A NOVEL APPROACH FOR DEVELOPING SAFE AND SINGLE DOSE VACCINES FOR EMERGING INFECTIOUS DISEASES

Preclinical Efficacy of Ebola, Marburg and Lassa Vaccines as examples

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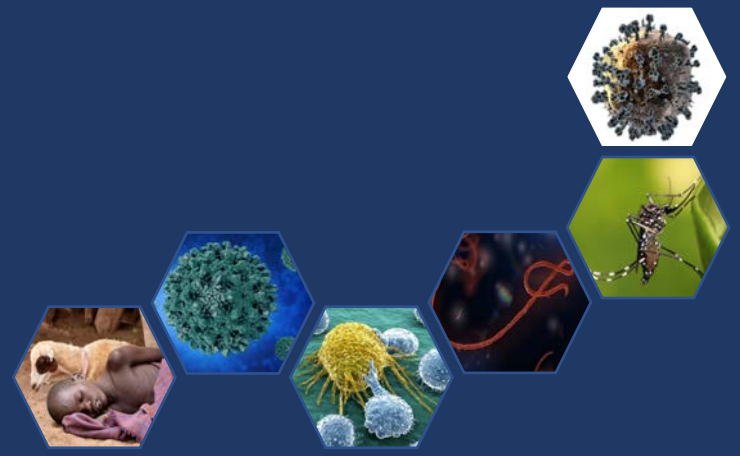
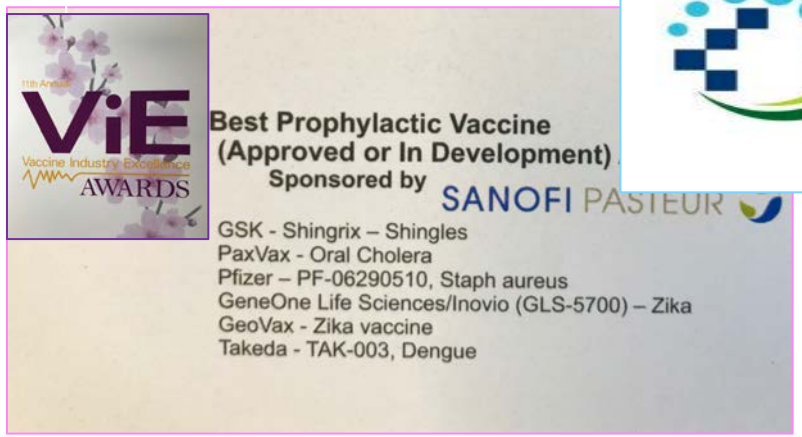
July 15 2019



GeoVax; 2018 Winner of Best Biotech Award, Finalists for Best Prophylactic Vaccine and Buzz of Bio

Winner of Best Biotech Award 2018



2019, 12th Vaccine Industry Excellence (ViE) Awards held at 19th World Vaccine Congress

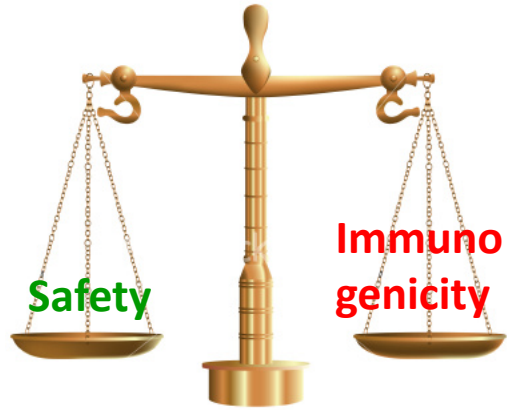
- GeoVax selected as Finalist in two award categories:
  - Best Therapeutic Vaccine Award; GeoVax MVA-VLP-MUC1
  - Best New Vaccine Technology Award; GeoVax Vaccine Platform

