Review

Potential Innovations in Modern-Day Human and Animal Vaccine Development

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Potential Innovations in Modern-Day Human and Animal Vaccine Development

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Abstract: The vaccine industry has undoubtedly contributed massively in the medical world, with hundreds of millions of lives saved as a result of the successful development of prophylactic and therapeutic vaccines against various infectious and oncological diseases. Simultaneously, there has been an ongoing evolutionary battle between polymorphic microbes and the human immune system, and various microbes have developed counter-responses against the human host immune system, by creating diverse "holes" of vulnerability in the innate immune system. Such mechanisms may have resulted due to the lower prophylactic and therapeutic focus upon sharpening the innate immune lines as directly as necessary. The overall objective of vaccine-development should be the sharpening of all immune departments that are targeted by various microbial agents for the purpose of transient innate immune suppression and the distribution of the microbial count/load at a systemic level. Likewise, it could be viable for the clinical research community to start focusing upon filling in the "gaps" of vulnerability that are now present in the pathways responsible for the proper natural immune activation and proportionate signalling toward the adaptive immune system. Perhaps, through such a process, the "road" toward the adaptive immune system, which is "old" and filled with "holes", could be gradually transformed into a perfectly uniform "highway", with all the required signals transmitted robustly from the innate to the adaptive immune system, before microbes manage to translate the various pathogenic proteins that transiently prevent such transmission altogether, until it becomes too late for the immune response to possibly develop in a proportionate and non-harmful manner to the organism. Such a scenario would be possible, given that it is almost impossible for human evolutionary growth to eventually stall and not risk experiencing a decrease as a result. Simultaneously, it is important for human society to bind by the principles of maintaining a healthy and nature-friendly lifestyle, given the philosophical quote of "We are what we eat." The overall objective should be the facilitation of human and animal immune evolution over viral and bacterial molecular self-camouflaging from all possible directions, as a sharper human and animal evolutionary growth resulting from such actions could "cost" the sharper evolutionary growth of microbes as such, given that evolutionary patterns are based upon the models observed in Physics, in Newton's Third Law of Motion, as well as in the First Law of Thermodynamics, which concerns the Conservation of Energy.

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Introduction

The overall context of advanced microbial evolution is caused and perpetuated by the "holes" created in the road to the adaptive immune system. A possible solution to the present dilemma of microbial evolution against human and animal immunity would be the assembly of an "immunological highway", from the activation of Pattern-Recognition Receptors, which represents the initial point of first-line immunity, to the recruitment of B- and T-Lymphocytes that is resulted from the adequate secretion of ISG products, which represents the gateway of the third-line

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immunity. The ultimate objective in vaccine development should involve the assembly of an immunological "highway", as it could significantly help the human immune system outcompete microbial evolution. In such a process of out competition, microbes would have their abilities of first-line immune evasion impaired and often proven useless by the increase of sensitisation and speed of first-line immune activation. In other words, it will be such an exchange that will result in the reclaim of power by the human immune system over microbial self-camouflaging methodologies. In order for such a procedure to occur, it may be important to address all the potential problems that society has been undergoing with regards to diet, lifestyle, as well as readiness of clinical response to illness. Furthermore, in order for a qualitative clinical prevention against future epidemics to occur, it may be important not only to thoroughly study the context in which various kinds of infectious diseases emerge in various areas of the world, but also to thoroughly study the numerous distinct human genomic and proteomic backgrounds, according to geographical areas and perhaps climate as well. By understanding the substantial diversity of the human genome, the clinical research communities may draw near the potential conclusion that one, uniform clinical response, even against one particular infectious illness may hardly exist. Whilst traditional, pathogen- or antigen-derived vaccines originally proved to be the most successful prophylactic and therapeutic approaches, helping the host immune system build an effective "memory" against the concerned pathogens on the broadest extent, the current context of microbial vs human evolution has changed to the extent that microbial agents now utilise the innate, first and second lines of immune defence, to eventually become more capable of evading previously built adaptive lymphocyte- and antibody-mediated immune responses. As a result, the solution to counteract evolved viral and bacterial pathogenic agents may be to perform a more thorough focus upon sensitising and modulating natural immunity, whilst continuing to focus on sharpening early and local adaptive immune activation, specific to vaccine-mediated immune responses. The envisaged set of medical preventive and therapeutic responses constitute a spectrum containing various shades of efficacy. Nonetheless, it is important for the safety of such clinical responses not to constitute a spectrum as well, meaning that all potentially harmful responses need to be outfiltered, even if such harm is solely remotely caused. Overall, the procedure of medical and clinical research against present and future public health crises may represent part of the most complex intellectual and practical efforts made in civilised society, and may only be rational for the medical research professional communities to be among the most highly respected globally.

