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AN ADENOVIRUS-BASED VACCINE MANUFACTURING TECHNOLOGY PLATFORM FOR MUCOSAL OR PARENTERAL IMMUNIZATION AGAINST POULTRY DISEASES IN SUB-SAHARAN AFRICA

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Developing novel vaccine technology platforms to respond to emergency situations such as pandemic threats or zoonotic diseases is a worldwide high priority. Public health at a global scale is frequently influenced by the risk of transmission of infectious diseases from wildlife and domestic animals. Thus, veterinary vaccination and animal health monitoring are highly relevant for the deployment of a preventative global policy in the context of “one world, one health”.

In regions such as Sub-Saharan Africa, farmers’ activities are frequently affected by the impact of diseases in poultry such as avian influenza and Newcastle disease (ND). ND is one of the most critical, with several outbreaks per year. Currently, protection is provided by vaccination with live vaccines produced only in embryonated eggs, with limitations related to egg supply and the possibility of virus shedding by vaccinated poultry, leading to disease in non-vaccinated birds.

The purpose of this work was to develop an adenovirus (Ad) vectored vaccine platform technology suitable for the rapid adaptation to ND or other avian viral threats. The project involved the phylogenetic analysis of local isolates of Newcastle disease virus (NDV) and the construction of adenoviral vectors expressing the F and HN antigens from NDV genotype VI, either as individual antigens or in bicistronic vectors. Remarkably, adenoviral rescue and generation of primary stocks was streamlined by developing a novel procedure for single step amplification in suspension cultures. Antigens expression was evaluated in vitro in HEK293SF and chicken fibroblast (DF-1) cells. The candidate vaccine production relies on a cost-effective process using HEK293SF suspension cells and serum-free medium, leading to high-cell density productive infection in bioreactors. The production phase with the different Ad variants was initiated in shake-flasks at cell densities of 2 x10⁶ cells/ml in Xell AG HEK-GM medium. Scalability was further demonstrated in batch and fed-bath controlled bioreactor runs (1-3L) with production at cell densities over 4x10⁶ cells/ml and infectious titers consistently above 5x10⁸ – 1x10⁹ TCID₅₀/mL (>10¹⁰VP/mL). Viruses were harvested at around 45hpi and subjected to cost-effective clarification and purification steps. They were formulated and stocked at 10¹⁰TCID₅₀/mL for animal immunization experiments. ELISA and hemagglutination inhibition assays on the analysis of the humoral immune response elicited in mice and chicken showed the induction of specific, functional IgG or IgY anti-F antibodies against NDV. Groups of chickens were further immunized twice with 1 x 10¹⁰ TCID₅₀ of the vectors, and full protection against a lethal NDV challenge was provided by the Ad-F-CMV vector expressing the F antigen. Mucosal protection through intranasal vaccination of chicken has also led to 100% protective efficacy against ND. Formulation, safety and stability studies have been also conducted. These results consolidate the bases of a streamlined, scalable, and robust vaccine manufacturing process for its deployment in the low- and medium-income countries affected by ND.