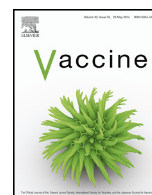
Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



A cytomegalovirus-based vaccine provides long-lasting protection against lethal Ebola virus challenge after a single dose

Q1 Yoshimi Tsuda [a,1], Christopher J. Parkins [b,2], Patrizia Caposio [b,2], Friederike Feldmann [c], Sara Botto [b], Susan Ball [d], Ilhem Messaoudi [e], Luka Cicin-Sain [f], Heinz Feldmann [a], Michael A. Jarvis [g,*]

[a] Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, USA
[b] Vaccine and Gene Therapy Institute, Oregon Health & Sciences University, Portland, Oregon, USA
[c] Rocky Mountain Veterinary Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, USA
[d] Centre for Biostatistics, Bioinformatics and Biomarkers, University of Plymouth, Devon, UK
Q2 [e] School of Medicine, University of California, Riverside, USA
[f] Helmholtz Centre for Infection Research, Braunschweig, Germany
Q3 [g] School of Biomedical and Healthcare Sciences University of Plymouth, Devon, UK

ARTICLE INFO

Article history:
Received 4 November 2014
Received in revised form 6 March 2015
Accepted 11 March 2015
Available online xxx

Keywords:
Ebolavirus
Vaccine
Disseminating
Great apes
Cytomegalovirus
Mouse
Protection
Durable
Ebola

ABSTRACT

Ebola virus (*Zaire ebolavirus*; EBOV) is a highly lethal hemorrhagic disease virus that most recently was responsible for two independent 2014 outbreaks in multiple countries in Western Africa, and the Democratic Republic of the Congo, respectively. Herein, we show that a cytomegalovirus (CMV)-based vaccine provides durable protective immunity from Ebola virus following a single vaccine dose. This study has implications for human vaccination against ebolaviruses, as well as for development of a 'disseminating' vaccine to target these viruses in wild African great apes.

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Q5 The original zoonotic source of the 2014 Ebola virus (*Zaire ebolavirus*; EBOV) outbreak in Western Africa is currently unclear [1,2]. Following transmission into the human population, the chain of ebolavirus infection is maintained by human-to-human transmission. Contact with wild animals serves as a main conduit for the initial zoonotic transmission of ebolaviruses into the human population [2–7]. Fruit bats are believed to be one potential source of human infection, and direct contact or exposure to environments inhabited and frequented by bats has been associated with human outbreaks [2,4,7]. Great apes (western lowland gorillas and chimpanzees) are a second significant source of transmission due, in large part, to the bushmeat trade which drives humans and wild animals together within an environment conducive to zoonotic transmission (i.e., hunting and butchering) [3–5]. Consistent with the importance of this route for zoonotic ebolavirus transmission, a 2014 EBOV outbreak in the Boende Health Zone in the Equateur Province in the Democratic Republic of Congo (DRC), independent from the West Africa epidemic, was a result of handling and preparation of bushmeat [8]. Ebolaviruses are also highly lethal in African great apes, and are regarded as a major threat to the survival of chimpanzees and gorillas in the wild [3,5,9–12].

Vaccination of great apes has been proposed as one strategy to decrease the transmission of ebolaviruses to humans, whilst at the same time also protecting these wild animal populations from the devastating effects of these viruses [4,13,14]. We recently proposed the use of a cytomegalovirus (CMV)-based 'disseminating' vaccine as one approach to achieve vaccine coverage in the inaccessible

Q4 * Corresponding author. Tel.: +44 1752584456.
E-mail addresses: michael.jarvis@plymouth.ac.uk, michael.jarvis@cantab.net (M.A. Jarvis).
[1] Present address: Department of Microbiology, Graduate School of Medicine, Hokkaido University, Sapporo, 060-8638, Japan.
[2] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.vaccine.2015.03.029
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Please cite this article in press as: Tsuda Y, et al. A cytomegalovirus-based vaccine provides long-lasting protection against lethal Ebola virus challenge after a single dose. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.03.029

