Journal of Nanomedicine & Biotherapeutic Discovery

Bamezai and Lal , J Nanomedine Biotherapeutic Discov 2014, 4:2
DOI: 10.4172/2155-983X.1000e129

Editorial Open Access

Self-assembling Nanoparticle: A Strategy for Designing Universal Flu Vaccine

Anil K Bamezai* and Divakar Lal

Department of Biology, Villanova University, Villanova, USA

Annual outbreaks of the seasonal influenza virus are expected in our modern world and each outbreak has the potential to emerge as an epidemic. The 1918 Spanish Flu that infected approximately 500 million people worldwide and caused an estimated 50 million deaths. Taubenberger and Morens [1] and Brockwell-Staats et al. [2], illustrates the devastating consequences of uncontrolled influenza spread. Molecular changes occurring in the RNA genome of the influenza virus formulate the underlying basis of persistent annual outbreaks. Changes occur primarily in the Hemagglutinin (HA) and Neuraminidase (NA) genes either due to point mutations (known as antigenic drift) or by acquisition of new RNA gene segments (designated as antigenic shift) [3]. The latter is the result of the exchange of RNA gene segments during co-infection of another host (birds and swine) harboring a different strain(s) of the influenza virus. The new strain that arises each year is minimally challenged by the pre-existing immunity generated by the previous year's vaccination due to weak immunological memory responses. For a vaccine to work effectively, multiple defense mechanisms involving both innate and adaptive arms of the immune response must be stimulated. It is the cooperation between these branches of immunity that generates long lasting memory cells capable of protecting against future infections. A virus, having undergone antigenic drifts and shifts, evades the host's immune system due to the absence of a quick and robust memory response within that host. Instead, the host generates a slow and weak primary immune response which is inefficient in eliminating the virus. While lack of or weak memory response allows a mutated influenza virus to go unchallenged, the mutated virus may provoke abnormally elevated innate immunity. In at least one influenza epidemic, the mutated version of the influenza virus (H1N1) elicited heightened immune response resulting in the deaths of infected individuals [4,5]. Designing a universal vaccine that invokes effective memory response that facilitates rapid clearance of the virus and delivered cheaply to the populous will address a major public health concern.

Identifying conserved antigens and epitopes in addition to the previously identified mutated versions of HA and NA viral proteins from various influenza strains will be critical in designing a universal vaccine [6]. Matrix protein 2, a protein highly conserved in influenza A strains and involved in removing the viral coating upon entry into the body, is one such promising candidate [7]. Receptor binding modulator HA1 and viral membrane facilitator HA2 represent conserved HA epitopes [8] that may serve as targets for future research. Packaging these conserved and various mutated viral proteins in conjunction with an adjuvant is another critical step in vaccine development. Adjuvants are a critical component of the vaccine that triggers the innate immune response. Recent vaccination methods to combat influenza epidemics include the usage of Virus-Like Particles (VLPs), Trivalent Inactivated Vaccines (TIVs), and quadrivalent inactivated influenza vaccines (IIV). Polypeptide protein chains from viral capsids have natural structural features to aggregate into particles and are dubbed as VLPs. These particles are noninfectious but display structures similar to the HA and NA antigens of a particular influenza strain on their exterior surface [9]. TIVs rely on attenuated or inactivated viruses developed in chicken eggs to induce an immune response, but they usually require multiple doses to confer substantial protection [10]. Quadrivalent IIVs rely on the same principles as TIVs to confer protection against influenza, however, eliciting protection against one additional strain of influenza that TIV does not CDC [11]. While VLPs simply mimic the structure of the influenza vaccine, TIVs and quadrivalent IIVs actually feature antigenic proteins, which are then subsequently recognized as foreign by the body. These strategies rely on exploiting the physical features of the respective HA and NA proteins in a specified influenza strain. Unfortunately, all the above strategies fall short in multiple ways. First, these annual vaccines show variability in effectiveness on a yearly basis. Another drawback involves the high cost and effort required to stay ahead of an influenza epidemic. Recently researched and animal tested self-assembling nanoparticle vaccines may be the solution to achieve universality with adjuvant benefits while minimizing many of the shortcomings associated with traditional vaccines. Including conserved and mutated epitopes in the vaccine and generating a nanoparticle with adjuvant properties will facilitate a robust memory response against future influenza infections. The vaccine was produced as a recombinant hybrid protein with HA influenza antigen as one part and ferritin, an iron binding protein from *Helicobacter pylori,* the second part. Ferritin was critical for assembly of the protein in a spherical shape allowing for the self-assembly of the 24 subunits, generating a nanoparticle. Ferritin, part of the recombinant protein, formed the core and HA the outer part with trimeric spikes giving the particle an octahedral symmetry [12]. Deriving ferritin from *Helicobacter pylori* ensured the absence of cross-reactivity with mammalian ferritin [12]. A concoction of HA antigens and conserved epitopes in these self-assembled ferritin nanoparticles would be a step towards a universal vaccine.

