
20. Tovey, M. G., & Lallemand, C. (2010). Safety, Tolerability, and Immunogenicity of Interferons. *Pharmaceuticals (Basel, Switzerland)*, 3(4), 1162–1186. <https://doi.org/10.3390/ph3041162>
21. Meyts, I., & Casanova, J. L. (2021). Viral infections in humans and mice with genetic deficiencies of the type I IFN response pathway. *European journal of immunology*, 51(5), 1039–1061. <https://doi.org/10.1002/eji.202048793>
22. Zhang, Q., Matuoizzo, D., Le Pen, J., Lee, D., Moens, L., Asano, T., Bohlen, J., Liu, Z., Moncada-Velez, M., Kendir-Demirkol, Y., Jing, H., Bizien, L., Marchal, A., Abolhassani, H., Delafontaine, S., Buccioli, G., COVID Human Genetic Effort, Bayhan, G. I., Keles, S., Kiykim, A., ... Casanova, J. L. (2022). Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *The Journal of experimental medicine*, 219(8), e20220131. <https://doi.org/10.1084/jem.20220131>
23. Abolhassani, H., Landegren, N., Bastard, P., Materna, M., Modaresi, M., Du, L., Aranda-Guillén, M., Sardh, F., Zuo, F., Zhang, P., Marcotte, H., Marr, N., Khan, T., Ata, M., Al-Ali, F., Pescarmona, R., Belot, A., Béziat, V., Zhang, Q., Casanova, J. L., ... Pan-Hammarström, Q. (2022). Inherited IFNAR1 Deficiency in a Child with Both Critical COVID-19 Pneumonia and Multisystem Inflammatory Syndrome. *Journal of clinical immunology*, 42(3), 471–483. <https://doi.org/10.1007/s10875-022-01215-7>
24. Su, H. C., Jing, H., Zhang, Y., & Casanova, J. L. (2023). Interfering with Interferons: A Critical Mechanism for Critical COVID-19 Pneumonia. *Annual review of immunology*, 41, 561–585. <https://doi.org/10.1146/annurev-immunol-101921-050835>
25. Jafarzadeh, A., Nemati, M., Saha, B., Bansode, Y. D., & Jafarzadeh, S. (2021). Protective Potentials of Type III Interferons in COVID-19 Patients: Lessons from Differential Properties of Type I- and III Interferons. *Viral immunology*, 34(5), 307–320. <https://doi.org/10.1089/vim.2020.0076>
26. Sorrentino, L., Silvestri, V., Oliveto, G., Scordio, M., Frasca, F., Fracella, M., Bitossi, C., D'Auria, A., Santinelli, L., Gabriele, L., Pierangeli, A., Mastroianni, C. M., d'Ettorre, G., Antonelli, G., Caruz, A., Ottini, L., & Scagnolari, C. (2022). Distribution of Interferon Lambda 4 Single Nucleotide Polymorphism