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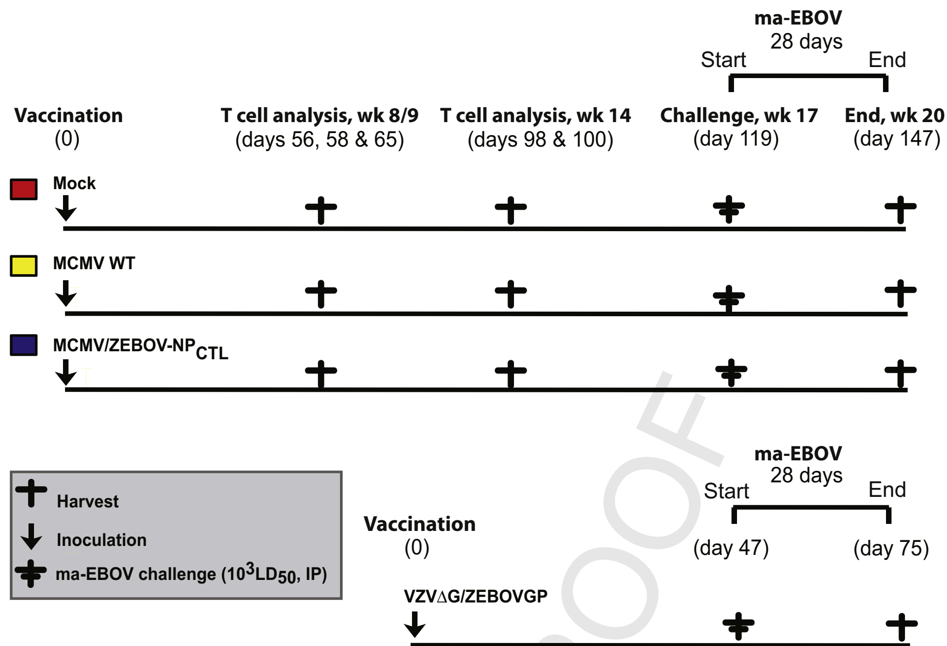

Fig. 1. Schematic showing mouse groups and sampling regimen in ma-EBOV challenge study of MCMV/ZEBOV-NP_{CTL}. C57BL/6 ($H2^b$-restricted) mice were immunized using a single IP dose of 5×10^5 pfu of MCMV/ZEBOV-NP_{CTL}. Control groups received MCMV WT or diluent (Mock). Splenocytes were harvested for analysis of T cell responses in groups of mice at times indicated (week 8/9: days 56, 58, 65 post-vaccination, and prior to challenge: days 96 and 100 post-vaccination). Antigen specific T cells were assayed by using ICS with a 6 h incubation in the presence of BFA with peptide. After 119 days (approx. 4 months) post-vaccination, mice were challenged with 1×10^3 LD_{50} ma-EBOV IP and disease course was followed for 28 days. VZVΔG/ZEBOVGP vaccinated mice served as a vaccine efficacy control group, and received a single IP dose of VZVΔG/ZEBOVGP (5×10^5 pfu) prior to the ma-EBOV challenge (47 days later).