Topics

- **MVA-VLP Vector Technology Platform**
  - Key Features and Competitive Advantages
- **Pipeline**
  - Current Disease Targets Utilizing the MVA-(VLP) Platform and Major Collaborators
- **Research and Development**
  - HIV Vaccine
    - MVA-VLP Vs. RV144
  - Preclinical Programs
    - Singe Dose Vaccines for EID
      - Zika
      - Hemorrhagic Fever (Ebola, Marburg, and Lassa fever vaccines)
    - Cancer Vaccines
      - MUC1 Therapeutic Vaccine
    - Other ID Vaccines
      - Therapeutic HBV and HPV Vaccines
      - Prophylactic multi antigen Malaria vaccine
      - Others

GeoVax MVA-(VLP) Vaccine Platform – Key Features

- **Vector: MVA (Modified Vaccinia Ankara) Vector------→ SAFETY**
  - Originally developed as "**safer** smallpox vaccine" for the immunocompromised
    - Vaccinia virus passaged 570x in CEF, lost 15% (30kb) of genome
    - Replication-competent in avian cells, replication-defective in mammals (human vaccinees)
    - Tested in >120,000 people; recognized as safe
- **Antigen: Transgenes----→IMMUNOGENICITY**
  - VLP mimic native viral structure (e.g. HIV, Filoviruses, HBV, malaria, oncology, etc.)
  - Non-VLP, expressed and assembled as multimeric forms (e.g. Zika NS1, malaria, HPV)
- **Vector+Antigen=MVA-(VLP) Plug and Play Platform**
  - Combines the **safety** of MVA with **immunogenicity** of VLPs or multimeric proteins
    - Tested in 500 subjects (MVA-VLP-HIV), extremely safe and immunogenic
  - VLPs/proteins produced **in the cells of the recipient (*in vivo*)**
    - Display native forms of virus surface proteins, stimulate both Ab and T-cell responses
  - Manufacturing advantages
    - No purification issues associated with subunit/VLPs produced *in vitro*
    - No adjuvant needed
    - No vector immunity (no smallpox vaccine in routine use)

