Review of: "A Harmless Avian Vaccine Virus Could Be Developed into an Off-the-Shelf “Antibiotic” for Viruses"

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Potential competing interests: No potential competing interests to declare.

Comments on ‘A Harmless Avian Vaccine Virus Could Be Developed into an Off-the-Shelf “Antibiotic” for Viruses’

The article presents a novel application of Infectious Bursal Disease Virus (IBDV), a repurposed avirulent double-stranded (ds) RNA vaccine virus, which has been shown to markedly enhance the expression of type I interferon (IFN) genes. The IBDV superinfection therapy (SIT) has demonstrated its safety and efficacy against a spectrum of viral infections, including hepatitis A, B, and C viruses (HAV, HBV, HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpes zoster viruses (HZV). This approach could potentially control a majority of viral infections prior to the development of adaptive immunity. The safety and efficacy of a reverse-engineered novel IBDV viral drug candidate, strain R903/78, were reaffirmed in a short-term Phase I/II study involving herpes zoster patients. With the availability of an off-the-shelf, stockpiled R903/78 drug, it is conceivable that millions of deaths and the economic burden equivalent to the US$12 trillion spent globally in response to COVID-19 could be significantly reduced.

The concept of this study has a significant impact on the field. However, this manuscript could benefit from addressing the following issues and questions:

- Applicability:

The manuscript suggests that the administration of the IBDV drug leads to an increased expression of type I interferon (IFN), which may provide non-specific immunity against a variety of infections beyond the primary targets. This raises questions about the applicability of this method to other diseases, such as influenza, rabies, Lyme disease, HIV, Ebola, SARS, and plague.

Pathogen-Specific Immunity: While the enhanced IFN expression may offer broad protection, the immune response to different pathogens can vary significantly, and the method's effectiveness may need to be tailored to the unique characteristics of each disease.

Adaptive Immunity Requirements: For pathogens that rely heavily on adaptive immunity, such as HIV and Ebola, the role of non-specific immunity conferred by IFN upregulation must be carefully assessed. It is possible that this method may need to be combined with other treatments or vaccines to provide comprehensive protection.

Modifications for Other Infections: The process may indeed require modifications when applied to different infections. For instance, the dosage, administration route, or even the formulation of the IBDV drug might need to be adjusted to achieve

optimal results against various pathogens.

Clinical Trials and Research: To determine the applicability and effectiveness of this method across different diseases, extensive clinical trials and research are necessary. This will involve testing the method on various pathogens and evaluating its impact on both non-specific and specific immunity.

Long-Term Efficacy and Safety: It is also important to consider the long-term efficacy and safety of using the IBDV drug for non-specific immunity. Studies should be conducted to monitor potential side effects and the duration of immunity provided by this approach.

In summary, while the enhanced expression of type I interferon after the administration of the IBDV drug shows promise in providing non-specific immunity, its applicability to a range of diseases, including those that require adaptive immunity, must be thoroughly investigated. This will involve tailoring the method to specific pathogens, conducting extensive clinical trials, and assessing both the short-term and long-term implications of this approach.

- Novelty and Improvement:

The manuscript highlights the findings that the oral poliovirus vaccine (OPV) has the potential to reduce the morbidity of influenza virus infection by a factor of 3.8. Furthermore, the administration of OPV has been observed to expedite the healing process in genital herpes simplex virus infections. Notably, a single dose of bivalent OPV has been shown to significantly decrease the incidence of COVID-19 among 1115 healthy volunteers, aged between 18 and 65.

The findings imply that live attenuated vaccines have the potential to induce broad-spectrum immunity, safeguarding against various infections not limited to their intended disease targets. This raises the question of how this current approach surpasses traditional methods. It is crucial to delineate the precise distinctions and novel aspects of the current techniques in contrast to those that have been previously established. What distinguishes this strategy, and how does it propel the field forward?

- Reactivation:

The manuscript mentions that HCV dominance over HBV could, in turn, be terminated following the eradication of HCV by direct-acting antiviral (DAA) therapy. Consequently, HBV infection is often reactivated. Is this phenomenon applicable to IBDV administration as well?