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Advanced drug delivery systems can assist in managing influenza virus infection: A hypothesis

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ABSTRACT

Outbreaks of influenza infections in the past have severely impacted global health and socioeconomic growth. Antivirals and vaccines are remarkable medical innovations that have been successful in reducing the rates of morbidity and mortality from this disease. However, the relentless emergence of drug resistance has led to a worrisome increase in the trend of influenza outbreaks, characterized by worsened clinical outcomes as well as increased economic burden. This has prompted the need for breakthrough innovations that can effectively manage influenza outbreaks. This article provides an insight into a novel hypothesis that describes how the integration of nanomedicine, with the development of drugs and vaccines can potentially enhance body immune response and the efficacies of anti-viral therapeutics to combat influenza infections.

Background

Infectious diseases are among the leading causes of mortality worldwide [1–3]. Outbreaks of such infectious diseases may be rampant and widespread, massively impacting global health and socioeconomic growth [3]. Viral infections, in particular, have affected millions across the globe. Key strategies in the delivery of effective treatment have been impeded due to several critical factors, including drug resistance [4]. These have resulted in a greater burden on public health systems, due to increased costs, that are primarily associated with frequent drug dosing, as well as, unaffordable medical care [5]. Such phenomena can be seen in the recent global outbreak of SARS-CoV-2 (COVID-19) infection, whereby, the absence of effective antivirals and vaccines have largely contributed to the high transmission rate of the disease [6,7].

Apart from COVID-19, influenza is another infectious disease that ranks high as one of the deadliest, characterized by a remarkably high rate of transmission that could cause a rapid spread. It is estimated that influenza kills approximately 500 thousand people yearly [4,8]. Killed virus vaccine as an intramuscular injection and attenuated live vaccine as a nasal spray, are the two most widely known vaccines for this deadly virus [9]. In the recent years, an increasing trend of influenza outbreaks have been observed, prompting medical researchers to design and develop suitable vaccines and novel therapeutic modalities [10]. Despite the availability of vaccines that may protect individuals from well-matched strains, it is well-known that the influenza virus has high mutation rates, resulting in frequent mismatches due to antigenic drift and shift, thereby, necessitating the development of a new vaccine every few years [11]. However, the development of a new vaccine is time-consuming. In addition, vaccine-development remains mostly applicable to developed countries, attributing to the cost factor involved. Moreover, long term use of standalone anti-influenza drugs and vaccines are often associated with adverse reactions and other shortcomings, that limit their effective clinical applications [12]. For instance, although the neuraminidase inhibitor oseltamivir has been

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widely employed as an anti-influenza drug, it was found that the drug does not offer benefits in patients with pre-existing medical conditions [12,13]. Besides, despite the suppression of influenza A virus replication from the usage of standalone rimantadine and amantadine, they are found to be ineffective against influenza B virus. Increased resistance of these drugs towards the influenza H3N2 subtype has also been observed in the recent years [12,14]. On the other hand, hypersensitivity and allergic reactions may also occur in the use of standalone vaccines, which are likely triggered by the component of such vaccines, such as egg protein [15]. Furthermore, instability of antigenic component of standalone vaccines as well as immune tolerance will also lead to reduced efficacy of these vaccines [16]. To sum up, all these shortcomings have hindered the effective management of influenza. Hence, newer technologies have been explored to overcome these limitations, which could address the raising concerns against outbreaks of viral infectious diseases. In this article, we aim to introduce a novel hypothesis that describes the potentials of nanomedicine-based approach in managing influenza viral infections, justified by several recent studies conducted in this field of research.

The hypothesis

A novel approach integrating nanomedicine with drug development, for drugs and vaccines that would treat influenza offers a promising direction to achieve higher goals in influenza research, as it may produce advanced nanosystems with optimised bio-physicochemical properties, leading to the eventual eradication of the influenza virus [12,17].

Evaluation of the hypothesis

Although, various drugs and vaccines have been reportedly identified as management options for influenza, these have not achieved their ideal efficacies. This is attributed to the rapid emergence of resistant viral strains and adverse reactions due to prolonged use of antivirals, as well as the unique ability of influenza viruses in host-switching and to evade antiviral measures [12,18]. Along with other obstacles such as poor drug solubility and poor permeability across biological barriers that impede the full therapeutic potential of anti-influenza drugs, these pose significant challenges in the effective management of influenza [19]. Thus, the development of novel innovative strategies for managing influenza is imperative to avoid any unfavourable public health and socioeconomic impact. Nanomedicine refers to the application of nanostructured materials, essentially, for the diagnosis, treatment, and prevention of diseases [20–24]. A diverse range of nanomaterials has been employed for the development of influenza vaccines and delivery systems for anti-influenza therapeutics [17,25]. Here, we present several types of nanomaterials that are commonly utilized in the management of influenza (Fig. 1).