- rs11322783 Genotypes in Patients with COVID-19. *Microorganisms*, 10(2), 363. <https://doi.org/10.3390/microorganisms10020363>
27. Zahid, W., Farooqui, N., Zahid, N., Ahmed, K., Anwar, M. F., Rizwan-Ul-Hasan, S., Hussain, A. R., Sarria-Santamera, A., & Abidi, S. H. (2023). Association of Interferon Lambda 3 and 4 Gene SNPs and Their Expression with COVID-19 Disease Severity: A Cross-Sectional Study. *Infection and drug resistance*, 16, 6619–6628. <https://doi.org/10.2147/IDR.S422095>
 28. Fang, M. Z., Jackson, S. S., & O'Brien, T. R. (2020). IFNL4: Notable variants and associated phenotypes. *Gene*, 730, 144289. <https://doi.org/10.1016/j.gene.2019.144289>
 29. Svensson Akusjärvi, S., & Zanoni, I. (2024). Yin and yang of interferons: lessons from the coronavirus disease 2019 (COVID-19) pandemic. *Current opinion in immunology*, 87, 102423. <https://doi.org/10.1016/j.coi.2024.102423>
 30. Mogensen T. H. (2022). Human genetics of SARS-CoV-2 infection and critical COVID-19. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 28(11), 1417–1421. <https://doi.org/10.1016/j.cmi.2022.02.022>
 31. Malik, A. E., Issekutz, T. B., & Derfalvi, B. (2021). The Role of Type III Interferons in Human Disease. *Clinical and investigative medicine. Medecine clinique et experimentale*, 44(2), E5–E18. <https://doi.org/10.25011/cim.v44i2.36622>
 32. Mesev, E. V., LeDesma, R. A., & Ploss, A. (2019). Decoding type I and III interferon signalling during viral infection. *Nature microbiology*, 4(6), 914–924. <https://doi.org/10.1038/s41564-019-0421-x>
 33. Rojas, J. M., Alejo, A., Martín, V., & Sevilla, N. (2021). Viral pathogen-induced mechanisms to antagonize mammalian interferon (IFN) signaling pathway. *Cellular and molecular life sciences: CMLS*, 78(4), 1423–1444. <https://doi.org/10.1007/s00018-020-03671-z>
 34. Takaoka, A., & Yanai, H. (2006). Interferon signalling network in innate defence. *Cellular microbiology*, 8(6), 907–922. <https://doi.org/10.1111/j.1462-5822.2006.00716.x>
 35. Tian, Y., Wang, M. L., & Zhao, J. (2019). Crosstalk between Autophagy and Type I Interferon Responses in Innate Antiviral Immunity. *Viruses*, 11(2), 132. <https://doi.org/10.3390/v11020132>
 36. Rabbani, M. A., Ribaud, M., Guo, J. T., & Barik, S. (2016). Identification of Interferon-Stimulated Gene Proteins That Inhibit Human Parainfluenza Virus Type 3. *Journal of virology*, 90(24), 11145–11156. <https://doi.org/10.1128/JVI.01551-16>
 37. Zhou, X., Michal, J. J., Zhang, L., Ding, B., Lunney, J. K., Liu, B., & Jiang, Z. (2013). Interferon induced IFIT family genes in host antiviral defense. *International journal of biological sciences*, 9(2), 200–208. <https://doi.org/10.7150/ijbs.5613>
 38. Loevenich, S., Malmo, J., Liberg, A. M., Sherstova, T., Li, Y., Rian, K., Johnsen, I. B., & Anthonsen, M. W. (2019). Cell-Type-Specific Transcription of Innate Immune Regulators in response to HMPV Infection. *Mediators of inflammation*, 2019, 4964239. <https://doi.org/10.1155/2019/4964239>
 39. Loevenich, S., Spahn, A. S., Rian, K., Boyartchuk, V., & Anthonsen, M. W. (2021). Human Metapneumovirus Induces IRF1 via TANK-Binding Kinase 1 and Type I IFN. *Frontiers in immunology*, 12, 563336. <https://doi.org/10.3389/fimmu.2021.563336>
 40. Tanaka, Y., Morita, N., Kitagawa, Y., Gotoh, B., & Komatsu, T. (2022). Human metapneumovirus M2-2 protein inhibits RIG-I signaling by preventing TRIM25-mediated RIG-I ubiquitination. *Frontiers in immunology*, 13, 970750. <https://doi.org/10.3389/fimmu.2022.970750>
 41. Hastings, A. K., Erickson, J. J., Schuster, J. E., Boyd, K. L., Tollefson, S. J., Johnson, M., Gilchuk, P., Joyce, S., & Williams, J. V. (2015). Role of type I interferon signaling in human metapneumovirus pathogenesis and control of viral replication. *Journal of virology*, 89(8), 4405–4420. <https://doi.org/10.1128/JVI.03275-14>
 42. van den Hoogen, B. G., van Boheemen, S., de Rijck, J., van Nieuwkoop, S., Smith, D. J., Laksono, B., Gultyaev, A., Osterhaus, A. D. M. E., & Fouchier, R. A. M. (2014). Excessive production and extreme editing of human metapneumovirus defective interfering RNA is associated with type I IFN induction. *The Journal of general virology*, 95(Pt 8), 1625–1633. <https://doi.org/10.1099/vir.0.066100-0>
 43. Schoggins J. W. (2019). Interferon-Stimulated Genes: What Do They All Do?. *Annual review of virology*, 6(1), 567–584. <https://doi.org/10.1146/annurev-virology-092818-015756>

44. Frenkel, D., Puckett, L., Petrovic, S., Xia, W., Chen, G., Vega, J., Dembinsky-Vaknin, A., Shen, J., Plante, M., Burt, D. S., & Weiner, H. L. (2008). A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. *Annals of neurology*, 63(5), 591–601. <https://doi.org/10.1002/ana.21340>
45. Frenkel, D., Maron, R., Burt, D. S., & Weiner, H. L. (2005). Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. *The Journal of clinical investigation*, 115(9), 2423–2433. <https://doi.org/10.1172/JCI23241>
46. Carp, T. N. (2025). Recent Human Metapneumovirus Outbreak in East Asia: The Time to Shift Immunological Gears is Now. <https://doi.org/10.20944/preprints202501.0759.v1>
47. Carp, T. N. (2024). Calibrating Human Immunity in the Context of Advanced Microbial Evolution and Self-Camouflaging. Preprints. <https://doi.org/10.20944/preprints202411.2046.v4>

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.