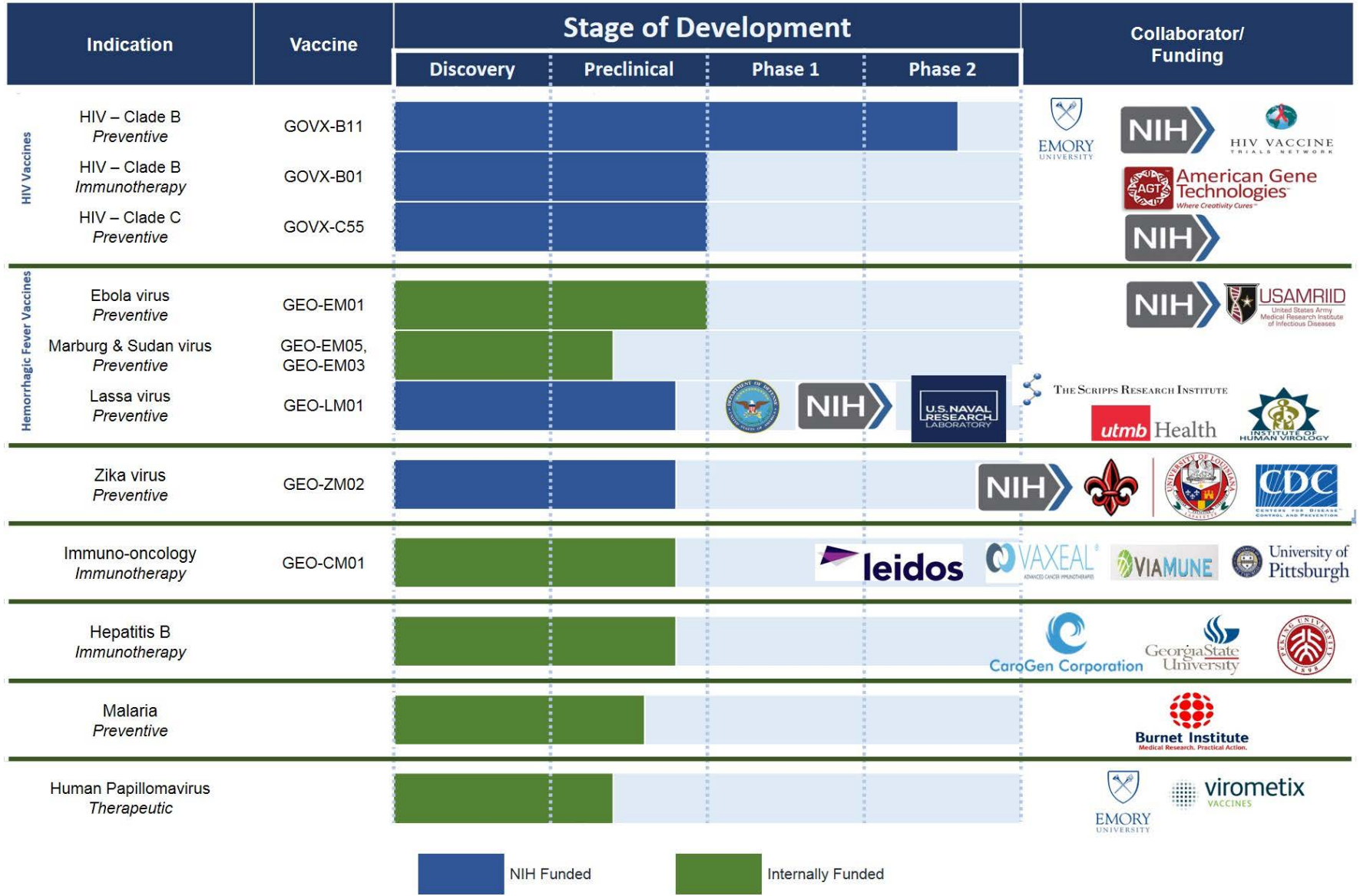


Attributes and/or Competitive Advantages of GeoVax MVA-VLP Vs. Other MVAs

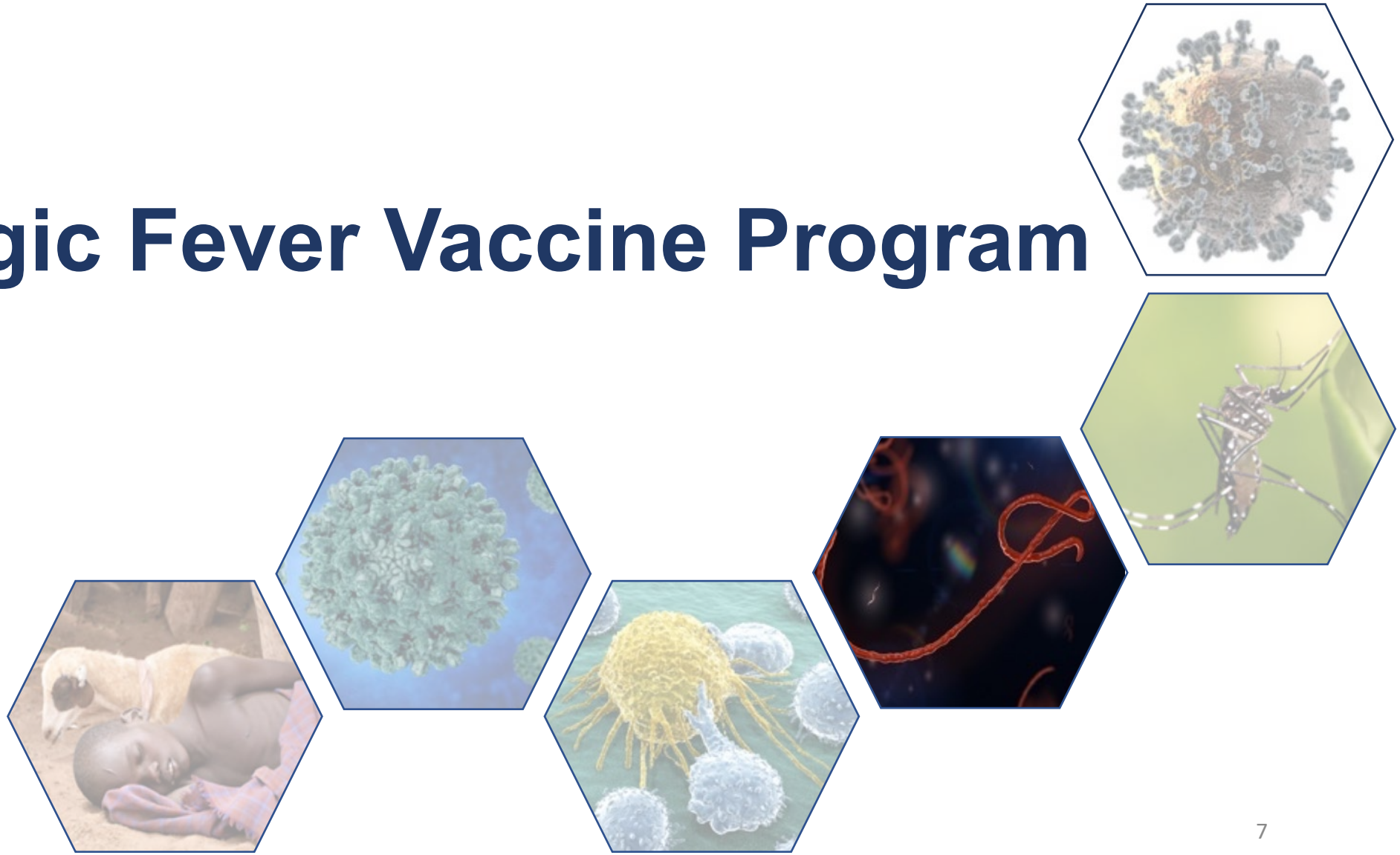
Vector	Single Dose	Immuno-genicity	Optimized VLP Formation	Modified Promoter	Optimized Seq./Read. Frames	Unique Insertion Sites	Transgene Stability	No Preexisting Immunity	Thermal Stability	Self Adjuvanted
GeoVax MVA-VLP	++	++	++	++	++	++	++	++	++	++
Other MVAs	-	+	+	+	+	+	?	++	++	++