Discussion

Investigating the context of microbial self-camouflaging

Polymorphic pathogenic viruses represent one of the most concerning molecular agents with regards to their evolutionary stages, as well as their diverse capabilities of inducing pathogenesis and virulence in human and animal host organisms. Oftentimes, such viral genomes translate two types of proteins with regards to induced pathophysiology: proteins enhancing virulence and proteins aiding viruses to evade first- and second-line immune defences, with the SARS-CoV-2-induced COVID-19 representing a relevant example of this. Namely, the novel coronavirus secretes the spike glycoprotein, which enters endothelial cells via ACE2-mediated endocytosis and directly induces local and then systemic pathophysiology, as well as a set of sixteen non-structural proteins (NSPs), which although do not directly induce pathophysiology, they substantially aid the virus in an overall process of molecular self-camouflaging, causing the host immune system not to recognise the virus, often until its load reaches multiple host organs. Given the fact that the virus causes a particularly lengthy time in which no symptoms are developed, it is possible that SARS-CoV-2 secretes a substantial amount of such non-structural proteins once it enters host cells, and it could be that the concentration of such proteins is higher than in the host cells infected by the H1N1 Influenza A Virus.

The main responsible SARS-CoV-2 NSPs are NSP10, NSP14 and NSP16. NSP10 joins NSP14 to form the NSP10/14 enzyme complex - NSP14 is the effector protein, whilst NSP10 is the activator protein when NSP14 functions as ExoN. NSP10 joins NSP16 to form the NSP10/16 2'-O-MTase complex - NSP16 is the effector protein, whilst NSP10 is the activator protein. NSP14 represents a

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multifunctional enzyme protein. Namely, it is known to be an N-terminal 3′-5′ exoribonuclease (ExoN) and a C-terminal N7-methyltransferase (N7 - MTase). Both such activities are critical for the life cycle of coronaviruses, suggesting that the enzyme protein represents a major target for the development of antiviral drug-like components. Whilst the N7-MTase function implicates the modification of the +ssRNA cap to aid the process of viral translation and replication, the ExoN function, which is particularly stimulated by nsp10, plays a direct role in synthesising new viral RNA, ensuring a long-term validity of the viral genome. Furthermore, the methyltransferase enzyme activity of NSP14 is independent from both the activator NSP10 protein and its own enzyme activity of ExoN, and the first motif of the ExoN domain is highly important for the integrity of NSP14 function. Likewise, such aspects regarding NSP14 bring major effects of pathogenesis by SARS-CoV-2. Potential clinical solutions against NSP14 particularly would implicate the development of inhibitors targeting specific regions of the NSP14's amino acid sequence, with the purpose of preventing the construction of the NSP10/NSP14 enzyme complex and interfere with the replication of coronaviruses, like SARS-CoV-1 and SARS-CoV-2. The double methylation of the 5′ viral genomic end, alongside the direct inhibition of the signalling transduction cascades leading to the activation of the transcription factors for INGs and ISGs, represent two primary methods polymorphic viral agents use in their attempts to evade first-line and second-line immune activations, thereby preventing the proper assembly of the bridge to the adequate activation of adaptive immune responses. There are two other mechanisms of transient immunosuppression that involve the disruption of the mitochondrial activation processes, as well as the usage of nanotubes developed by host cells for the purpose of intercellular signal transmission, for the purpose of catalysed viral load and protein distribution. A possible solution for the ongoing dilemma of virally-induced innate immune evasion is the wider inclusion of innate immune elements in the efforts of vaccine and therapeutic development. Viral immune evasion also occurs through the abundant synthesis of NSPs 1 and 2, which are responsible for a more direct form of hijacking the activating pathways for the INGs and ISGs. Such viral NSPs make a "lethal" combination with NSPs 10, 14 and 16 for the interferon system, which constitutes the principal element of first-line and second-line immune defences. Furthermore, a delayed activation of the interferon system lowers the quality of the activation of the complement system as well. Novel polymorphic viruses were found to translate such non-structural proteins more abundantly, and it is perhaps such increased quantity of viral protein that is rather directly proportional with the rates of morbidity and lethality displayed by the illnesses they cause.