Virus-like particles

Virus-like particles (VLPs) are spherical supramolecular assemblies produced by the expression of viral envelope or capsid proteins. Typically, VLPs mimic the natural assemblies of the antigenic epitopes of their corresponding viruses, but may not contain any infectious genetic material. This significant feature of VLPs permits the immune system to recognize VLPs similar to the original virus to promote efficient phagocytosis by antigen presenting cells, thereby, conferring cross-protection against multiple influenza virus serotypes via induction of humoral and cellular immune responses [11,26].

Self-assembling protein nanoparticles

Self-assembling protein nanoparticles (SAPNPs) have also been widely employed as a platform for influenza vaccine development. They are obtained from oligomerized monomeric proteins and may often display antigens in a repetitive array. This would induce a strong humoral immune response. SAPNPs could also be custom engineered to obtain comparable diameters to those of the original viruses. Coupled with their ability to allow the incorporation of CD4 and CD8 epitopes into their core, they could act as strong T cell immunogens. Besides, recent advancements have enabled the association of flagellin molecules into SAPNPs to trigger Toll-like receptor 5-based immunity [27].

Desolvation-driven nanoparticles

Desolvation-driven protein nanoparticles are another type of nanostructures formed via aggregation of protein molecules, as a result of altered physical or chemical conditions. These nanostructures may undergo crosslinking with multiple proteins on their surfaces, producing nanosystems with multiple layers that may accommodate various immunogens that present different antigens, thus providing a synergistic immune response [11].

Polymeric nanoparticles

Polymeric nanoparticles are commonly utilised in the delivery of anti-influenza drugs and vaccines. These are particularly attractive due to their biodegradability and biocompatibility, as well as, adjustable properties that allows incorporation of various drugs and antigens within them [17,28–31]. For drug delivery, surface modifications of nanosystems with hydrophilic polymers such as polyethylene glycol are crucial to minimize non-specific interactions with serum proteins, as well as, to evade phagocytotic uptake, thereby, prolonging the half-life and improved pharmacokinetic profile of such anti-influenza drugs [5,32,33]. Vaccine-delivery using polymeric nanoparticles has shown to induce useful anti-inflammatory responses and facilitate cross-protective antibody and T cell immune responses. Typically, these are formulated by mixing polymers such as poly(lactic-co-glycolic acid) with influenza epitopes in a solvent [11,32]. Boesteanu *et al.*, developed a universal vaccine by encapsulating live influenza virus in a biopolymer and delivered it to experimental mice subcutaneously. The use of alginate biopolymer to encapsulate the live virus was an effort aimed at providing an additional layer of protection through live virus aerosols. The vaccine was found to be safe, whereby, it protected the mice from heterosubtypical fatal abnormalities and triggered strong CD8 + T immune responses [34]. Fluquit (STP 702), a polymer-based nanotherapeutic substance from Sirnaomics Inc. is currently under preclinical evaluation. This formulation incorporates siRNA and targets the H5N1 (avian flu) and H1N1 (swine flu) influenza, while, cervisil (STP909), a nanobased drug candidate, encapsulates siRNA for the treatment of HPV16 and HPV18.

Inorganic nanoparticles

Inorganic nanoparticles have also gained considerable attention for their potential to improve therapeutic outcomes, drug biodistribution, as well as, drug pharmacokinetics [35]. Among them, gold nanoparticles (AuNPs) are one of the most widely employed inorganic nanomaterials in vaccine development [36]. Their properties are generally attributed to their physical nature, which allows surface conjugation of target antigens and adjuvants at high densities leading to an improved antigen presentation. Studies have demonstrated that AuNPs can be readily internalized by dendritic cells and macrophages, which lead to their activation. Furthermore, AuNPs are inert in nature, therefore, they do not elicit any carrier-specific immune response post-immunization, which makes them an appealing platform for nanovaccine engineering [26,37].