++ High + Medium - Low ? No info

MVA-(VLP) Technology Pipeline & Collaborators



Hemorrhagic Fever Vaccine Program



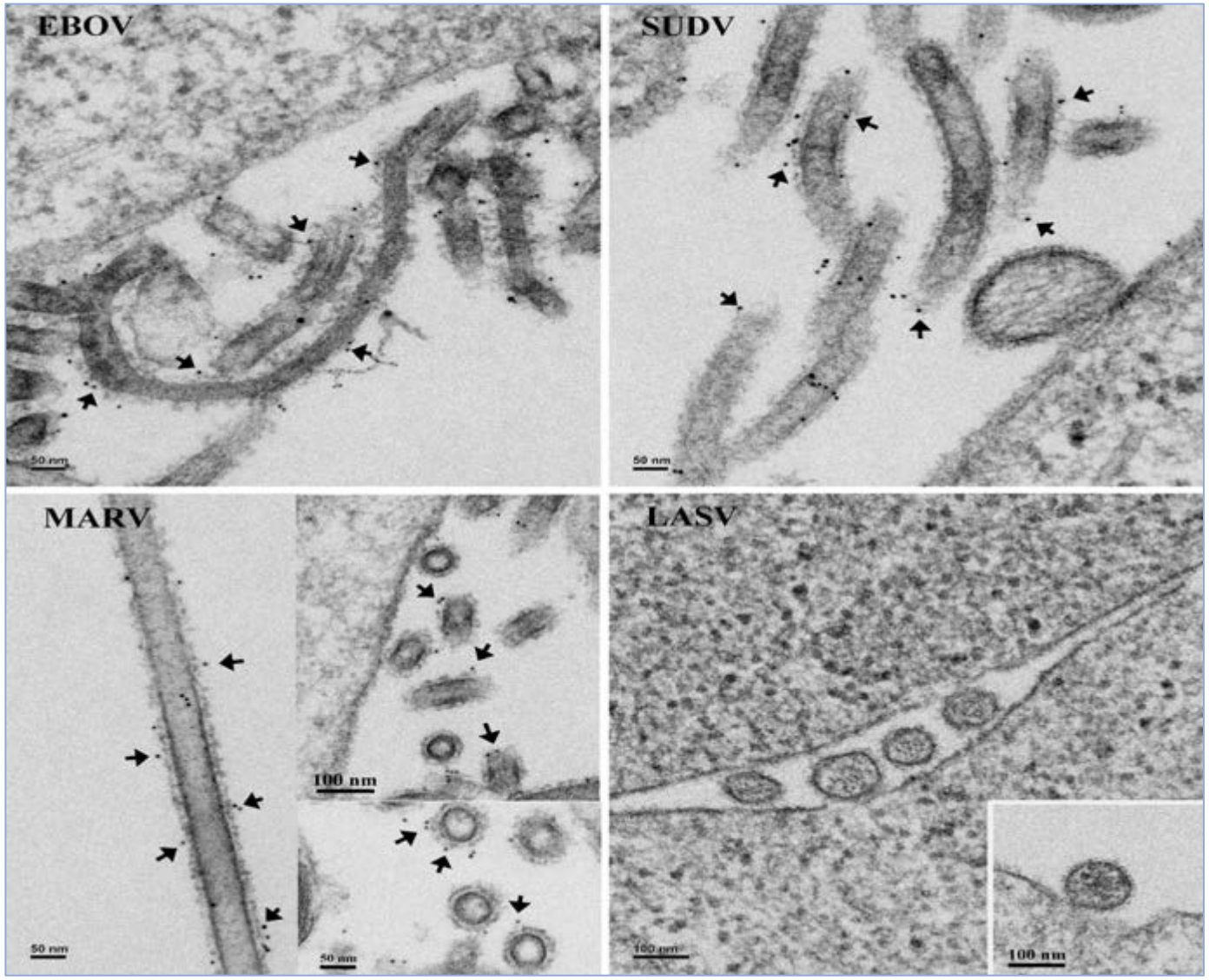
Hemorrhagic Fever Viruses Remain a Global Threat; The Need for a Broadly Protective Vaccine