The HIV-1-induced AIDS pandemic seems to be a key example of the manner pathogenic viruses ultimately target central elements of the immune system, which are represented by helper CD4+ and cytotoxic CD8+ adaptive T-Lymphocytes, by first silencing the peripheral sides of innate immunity. It is possible that microbes ultimately need to hijack two major sectors of the human and animal immune systems: the interferon system contained by first- and second-line immunity, and the innate and adaptive lymphocyte systems contained by second- and third-line immunity. If the interferon system is successfully hijacked, then the host immune system will produce erroneous and harmful responses. If the lymphocyte system is successfully hijacked, then the host immune system will be progressively suppressed, with the final outcome of total compromisation. The HIV-1 retrovirus seems to be the second most evolutionarily advanced microbe, as it is capable of both hijacking the interferon system and suppressing lymphocyte-based immunity, meaning that microbial evolution may have reached an area dangerously close to the point of suppressing human and animal immune system in the most direct possible way. There may only be one method of attempting a reverse of such a counter-evolutionary process: by utilising the interferon system as a catalysis of first- and second-line immune sensitisation against molecular self-camouflaging methods by pathogens, and by treating innate and adaptive lymphocytes with key elements of the interferon system before potentially utilising them as an immune system-based vaccine candidate against any potential exposure to microbial agents like HIV-1.

The importance of detecting secondary infection during latter stages of respiratory infectious disease

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Bacterial and fungal secondary infections constitute one of the main factors that resulted in the death of COVID-19 patients during the SARS-CoV-2-induced pandemic. Likewise, it may be important to extend methods of molecular testing for the detection of such microbes before the state of disease worsens, before authorising the administration of antibiotic, antibacterial or antifungal agents to patients who tested positive for the presence of secondary bacteria or fungi respectively. Furthermore, the emergence of secondary infections may represent a sign of an existing transient immunosuppression caused by the initial infectious agent, which occurred through the hijacking of the host organism's interferon system, and which particularly affects people with directly or indirectly weakened immune systems.

How did microbial evolution impair human homeostasis and affect the growth of the average human lifespan?

Excessive levels of human disease have been widely resulted from an advanced microbial evolution over human immunity. Such excess has reflected an excessive level of reactive oxygen species production, as well as one of demand for metabolic energy consumption, which is widely associated with faster rates of aging. As a result, it could be that a thorough reverse in the ongoing process of human immunity - microbe evolutionary struggle will lower the demand for metabolic energy exchange, contributing significantly to a slowdown of the overall process of human aging. A lower extent of human disease would contribute to a decrease in the overall level of human suffering. Whilst it is known that joy increases the psychologically perceived speed of time and suffering decreases it, suffering is the factor for automation of tasks that are of a more complex nature, which means that suffering ultimately increases the perceived speed of time and therefore decreases the perceived lifespan. If such levels of suffering are decreased, then the perceived lifespan will increase, alongside the process of human lifespan prolongation by a decrease in the rate of pathogenesis by infectious microbes. Overall, if levels of disease will decrease and human lifespan will be increased, life will also be felt more abundantly and longer. For example, if the average lifespan will gradually increase by 10 years, it will be psychologically felt as if it increased by 15 to 20 years. If the average lifespan will eventually increase by 20 years, then the increase could be psychologically felt as 30 to 40 years.

Does technology abuse and dependence affect the performance of human immunity?

