

Commentary

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

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A repurposed apathogenic double stranded (ds) RNA vaccine virus, the infectious bursal disease virus (IBDV), significantly upregulates the expressions of type I interferon (IFN) genes. IBDV superinfection therapy (SIT) has been proven to be safe and effective against hepatitis A, B, and C viruses (HAV, HBV, HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpes zoster viruses (HZV). IBDV might be used to control most virus infections before adaptive immunity develops. The safety and efficacy of a reverse engineered new IBDV viral drug candidate, strain R903/78, could be reconfirmed in herpes zoster patients in a short-term Phase I/II study. With an off-the-shelf, stockpiled R903/78 drug, many millions of deaths and a repeat of the US\$12 trillion the world spent on COVID-19 could be mitigated.

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Holmes et al., predicted that during the next fifty years an important area for research in virology will be the competition of viruses. Viral interference should enable the development of better strategies for virus control^[1]. There is no need to wait fifty years because the idea of fighting fire with fire, i.e., using non-pathogenic viruses to control unrelated infections, has already been translated into a host-directed antiviral therapy and successfully tested against five different families of viruses^[2].

The objective of this article, therefore, is to argue that the infectious bursal disease virus (IBDV) drug candidate, strain R903/78 could be developed in to an off-the-shelf stockpiled post-infection antiviral drug with modest funding within a relatively short time. In the era of large-scale vaccine hesitancy and skepticism a broad-spectrum oral affordable antiviral drug could complement vaccination and improve

pandemic preparedness. Actually, vaccination alone will not be sufficient to control future pandemics caused by rapidly evolving RNA viruses. Let alone, that the frequency of zoonotic diseases is increasing because people exert pressures on nature, particularly via the huge livestock industry^[3].

Zoonotic diseases are some of the most common and/ or most dangerous diseases, including influenza, rabies, Lyme disease, HIV, Ebola, SARS, and plague. The ability of zoonotic pathogens to transmit to humans is behind the concept of One Health, postulating the interdependence between animal and human health and aiming at improving preparedness for emerging infectious diseases. Probably the greatest known zoonotic risk to human health worldwide presented by pandemic influenza. In the past 106 years there were already four influenza pandemics, and experts predict that another influenza pandemic is inevitable. In a few months, a pandemic flu strain could infect around 30% of the global population and could result in 200 million deaths during its first wave^[3].

The primary carriers of influenza are poultry and pigs. Close to 20 billion chickens and 1 billion pigs are produced annually worldwide, which are the primary drivers of influenza pandemic risk to humans. The low-pathogenic strain of wild birds can be transformed into a highly pathogenic form that can cause mass mortality in poultry and, potentially, in people. Pigs serve as the genetic engineering laboratory of nature. They are ideal mixing vessels, combining existing strains of influenza from birds or other animals, and transmit them to humans amplifying the pandemic risk. Livestock, therefore, is one of our 'blind spots in biodefense'^[4]. After COVID-19, we no longer have to imagine what an influenza pandemic would look like.

The fighting fire with fire idea has already been tested during the 1960s and 1970s. Large-scale clinical studies involving more than 60,000 individuals demonstrated that existing live vaccines can indeed protect against unrelated infections. Oral poliovirus vaccine (OPV) reduced morbidity of influenza virus infection 3.8-fold. OPV vaccination also had accelerating healing effect on genital herpes simplex virus infections. Based on these pivotal early studies, Chumakov et al., proposed that live vaccines may temporarily protect against COVID-19^[5]. This prediction was confirmed by Yagovkina et al., who demonstrated that a single dose of bivalent OPV significantly reduced the number of COVID-19 cases in 1115 healthy volunteers (aged 18 to 65). This is consistent with the hypothesis that live attenuated vaccines can induce non-specific protection against off-target infections^[6].