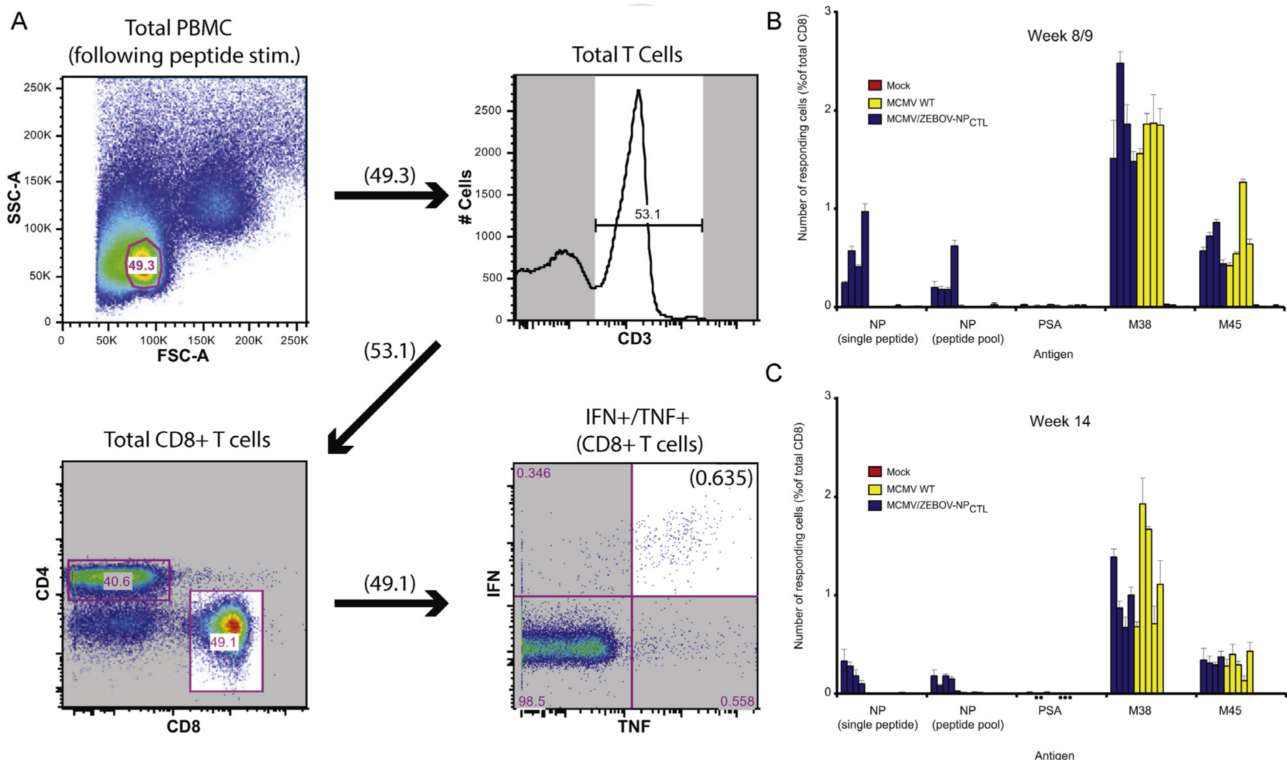

Fig. 2. $CD8^+$ T cell responses following immunization with MCMV/$ZEBOV_{CTL}$. Female C57BL/6 $H2^b$-restricted mice were immunized IP using a single inoculation of 5×10^5 pfu of MCMV/ZEBOV-NP_{CTL}. Control groups received MCMV WT (5×10^5 pfu) or diluent (Mock). Splenocytes were harvested for analysis of T cell responses. (A) Schematic showing gating strategy for ICS. NP-specific T cells for a representative MCMV/ZEBOV-NP_{CTL} vaccinated mouse is shown. (B) 8/9 weeks (days 56, 58 and 65 post-vaccination), and (C) week 14 (days 98 and 100 post-vaccination). T cells were analyzed by using ICS with a 6 h incubation in the presence of BFA with indicated peptide as previously described [14]. Human prostate-specific antigen (PSA) is an irrelevant control peptide [20], and NP (peptide pool) is an overlapping peptide pool (15-mer, 5 amino acid overlap) representing the full length EBOV NP protein. Levels of responding (IFNγ and TNFα double-positive) $CD8^+$ T cells in individual mice are shown. All mice receiving MCMV had $CD8^+$ T cell responses against MCMV M38 and M45, MCMV endogenous 'inflationary' and 'non-inflationary' antigens, respectively. Mock-infected mice showed no MCMV-specific T cell responses as expected. All MCMV/ZEBOV-NP_{CTL} immunized mice showed significant CD8-restricted T cell responses against the NP target antigen (2-tailed *t*-test, $p < 0.05$) consistent with previous results [14]. All mice were 29 weeks old at time of vaccination other than the Mock group assessed at Week 14, which were 21 weeks old. • = not tested.

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