Humans represent living organisms that are completely natural. Likewise, the bond between humans and their surrounding natural environment ought to be strong in order for human health and welfare to be preserved on a long-term basis. It is the substantial human connection with Mother Nature, as well as the substantial connection between fellow human beings, that preserves human health and maintains a steep evolutionary growth of humans on Earth. Technology and automation-based dependencies may also lead to a false perception of physical lifespan prolongation, given that the human body may adjust to the changes seen within the bridge of Relativity-Psychology as an adaptive response. Ultimately, such a response will make very little difference with regards to the perception of lifespan shortening through such an acceleration of the perceived time speed. Whilst it remains essential to adapt to new changes and include technological catalysis into the human lifestyle, particularly within urban areas, it is at least as essential for humans not to become dominated by technological catalysis, meaning that humans should not become dependent upon it, lest human evolution would again eventually be at peril as a result. Technology-abuse may display patterns of manifestation similar in nature with the problem of alcohol and drug-abuse, and it is possible that the overall performance of the human immune system is also affected by long-term technology-abuse. Existing projects in which human biology and psychology are desired to be combined with technology, and in which even the human DNA is desired to be combined with nanotechnology, would perform the final steps of "sucking life" out of the human flesh. In such a case, the being would be as passengers in a car, whilst the driver would become the technological factor that was meant to be a catalyst for important human activities on Earth (Carp T., 2024).

What could thoroughly accurate medical prophylactic and therapeutic approaches bring to the human population?

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Not only could accurate medical approaches help humanity overcome future epidemic and pandemic illnesses caused by microbial agents with high levels of molecular self-camouflaging, but they could also help human metabolism improve to the extent that, in the following several decades, the average human lifespan would experience a growth, in the end even with up to a couple of decades, given that excessive levels and frequency of the onset of human infectious disease may be responsible with a substantial increase in the level of demand for metabolic energy consumption by numerous kinds of cells, given the existing growth in the level of synthesised Reactive Oxygen Species (ROS), leading to more widespread extent of oxidative stress and on a long-term basis, to faster processes of human aging. Furthermore, an increased frequency and extent of infectious disease onset is generally associated with increased incidences of the onset of oncological diseases, given that repeated exposures to RNA molecules specific to pathogenic agents may locally increase the probability of host genotoxicity and mutagenesis, particularly in groups of people with immunological or oncological family history of disease (Carp T. et al., 2024).

Possible methods of vaccine development:

I) Immune system-based vaccine candidates:

1. Innate immunity-based vaccines:

a) Low-dose human recombinant Type I and Type III Interferons administered at the mucosal level

b) Human recombinant plasmacytoid dendritic cells (pDCs)

c) Human recombinant natural killer lymphocytes (NKs)

2. Adaptive immunity-based vaccines:

a) Helper CD4+ and Cytotoxic CD8+ T-lymphocytes treated with a low dose of human recombinant Type I and Type III Interferons beforehand

b) Mature B-Lymphocytes (expressing IgM and IgG antibodies)

II) Pathogen-derived vaccine candidates:

1. Whole pathogen-based vaccines (inactive DNA or RNA-based):

a) UV-attenuated live pathogens

b) Neutralised pathogens

c) Live pathogens with most genes inactivated

2. Antigen-based vaccines (protein-based)

In some cases, many of vaccine candidates could be used in combination, to ensure a long-term development of immune memory against pathogens causative of life-threatening human and animal infectious and oncogenic diseases. In some public health contexts and population groups, several vaccine adjuvants could also be administered to ensure that the host immunity develops the desired extent and duration of "memory" against such pathogens causative of life-threatening infectious diseases.

Researchers could perform genetic research upon viral agents to be used for vaccine development purposes. Namely, the majority of the viral genomic profile could be only partially inactivated, with only a few genes to only be wholly inactivated. Or viceversa, the majority of the viral genome could be completely inactivated, with only a few spare genes to solely undergo partial inactivation. Such genes constituting a minority of the viral genome would be involved, either in clinical pathogenesis or also in the aid for the onset of disease. In the current context of advanced microbial evolution and molecular self-camouflaging of several polymorphic viruses, researchers could inactivate all genes, except the ones responsible with induced immune evasion. For example, Influenza A viruses could only have their NSP- and perhaps HA-encoding genes slightly active, with the rest of the genomic profile completely inactive, to stimulate the human body to build responses faster than the viral approach of NSP expression and induction of innate immune silencing. A disadvantage of such an approach would apply for RNA-based viral genomes, given the existence of the human protein DNA Theta Polymerase, which was found to select remote areas of the viral RNA and transform it into double-stranded DNA, before the new DNA would be inserted into the host cell's DNA, locally causing adverse events, such as induced mutagenesis, genotoxicity and

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expression of genetic information foreign to the host cell's genome. Despite the fact that such events are deemed as uncommon, the first principle of medicine, which is to cause no harm in the process of treating and managing disease, does not allow for such candidate approaches to pass the ultimate tests, which would lead to the widespread distribution of such vaccine candidates globally.