Clinical observations of natural viral interference paved the way for viral therapies. Hepatitis B virus (HBV) infection is often terminated after accidental coinfection by hepatitis C virus (HCV). HCV

dominance over HBV could in turn be terminated following eradication of HCV by direct-acting antiviral (DAA) therapy. Consequently, HBV infection is often reactivated. When both interfering viruses are pathogenic, disease (e.g., hepatitis) persists. Apathogenic viruses could however be exploited to control acute or chronic viral diseases. Such intentional coinfection is the *superinfection therapy* (SIT).

The IBDV drug candidate of SIT is orally administered to patients suffering from acute or chronic viral diseases. IBDV delivers its double stranded (ds) RNA cargo into host cells, where the dsRNA activates the native antiviral interferon (IFN) gene defense system via Toll-like receptors (TLRs). IBDV strongly induces IFN- β and IFN- λ , while IFN- γ is not induced. As IBDV did not lyse several mammalian cell lines, inflammation and antiviral efficacy are separated. In such a way, the therapeutic window is opened up such that IBDV maximizes antiviral efficacy with only minimal side effects^[7]. Repeated oral IBDV administration is required to maintain artificial viremia. This is feasible because a breakthrough infection can be achieved even in the presence of high levels of IBDV neutralizing antibodies. IBDV treatment never induced an excessive release of pro-inflammatory cytokines, even though chronic HBV or HCV patients with decompensated liver disease had high-level viremia, which is a key driver of the cytokine storm.

IBDV has been proven to be safe and effective in marmoset monkeys and more than 50 patients against hepatitis A, B, and C viruses (HAV, HBV, HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpes zoster virus (HZV)^[7]. The immunostimulatory power of IBDV is obvious to the naked eye, when a severe herpes zoster ophthalmicus (HZO) infection of the first author of this paper was healed within a few days.

The Safety and Efficacy of Reverse Engineered IBDV R903/78 Drug Candidate Could Be Reconfirmed in Herpes Zoster Patients

Attenuated IBDV has been used safely over 60 years in IBDV mass vaccination programs in the poultry industry. Although attenuated avian vaccine viruses carry only a very low risk of mutation associated zoonosis, it is a legitimate concern for the regulatory authorities. Therefore, an IBDV vaccine virus was recreated by reverse genetics technology as an artificial virus, the R903/78 drug candidate. This virus can be produced without labor-intensive re-plating in the event of the appearance of contaminating quasi-species. Experts of US National Institutes of Health-sponsored ACTIV public-private partnership concluded that the IBDV strain R903/78 shows merit as a potential treatment for COVID-19.

The crusting time of vesicles following a standard of care acyclovir monotherapy with acyclovir plus an add-on R903/78 combination therapy could be compared during a short-term (one week) Phase I/II study in herpes zoster patients. The long-term safety and efficacy of the R903/78 drug candidate could be evaluated in virally suppressed HBeAg-negative chronic hepatitis B (CHB) patients. Those CHB patients who could not achieve functional cure during R903/78 monotherapy, should be treated by sequential ultra-low dose ipilimumab plus nivolumab therapy (see in^[7]).

Over the last fifty years the paradigm-changing idea of using non-pathogenic viruses to control viral diseases was translated into experimental antiviral therapies. Notwithstanding, the therapeutic exploitation of viral competition has still been unfairly overlooked when another influenza pandemic is inevitable. The avian H5N1 influenza virus is currently spreading through dairy cows and other mammals with transmission to humans demonstrating that high density commercial farming of animals poses a major pandemic threat. As the most high-risk pandemic threat is the flu virus, it should be prioritized for resources. Development of the R903/78 drug candidate in to an off-the-shelf stockpiled broad-spectrum post-infection antiviral drug could mitigate future pandemic deaths. This way, a repeat of the US\$12 trillion the world spent on COVID-19 could also be reduced.

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Conflicts of interest

Tibor Bakacs declares stock/stock options from HepC Inc. and he is also a shareholder of HepC Inc. Konstantin Chumakov has nothing to declare.

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