- **Filoviruses - 30 Outbreaks Since 1976**
  - 2013-16, EVD, W Africa 28,616 cases, 11,310 deaths **(CFR 40%)**
  - 2017, EVD, DRC 18 cases, 3 deaths
  - 2018, Nov 24, EVD worst in DRC history; 365 confirmed cases, 236 confirmed deaths **(CFR 65%)**
    - Potential spreading to Uganda, Rwanda and S. Sudan
  - Additional outbreaks certain, indigenous reservoirs (fruit bats)
- **Arenaviruses - Lassa fever - endemic in the same region**
  - > 300,000 infections and 67,000 deaths annually
  - Nov 18, 2018: 562 confirmed, 144 deaths in Nigeria (CFR 26%)
- **An ideal vaccine to prevent or contain future HF outbreaks must;**
  - Address strain diversity by offering broad coverage
  - Activate both the humoral and cellular arms of the immune system
  - Be safe in subjects with underlying health issues
  - Preferably offer full protection after a single-dose

June 2016 End of Ebola Outbreak: The recovery and discharge of a 2-yo boy, the final patient in a latest flare-up in Liberia. His 5-yo brother recovered a week earlier

Apr 2018: Nigerian health authorities are calling the current outbreak of LF "unprecedented." LF is spread primarily through the urine or feces of the multimammate rats (Reuters/Simon Akam)