What is different in the case of the SARS-CoV-2 pandemic?

The difference between SARS-CoV-2 and IAV is that, whilst the novel coronavirus consists of positive-sense, single-stranded RNA and likewise, much more of its genomic profile consists of messenger RNA (mRNA), the latter consists of negative-sense, single-stranded RNA, meaning that not as much of the viral RNA is expressible. As a result, the host enzyme DNA Theta Polymerase would access more of the host viral genome, regardless of the extent of genomic activity, leading to the development of a few extra risks of genomic toxicity for human host cells. Moreover, it has been shown that the SARS-CoV-2 virus is more capable of inducing systemic and higher rates of virulence, via the spike glycoprotein, making it significantly more complicated for researchers to develop wholly safe and effective vaccines, either based upon inactivated SARS-CoV-2 copies, or based upon the spike glycoprotein, which was also indicated to display superantigen-like traits, given also the particularly high binding affinity to the human ACE2 receptor, the approximate 79% proportion of homology with human proteins, which could particularly explain the increased rates of autoimmune disease-induction of SARS-CoV-2 infection via the spike glycoprotein expression in the infected host cells, and the overall unusually high degree of adaptability to human cells. Unlike SARS-CoV-2, the H1N1, H5N1, H5N2, H5N8 and H7N9 strains of IAV does not display levels of adaptability to human cells that are as high, despite the major rates of virulence and mortality rates that avian influenza has displayed in poultry. Moreover, it was discovered through in-vitro studies that, inside human hepatic cells, the vaccine spike protein-encoding mRNA had approximately 1% of its sequence reverse transcribed into double-stranded DNA, through the catalysis of LINE-1 Reverse Transcriptase, before the newly-synthesised DNA molecule would be inserted into the host cell's genome through the catalysis of DNA Integrase. Likewise, risks of genetic adverse events are overall significantly higher for SARS-CoV-2-derived vaccine candidates, and they would also be substantially higher for spike protein-encoding mRNA alone. The SARS-CoV-2-induced COVID-19 pandemic has confirmed that the context of microbial evolution has indefinitely changed, and concrete signs have started appearing with the HIV-induced AIDS pandemic. Both microbial agents are at least considerably causative of both autoimmune reactions and immunological suppression, and it is also both microbes that undergo existing levels of molecular self-camouflaging against the interferon system. Likewise, an unprecedented change of microbial evolutionary context will pressurise the scientific community to perform unprecedented changes of direction with regards to therapeutic and vaccine-based research.

2. Antigen-based vaccines (protein or mRNA-based):

Alongside the usage of specific viral antigens that are particularly responsible for pathogenesis and induced virulence, researchers could isolate NSP copies and develop methods for the human body to immunologically detect and dispose of the viral protein copies, stimulating the innate and adaptive immune systems to develop their "memory" specifically against the concerned viral proteins. Currently, it is virtually impossible to stimulate the immune system to "learn" to lyse the viral NSPs via trained immunity, and consequently, medical researchers would require to develop immunoglobulin molecules with extra features of "lock-and-key" types of endocytosis, which would namely involve receptor-mediated endocytosis, to enter infected cells and particularly target the viral NSPs. Such antibodies would be deemed as "super-antibodies" and implicate IgM molecules. Other approaches could involve the development and design of small, drug-like components, to target viral NSPs and enzyme complexes that overall constitute the mechanistic camouflage of such viruses.