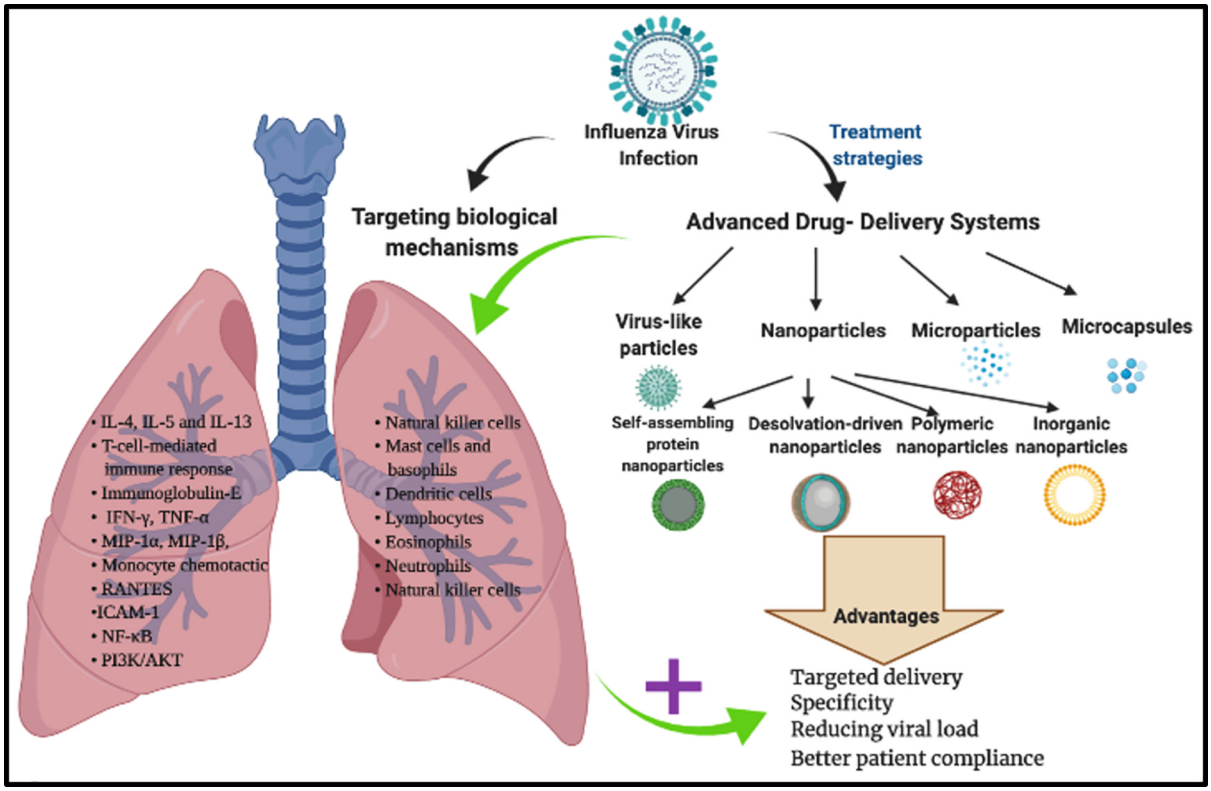

Fig. 1. Various drug delivery strategies employed in the management of Influenza.

Microparticles

Microparticles can be an ideal delivery system for the design of oral vaccines in managing influenza. Microparticles are small free flowing particles which consist of natural or synthetic polymers with diameters ranging from 1 to 1000 μm. Studies have found that DNA-adsorbed cationic microparticles are capable of inducing enhanced immune response in contrast to standalone DNA [38]. Besides, studies also demonstrated that microparticles exhibited efficient DNA adsorption and has high loading capacity which enables them to deliver several plasmids simultaneously to fight viral infections. In addition, microparticles can protect the antigens and keep them intact when passing through the stomach [16,38]. Chen *et al.,* developed acetylated dextran microparticles encapsulating M2e and cGAMP, which presented robust immune responses as well as cross reactivity against various influenza virus strains, suggesting that microparticles can be developed into a powerful and effective vaccine delivery system [39].

Microcapsules

Microcapsules have been widely demonstrated as a useful tool for delivery of genetic materials for treatment of various diseases. Specifically, layer-by-layer assembled hollow polyelectrolytes microcapsules has gained tremendous attention in the management of influenza due to their biomimetic property, as well as their unique engineered features such as shape, size, thickness, composition, and their ability to incorporate multiple types of biomolecules [40]. Gao *et al.,* formulated a layer-by-layer assembled hybrid inorganic–organic microcapsules encapsulating three different types of siRNAs to target influenza H1N1 virus. Significant suppression of viral nucleoprotein levels was observed, leading to inhibition of influenza virus production [41]. These results suggested that microcapsules can be developed into an advanced antiviral biomolecules delivery system for managing influenza virus infections, attributed to their low toxicity and high cellular uptake, as well as efficient intracellular delivery as the loaded biomolecules can be protected from premature degradation [41,42].