VLPs Produced by all 4 Components of the MVA-VLP-Tetravalent Vaccine



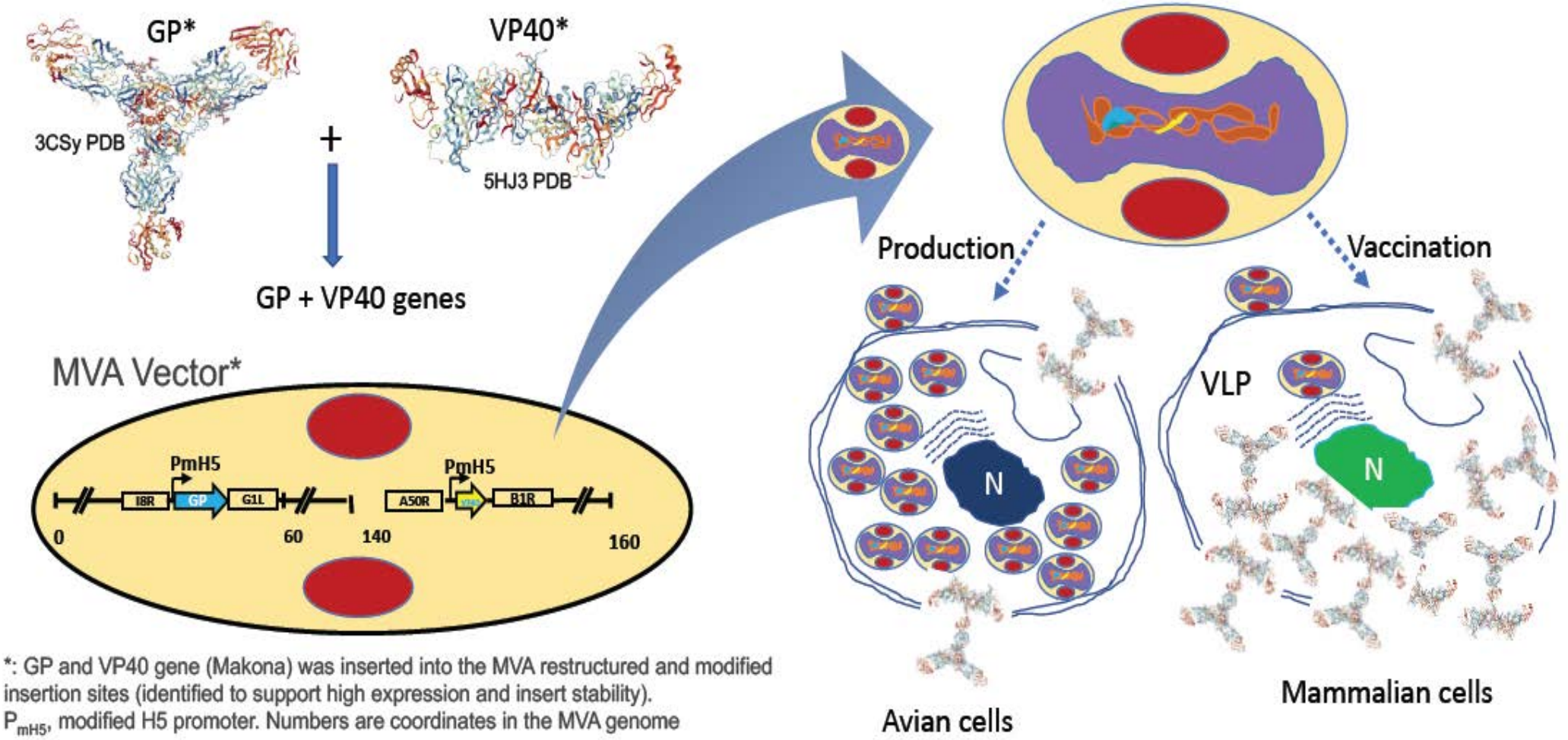
Electron micrographs of:

