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A Modified Vaccinia Ankara Virus (MVA) Vaccine Expressing African Horse Sickness Virus (AHSV) VP2 Protects Against AHSV Challenge in an IFNAR −/− Mouse Model

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Abstract

African horse sickness (AHS) is a lethal viral disease of equids, which is transmitted by *Culicoides* midges that become infected after biting a viraemic host. The use of live attenuated vaccines has been vital for the control of this disease in endemic regions. However, there are safety concerns over their use in non-endemic countries. Research efforts over the last two decades have therefore focused on developing alternative vaccines based on recombinant baculovirus or live viral vectors expressing structural components of the AHS virion. However, ethical and financial considerations, relating to the use of infected horses in high biosecurity installations, have made progress very slow. We have therefore assessed the potential of an experimental mouse-model for AHSV infection for vaccine and immunology research. We initially characterised AHSV infection in this model, then tested the protective efficacy of a recombinant vaccine based on modified vaccinia Ankara expressing AHS-4 VP2 (MVA-VP2).

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Introduction

African horse sickness (AHS) is a lethal viral disease of equids, caused by an orbivirus that is closely related to bluetongue virus (BTV). The African horsesickness virus (AHSV) is transmitted by biting midges of the genus *Culicoides*, which become infected after taking a blood meal from an infected and viraemic host. [1]. The disease is endemic to Sub-Saharan Africa but sporadic outbreaks have had devastating effects in Northern Africa, Europe, Middle East and India [2,3,4,5].

The AHSV genome is composed of ten linear segments of dsRNA, encoding seven structural proteins VP1 to VP7 and four non-structural proteins NS1, NS2, NS3 and NS3a [6]. The AHSV particle is organised as three concentric layers of proteins. The outer capsid, which is composed of two proteins, VP2 and VP5, interacts with neutralizing antibodies that are generated during infection of the mammalian host. There are nine distinct serotypes of AHSV, which can be distinguished in virus or serum neutralisation tests (VNT or SNT). The identity of each serotype is controlled primarily by the amino acid sequence of VP2, which contains the majority of neutralising epitopes and is the principal serotype-specific antigen of AHSV [7,8]. Animals that survive infection by a single AHSV serotype are subsequently protected against the homologous type, although they can still be infected by the other serotypes. The AHSV core consists of two major proteins that form distinct capsid layers: VP7 forms the core surface layer; while VP3 forms the innermost 'subcore' shell. The subcore also contains three minor proteins, VP1, VP4 and VP6 that form core associated transcriptase complexes, and surrounds the 10 segments of the viral genome (numbered segment 1 to segment 10 [Seg-1 to Seg-10] in order of decreasing molecular weight)[6].

One of the most effective intervention strategies to combat AHS is vaccination, allowing horses to survive in endemic regions. Live attenuated strains of AHSV that were developed as vaccines have been available for more than 60 years and are still routinely used in South Africa and other endemic countries [9]. However this type of vaccines causes viraemia in the host and therefore has the potential to be transmitted in the field [10]. Recent experience with similar 'live' BTV vaccines in Europe shows that they can also exchange genome segments (reassort) with field strains [11,12], potentially resulting in reversion to virulence. Since these live vaccines work by causing 'infection' in the host, it is also difficult, or impossible, to design serological assays that will reliably distinguish (naturally) infected and vaccinated animals ('DIVA'), making surveillance more difficult or more expensive. These drawbacks are considered to make the live vaccines unsuitable for