Earlier efforts to generate nanoparticle-based vaccinations also hold promise. Transgenic HA produced in *Agrobacterium tumefaciens* coated on a silica-based nanoparticle, posesses inherent adjuvant properties [13]. Chitosan-based nanoparticles coat mucosal tissues with a vaccine, while using chitosan to propel the vaccine through the nasal cavity against ciliary activity [14]. Calcium phosphate (CaP) nanoparticles has capacity to encapsulate bacterial and viral unmethylated CpG DNA sequences capable of initiating innate immune response after getting recognized by TLR- 9 on host immune cells [15]. Incorporating unmethylated CpG in CaP nanoparticles induces a stronger antibody response as well [16]. Additionally, CaP enhances the functioning and maturation of dendritic cells, ultimately increasing $CD4^+$ and $CD8^+$ T-cell responses that are critical as well [15,17]. Using highly

***Corresponding author:** Anil K Bamezai, Department of Biology, Villanova University, USA, Tel: (610) 519-4847; E-mail: anil.bamezai@villanova.edu

Received March 01, 2014; **Accepted** March 03, 2014; **Published** March 05, 2014

Citation: Bamezai A, Lal D (2014) Self-assembling Nanoparticle: A Strategy for Designing Universal Flu Vaccine. J Nanomedine Biotherapeutic Discov 4: e129. doi:10.4172/2155-983X.1000e129

manipulative techniques, such as Particle Replication in Non-wetting Templates (PRINT®) Technology, researchers can gain an extraordinary ability to design influenza nanoparticle vaccines. Traditional vaccines have imposed challenges for controlling particle size, shape, and composition, while simultaneously eliciting high efficacy levels; PRINT technology, however, surpasses these impediments [18]. Eradicating irrelevant structural materials to increase the adjuvant carrying capacity via PRINT synthesis [18] may boost the immune response to create a more efficacious vaccine.

As traditional vaccines are phased out and replaced with nanoparticles in search for a universal influenza nanoparticle vaccine, challenges still lie ahead. One major challenge is the delivery route of the vaccine to maximize stimulation of both innate and cell-mediated adaptive arms of host's immune response. In addition, it is critical for a vaccine to stimulate the host to produce antibodies of a specific isotype that are effective in clearing the virus. Traditional inactivated vaccines are administered via intramuscular injection while attenuated vaccines are administered in an intranasal manner [19]. Notably, a limitation of using attenuated vaccines rests in the fact that individuals with weakened immune systems may not be recipients of such vaccines [10]. VLPs utilize intranasal and IM injections [20], but the manufacturing processes involving animal and insect cells [21] may prove to be burdensome and inefficient. Exploiting the self-assembling nature of the HA-ferritin nanoparticle [12] and packaging it with additional conserved epitopes along with adjuvants for either intramuscular delivery or new inhalable approaches will be a step forward towards generating a universal vaccine.