- MVA-VLP-EBOV
- MVA-VLP-SUDV
- MVA-VLP-MARV
- MVA-VLP-LASV

VLPs morphologically similar to wild type viruses

MVA-VLP Ebola Vaccine

Filovirus Antigens

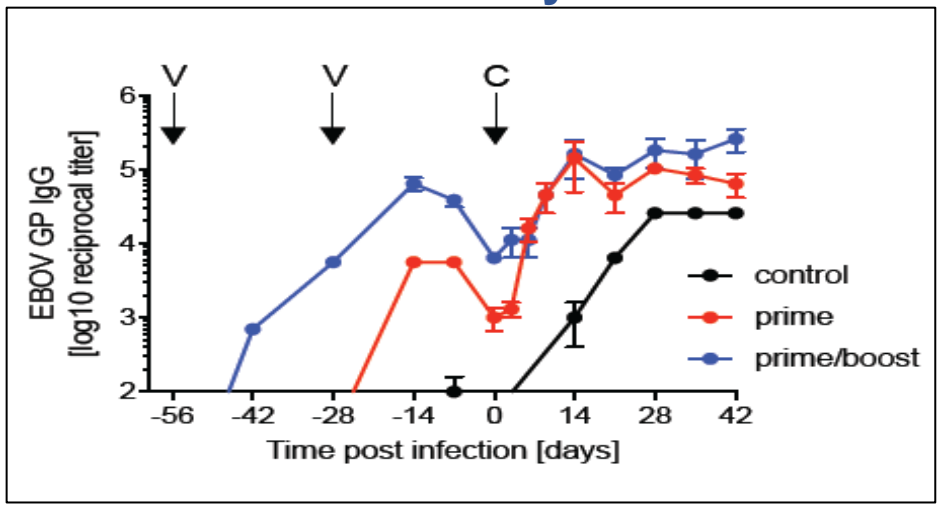


MVA-VLP-EBOV

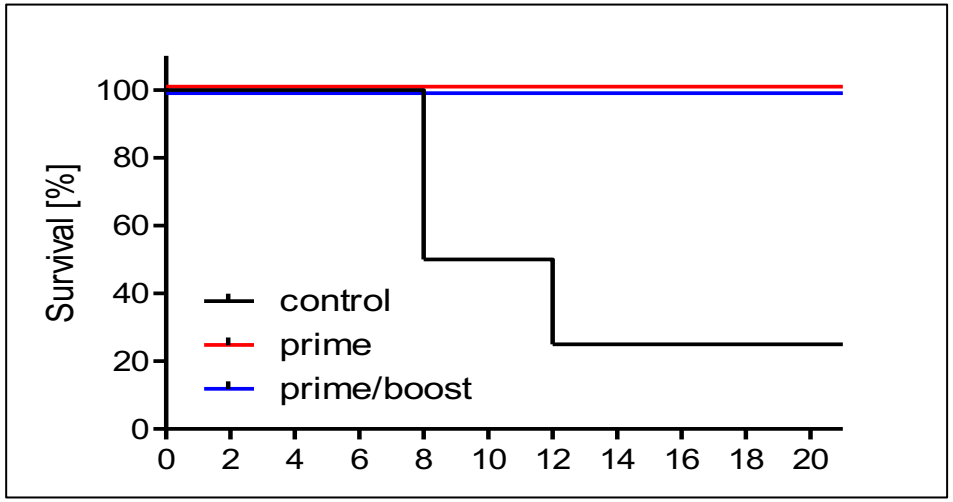
*: GP and VP40 gene (Makona) was inserted into the MVA restructured and modified insertion sites (identified to support high expression and insert stability).
P_{mH5}, modified H5 promoter. Numbers are coordinates in the MVA genome