Exploring proportional host immune system-based vaccine candidates, as well as vaccine adjuvants

There are several proportional approaches that would constitute adjuvants for vaccine candidates. Some clinical approaches would fit both the definition of vaccine adjuvants and vaccine candidates. Such approaches would be based upon immunological cytokines, chemokines and cells,

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given that the innate and the adaptive immune compartments have now been shown to have their characteristics substantially interpolated. Namely, it was discovered that innate and adaptive immunity both contain their own "specific memory", and that certain major pathways of activation and mechanism in both innate and adaptive immunity display specificity. Scientists have started deeming innate immunity as "adaptive" and adaptive immunity as "nonspecific" as a result, placing an emphasis upon the fact that common aspects are wider in extent than previously projected. As a result, the perception upon vaccine development could become significantly changed.

Potential prophylactic and early therapeutic vaccine adjuvants that would likely also count as vaccine candidates:

1. Type I and Type III Interferons
2. Plasmacytoid Dendritic cells
3. Natural killer cells
4. Adaptive B- and T-lymphocytes

Potential vaccine adjuvants that most likely would not contain traits of immunising components:

1. A healthy diet and lifestyle
2. Sleep therapies (i.e. a regular inclusion of evening sleep into the daily schedule of rest)
3. Type II Interferons
4. Specialised IgM antibodies given extra features facilitating "lock-and-key"-mediated cellular entry (i.e. super-antibodies)
5. Cholecalciferol
6. Ascorbic acid
7. Folic acid
8. Methylene blue
9. Zinc
10. Ionophores for the entry of Zinc into cells via channel ion activation-based endocytosis (such as quercetin, curcumin and probably low-dose quinine and in some cases ivermectin as well)
11. UVA, UVB and UVC light administered through breathing tubes to treat infected bronchi and primary bronchioles, by stimulating the synthesis of cholecalciferol in infected cells and tissues
12. Anti-asthmatic compounds, such as clarithromycin, ventolin, flixotide, ketoprofen and prednisone, with local administration of aspirin in people more advanced in age and/or with more significant underlying health conditions.
13. Anti-NSP drug-like compounds, such as TP29, sinefungin and oral methioninase.
14. Electricity-based therapies built upon the model discovered and used by Nikola Tesla, with the purpose of stimulating the cholecalciferol-based activatory pathways into the host immune system.
15. Electricity-based therapy, perhaps using models developed by Nikola Tesla
16. Frequency-based microbial targeting, perhaps using models developed by Dr. Rife

Conclusion

The innate and adaptive immune departments represent two autonomous, yet paradoxically interdependent regions of the overall immune system of organs. The innate immune system represents the periphery, whilst the adaptive immune system represents the centre. Nonetheless, it is a paradox that in this case, the periphery represents the foundation for the centre, meaning that if the periphery falls, then the centre may eventually fall as well, and the viceversa may also occur. Such an aspect may reflect theories developed in philosophy with regards to the existing relationship of harmony and dependence between a central and a peripheral body of ideas, as well as in astronomical science with regards to the interdependence relationship between the Solar System and other systems of celestial bodies, as the emotional intelligence, perspective and behaviour of the principal living

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organisms of the Earth may also influence specific astronomical events, given the powerful properties of the energy of love transmitted by the living organisms. Numerous scientific and philosophical researchers hypothesised that true, unconditional love represents the energy that is Universally powerful, and it may be that it is more powerful than light, thereby not being impossible that it exceeds even the force of black holes that attract light itself. Fullness of Universal love attracts order, stability and protection from natural and cosmic hazards, whilst a lack of Universal love may only attract disorder, instability and destructive natural and cosmic phenomena, as disorder and destruction represent the lack of order and assembly. In such a case, opposition in fact represents a lack of the proposition. Returning to the topic of the possible need to adjust vaccine research to novel contexts of microbial evolution, it is likewise increasingly possible that researchers will need to make natural immunity-based vaccines and vaccine adjuvants a broader topic of discussion and clinical research throughout the world, given the fact that the evolutionary processes of microbes against natural immunity "displayed no mercy", by causing widespread disruptions in the bridge of transmission between innate immune signalling and the adequate recruitment of central adaptive immune cells. Will the vaccine industry ultimately still manage to develop prophylactic and therapeutic agents as successful if insufficient attention is paid to the recent substantial developments of polymorphic viruses against the innate immune lines? The statistical probability that the medical preventive and therapeutic responses require a change of direction seems to be continuously increasing, as novel pathogenic agents seem to be increasingly capable of evading the host immune lines of recognition and defence.

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