Dendrimers

Dendrimers are another type of nanomaterial that have been explored for their potential application in the delivery of antigenic molecules in the management of influenza. Dendrimers are three-dimensional, branched and star-shaped delivery systems that possess unique properties such as great water solubility, good biocompatibility, and low polydispersity index [43–49]. Polypropyleneimine and polyaminoamine dendrimers are the most utilized for vaccine delivery against influenza virus, whereby a dose of dendrimer encapsulating various antigens has been found to elicit powerful antibody and T-cell responses against influenza H1N1 virus [44]. Studies have shown that dendrimers are able to overcome resistance and exhibit high uptake by the host cells which allows them to release antigenic molecules at their targeted site, thus inducing immunogenic response. Besides, it is possible to synthesize dendrimers with specific biological and physicochemical properties, as well as to customize the release mechanism of encapsulated molecules from dendrimers. Multiple ligands can also be conjugated, offering them with higher specificity and efficacy in the delivery of various drugs and vaccines [43,44,50,51]. Hence, these unique features of dendrimers make them particularly suitable as the candidates for developing novel drugs and vaccines delivery systems in the management of influenza viral infections.

Recent applications in influenza management

In the following section, we compiled some of the most recent studies conducted by various researchers to demonstrate the feasibility of nanomaterial use in the management of influenza with respect to their intrinsic properties and advantages.

Nanomaterial enhance bioavailability

Most drugs which are used in the treatment of influenza have low bioavailability due to poor solubility and permeability, thereby, requiring the administration of a higher dosage, which may subsequently lead to adverse drug reactions. For instance, saliphenylhalamide is a well-documented anti-influenza drug that inhibits the acidification of endosomes, but has limited clinical application due to its poor solubility [12]. Bimbo *et al.,* loaded saliphenylhalamide into thermally hydrocarbonized porous silicon nanoparticles and investigated the anti-influenza activity of this nanoformulation. Their findings suggested that, the porous silicon-based nanosystem improved the bioavailability of saliphenylhalamide and inhibited influenza A virus infection *in-vitro* with low cytotoxicity and greater stability. Furthermore, the findings from the study suggested that porous silicon nanoparticles may be utilized to improve the delivery of anti-influenza drugs to targeted cells [12,52]. Alghrair *et al.,* in their study, conjugated FluPep, an established inhibitor of influenza A virus infectivity, to gold and silver nanoparticles and their antiviral potencies were further evaluated. The study revealed that, the FluPep functionalised nanoparticles remained stable and the conjugation decreased IC_{50} values to about 10% in comparison to that of free FluPep. The findings further suggested that gold and silver nanoparticles may improve the solubility of functional peptides, thereby enhancing their biological activities to produce enhanced antiviral activity compared to free peptides. Therefore, utilization of inorganic nanoparticles may be a viable option to develop novel nanoformulations that may efficiently curb influenza infections [53]. Rungrojcharoenkit *et al.,* reported the preparation of influenza hemagglutinin subunit 2 (HA2) and nucleoprotein (NP) loaded trimethyl chitosan nanoparticles (TMCNPs), where they measured the immunity responses of the nanoparticles in primary human intranasal epithelial cells. The findings revealed a significant induction of cytokines and chemokines in HA2 and NP-loaded nanoparticles treated cells in contrast to free HA2 and NP alone. TMCNPs also assisted in effective delivery of HA2 and NP proteins to the cells, leading to a remarkable reduction in the replication of the influenza virus *in-vitro*. This may be attributed to the highly water-soluble and cationic properties of TMCNPs, which resulted in an increased retention time of HA2 and NP proteins at mucosal sites [26,54].