References

1. Taubenberger JK, Morens DM (2006) 1918 Influenza: the mother of all pandemics. Emerg Infect Dis 12: 15-22.
2. Brockwell-Staats C, Webster RG, Webby RJ (2009) Diversity of influenza viruses in swine and the emergence of a novel human pandemic influenza A. Influenza Other Respir Viruses 3: 207-213.
3. Carrat F, Flahault A (2007) Influenza vaccine: the challenge of antigenic drift. Vaccine 25: 6852-6862.
4. Taubenberger JK, Baltimore D, Doherty PC, Markel H, Morens DM, et al. (2012) Reconstruction of the 1918 influenza virus: unexpected rewards from the past. MBio.
5. Ye J, Sorrell EM, Cai Y, Shao H, Xu K, et al. (2010) Variations in the hemagglutinin of the 2009 H1N1 pandemic virus: potential for strains with altered virulence phenotype? PLoS Pathog 6: e1001145.
6. Krammer F, Palese P (2014) Universal influenza virus vaccines: need for clinical trials. Nat Immunol 15: 3-5.
7. Wang L, Zhang H, Compans RW, Wang BZ (2013) Universal Influenza Vaccines - A Short Review. Journal of Immunology and Clinical Research. Pp. 1-7.
8. Ekiert DC, Bhabha G, Elsliger MA, Friesen RH, Jongeneelen M, et al. (2009) Antibody recognition of a highly conserved influenza virus epitope. Science 324: 246-251.
9. Patterson DP, Rynda-Apple A, Harmsen AL, Harmsen AG, Douglas T (2013) Biomimetic antigenic nanoparticles elicit controlled protective immune response to influenza. ACS Nano 7: 3036-3044.
10. Offit PA (2013) How Are Vaccines Made? Retrieved February 1, 2014, from The Children's Hospital of Philadelphia.
11. CDC (2013) Seasonal Influenza Vaccine Safety: A Summary for Clinicians from Center for Disease Control and Prevention.
12. Kanekiyo M, Wei CJ, Yassine HM, McTamney PM, Boyington JC, et al. (2013) Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies. Nature 499: 102-106.
13. Neuhaus V, Schwarz K, Klee A, Seehase S, Forster C, et al. (2013) Functional Testing of an Inhalable Nanoparticle Based Influenza Vaccine Using a Human Precision Cut Lung Slice Technique. Public Library of Science ONE. Pp. 1-10.
14. Sawaengsak C, Mori Y, Yamanishi K, Mitrevej A, Sinhaipanid N (2013) Chitosan Nanoparticle Encapsulated Hemagglutinin-Split Influenza Virus Mucosal Vaccine. AAPS PharmSciTech Pp. 1-9.
15. Knuschke T, Sokolova V, Rotan O, Wadwa M, Tenbusch M, et al. (2013). Immunization with Biodegradable Nanoparticles Efficiently Induces Cellular Immunity and Protects against Influenza Virus Infecction. J Immunol 190: 6221-6229.
16. Zhou W, Moguche AO, Chiu D, Murali-Krishna K, Baneyx F (2013) Just-in-time vaccines: Biomineralized calcium phosphate core-immunogen shell nanoparticles induce long-lasting CD8+ T cell responses in mice. Nanomedicine.
17. Sokolova V, Knuschke T, Buer J, Westendorf AM, Epple M (2011) Quantitative determination of the composition of multi-shell calcium phosphate-oligonucleotide nanoparticles and their application for the activation of dendritic cells. Acta Biomater 7: 4029-4036.
18. Galloway AL, Murphy A, DeSimone JM, Di J, Hermann JP, et al. (2013) Development of a Nanoparticle-Based Influenza Vaccine Uzing the PRINT Technology. Nanomedicine 9: 523-531.
19. CDC (2013) Vaccine Information Statements (VIS) from Center for Disease Control and Prevention.
20. Galarza JM, Latham T, Cupo A (2005) Virus-like particle vaccine conferred complete protection against a lethal influenza virus challenge. Viral Immunol 18: 365-372.
21. Thompson CM, Petiot E, Lennaertz A, Henry O, Kamen AA (2013) Analytical technologies for influenza virus-like particle candidate vaccines: challenges and emerging approaches. Virol J 10: 141.