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Commentary

One Against All: A Broadly Influenza Neutralizing Man-made Monoclonal Antibody Passes Phase I

Xavier Saelens

Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium
Medical Biotechnology Center, VIB, Ghent, Belgium
Technologiepar 927, 9052 Ghent, Belgium

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Influenza affects us all. This respiratory disease is caused by influenza A and B viruses in humans and is well known to 'return' each year during the winter season in temperate climate zones. For most people "the flu" is a discomforting and self-limiting condition that keeps one in bed for a few days with fever, a sore throat, headache and muscle aches. Severe disease or even mortality occurs in a very low proportion of influenza virus-infected individuals: on average less than 0.1% in the case of seasonal influenza. During some of the past pandemics this percentage was significantly higher. People with pre-existing chronic pulmonary disease and the elderly have an increased risk of developing potentially life-threatening complications following infection with influenza virus.

In this issue of *EBioMedicine*, Visterra Inc., a biotechnology company based in Cambridge (Massachusetts, USA), reports on the safety and bio-distribution of a new drug candidate against influenza A (Wollacott et al., 2016). The tested drug is a human monoclonal antibody, named VIS410, that reacts with a conserved epitope in the stem of influenza A hemagglutinin (HA). Vaccines and antivirals are already marketed for influenza. Close to one billion doses of licensed influenza vaccines are used prophylactically each year. These vaccines are safe and can reduce disease and death caused by influenza viruses (Beyer et al., 2013). In addition, there are a number of small molecule antivirals against influenza on the market. These are most effective when applied prophylactically or as soon as possible after symptoms start (Jefferson et al., 2014). However, these interventions are not fail-proof and there are numerous efforts to develop influenza vaccines with increased, prolonged or broadened protective potential. Furthermore, the currently used anti-influenza drugs often give rise to resistant viruses and require daily intake to sustain effective concentrations in circulation. New antivirals that could overcome these shortcomings are thus on the wish list as well.

This report on VIS410 summarizes the findings of a double-blind, placebo-controlled phase 1 study that was performed in healthy adults (Wollacott et al., 2016). Volunteers received one dose of either placebo ($n = 11$) or 2, 5, 15, 30 or 50 mg/kg of VIS410 ($n = 30$ in total) by intravenous infusion over a minimum period of 2 h. The overall conclusion was that VIS410 was generally safe, although gastrointestinal symptoms (notably diarrhea) were reported in 10 out of 30 VIS410 recipients and none in the placebo group. Maximum serum concentrations of VIS410 ranged from 58.6 μg/mL at a 2 mg/kg dose to 1316 μg/mL at a 50 mg/kg dose and these were reached almost immediately after infusion. As expected for an IgG antibody, the serum half-life of the drug was approximately 14 days.

There is a tremendous interest in the development of broad influenza virus-neutralizing monoclonal antibodies and in vaccines that can induce such antibodies (Kanekiyo et al., 2013). Several companies, including Genentech and Crucell have completed early phase clinical studies with their candidate broadly reactive anti-HA stem human monoclonal antibodies. VIS410, however, is not just another HA-stem specific human monoclonal antibody. This human IgG1 monoclonal antibody is the result of man-made design and protein engineering and so is not derived from a natural source. In addition, VIS410's epitope in HA is based on a prediction made by an algorithm that searches for patches of surface exposed amino acids that are involved in multiple inter-residue interactions. Such amino acids are part of a so called significant interaction network (SIN) and are therefore likely to contribute crucially to the folding, stability and function of a protein. This implies a low tolerance for mutations at positions with a high SIN score and thus, in the context of influenza HA, high sequence conservation. VIS410 targets a conformational epitope in the stem of HA of group 1 (*e.g.* H1, H2, H5), and group 2 (*e.g.* H3 and H7) influenza viruses. The antibody can neutralize H1N1 and H3N2 but not H7N9 viruses *in vitro* (Baranovich et al., 2016; Tharakaraman et al., 2015). Nevertheless, VIS410 treatment protects mice against challenge with H7N9 virus and so, like other broadly-neutralizing antibodies, most likely depends on cooperation with Fcγ Receptors for *in vivo* protection (DiLillo et al., 2014). Whether influenza A viruses can evolve to escape from VIS410 protection remains to be determined.

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E-mail address: Xavier.saelens@vib-ugent.be.

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From a cost–benefit perspective the use of a recombinant monoclonal antibody-based therapy against influenza could be considered for elderly individuals because influenza-associated hospitalizations are highest in this age group (Thompson et al., 2004). In their phase I study report, Wollacott et al. applied a microsimulation method to estimate the potential benefit of prophylactic use of VIS410 in different age groups (Wollacott et al., 2016). This simulation suggested that starting prophylactic treatment eight weeks prior to the peak of an influenza epidemic, could reduce the risk of influenza A-related hospitalization of elderly individuals by 30.9%. If true in real life this would be impressive. Interestingly, elderly people already have higher concentrations of HA-stem specific antibodies in circulation compared to younger people (Nachbagauer et al., 2016). However, the levels of these natural antibodies are probably far below the levels of 1–2 mg/mL as proposed by Wollacott et al., so infusion of gram amounts of VIS410 per individual would be needed to reach that concentration. To apply this amount of antibody to even a fraction of the population will require considerable production and downstream processing facilities. Another concern is that VIS410 does not work against influenza B. Even though influenza B attack rates in the elderly are lower than those of H1N1 and H3N2 (Bedford et al., 2015), the proposed prophylactic treatment should ultimately also include an antibody against this virus.

Antibodies are among the most frequently used protein therapeutics; mostly for the treatment of cancer and chronic inflammatory diseases. Interest to develop antibodies to prevent and treat infectious diseases is clearly on the rise. Given the extraordinary antigenic flexibility of human influenza viruses, it will be wise to bet on more than one horse and to come up with an antibody combination therapy that targets multiple conserved epitopes in the viral membrane proteins. VIS410 may well fit in such a blend.

Competing Interest

Part of the research in the group of Xavier Saelens is supported by a research collaboration with Sanofi Pasteur.

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