Nanomaterials possess biomimetic property

Biomimetic property of nanomaterials could be crucial in the design of influenza vaccines, as it allows them to effectively trigger innate immune responses against multiple strains of influenza virus. Wang *et al.,* encapsulated 2′,3′-cyclic guanosine monophosphate-adenosine monophosphate in pulmonary surfactant-biomimetic liposomes (PS-cGAMP) to activate the stimulator of interferon genes (STING). PS-cGAMP demonstrated the activation of immune cells and alveolar epithelial cells via the STING pathway without breaching the pulmonary surfactant barrier, resulting in a broad spectrum of cross-protection against influenza viruses [55]. Besides, Wang *et al.,* had further fabricated double layered protein nanoparticles via ethanol desolvation and chemical crosslinking of influenza matrix protein 2 ectodomain-neuraminidase (M2e-NA) recombinant proteins. The findings demonstrated that, the layered M2e-NA nanoparticles induced a strong cytotoxic T cell response, contributing to long-lasting immune protection. This may be possibly due to the repetitive antigenic surfaces that mimic influenza pathogenic structures, which had activated the host immune system to fight against the pathogens. Therefore, layered protein nanoparticles could be utilized in the design of a universal influenza vaccine, or could be used as the synergistic component of such vaccines for further enhancement of protection against influenza infections [56]. The benefits of biomimetic nanoparticles were also investigated by Lee *et al.*, whereby, a hemagglutinin (HA)-displayed polymeric nanoball has been showed to promote HA-specific immune activation in an experimental mice model. HA is a highly conserved surface protein found in various influenza virus strains. Such repetitive HAs mimic the natural structure of influenza virus, resulting in cross-protection and effective prevention from influenza infections [57].

Nanomaterials possess unique physical properties

A study by Kim *et al.,* fabricated porous gold nanoparticles (PoAuNPs) to target HA. A remarkable decline in the infectivity of various influenza strains was observed, which corresponded with increased cell viability of 96.8% as compared to 33.9% in non-treated cells. Further evaluation showed that PoAuNPs suppressed viral entry process and inhibited viral membrane fusion via conformational deformation of HA. Such an effective suppression of influenza infections may be due to the presence of a large surface area on PoAuNPs that allows greater interactions with HA [58]. Another study by Ghaffari *et al.* evaluated the antiviral activity of PEGylated zinc oxide (ZnO) nanoparticles against influenza H1N1 viral strains. It was found that at their highest non-toxic concentration, PEGylated ZnO nanoparticles demonstrated an enhanced viral inhibition rate of 94.6%, thereby offering themselves as novel and promising antiviral agents against influenza H1N1 infections. This phenomenon is attributed to the intrinsic physical property of poly(ethylene glycol) (PEG) which confers increased surface hydrophilicity, thus reducing cellular uptake and clearance of these nanoparticles [59].

Clinical trials

Although there have been multiple pre-clinical studies performed on the use of nanomaterials in influenza, only a few have been tested for their efficacies in human subjects. One example is NanoFlu™, which is a quadrivalent VLP-based vaccine adjuvanted with Matrix-M™. It is currently in phase 3 clinical study to evaluate its immunogenicity and safety as compared to a licensed influenza vaccine, Fluzone® in older adults [60]. NanoFlu™ has previously completed phase 1 and 2 of clinical studies in 2018, whereby it was found that the VLP-based vaccine induced remarkable hemagglutinin inhibition responses that supressed influenza infectivity [26]. In a nutshell, clinical trials are essential to establish clear safety and efficacy profiles of novel nanomedicine-based influenza management. This is because the results obtained from cell line and animal models may vary drastically due to complex host interactions and metabolic responses, as any negative effects may not be observed in both *in-vitro* and *in-vivo* models.

Consequences of the hypothesis

The continued emergence and evolution of the influenza virus have brought stupendous challenges; even as conventional management approaches have been proven difficult in managing the disease. This hypothesis offers a novel approach to the management of influenza. It demonstrated how advanced drug delivery systems including nanomedicine and nanotechnology are poised to revolutionise influenza management strategies due to their remarkable biocompatibility and unique capabilities to increase bioavailability, improve targeting, and decreased toxicity, as well as, their capability to induce immune response in the body owing to their biomimetic property, Fig. 1. Nevertheless, studies on this area of research remains relatively limited. A major drawback of nanomedicine-based approach is that small changes in size and shape of nanomaterials, as well as chemical composition may significantly affect physical and chemical interactions, thereby influencing their toxicity profile and their practicability for biomedical applications. Therefore, with the growing applications of nanomaterials in the management of influenza, there is an urgent need to determine any potential short- and long-term health risks, such as to extrapolate the acute *in-vitro* findings to predict possible chronic and other unforeseen *in-vivo* effects [61,62]. Hence, it is hoped that this hypothesis

will trigger further exploration into nanomedicine-based approach to elucidate the in-depth mechanisms involved, along with their safety, to pave way for a paradigm shift in influenza management approaches.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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