Protective Efficacy of MVA-VLP Ebola Vaccine in Rhesus Monkeys*

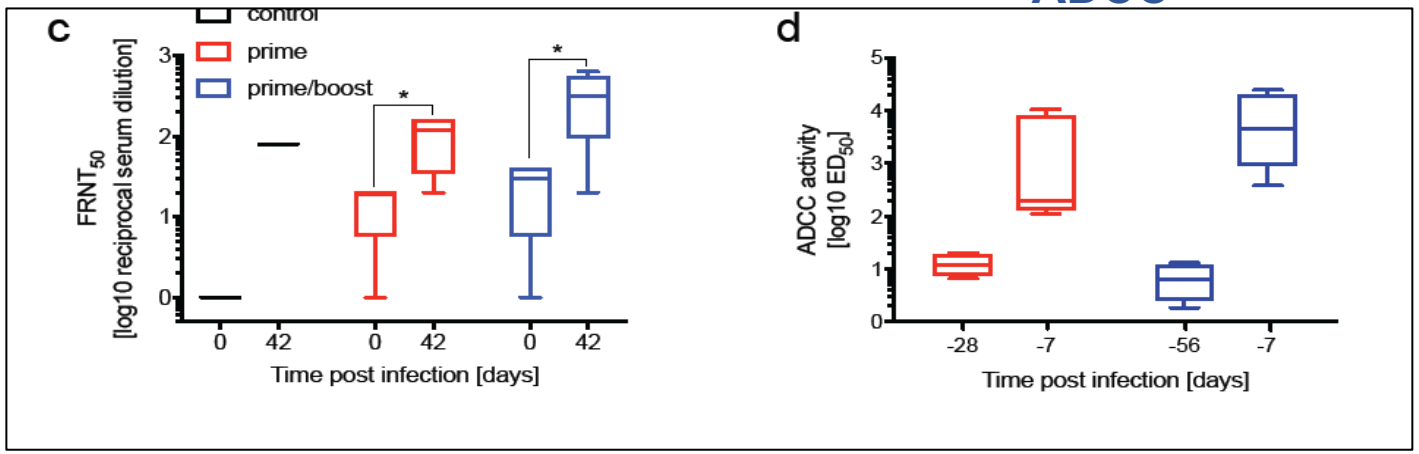
Antibody



Survival

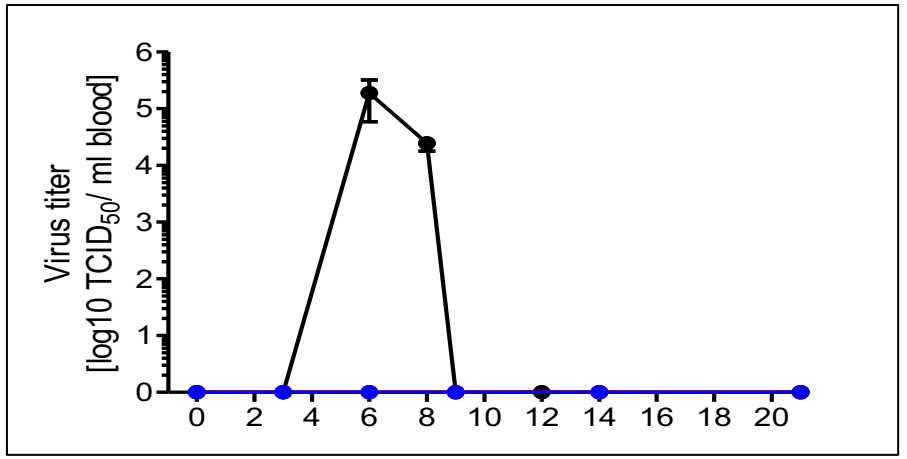


Neutralization



ADCC

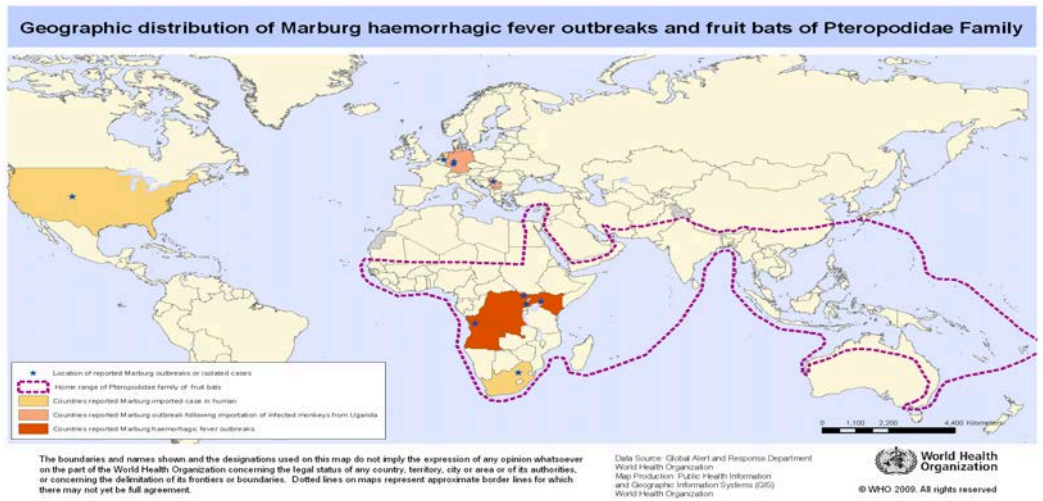
Viremia



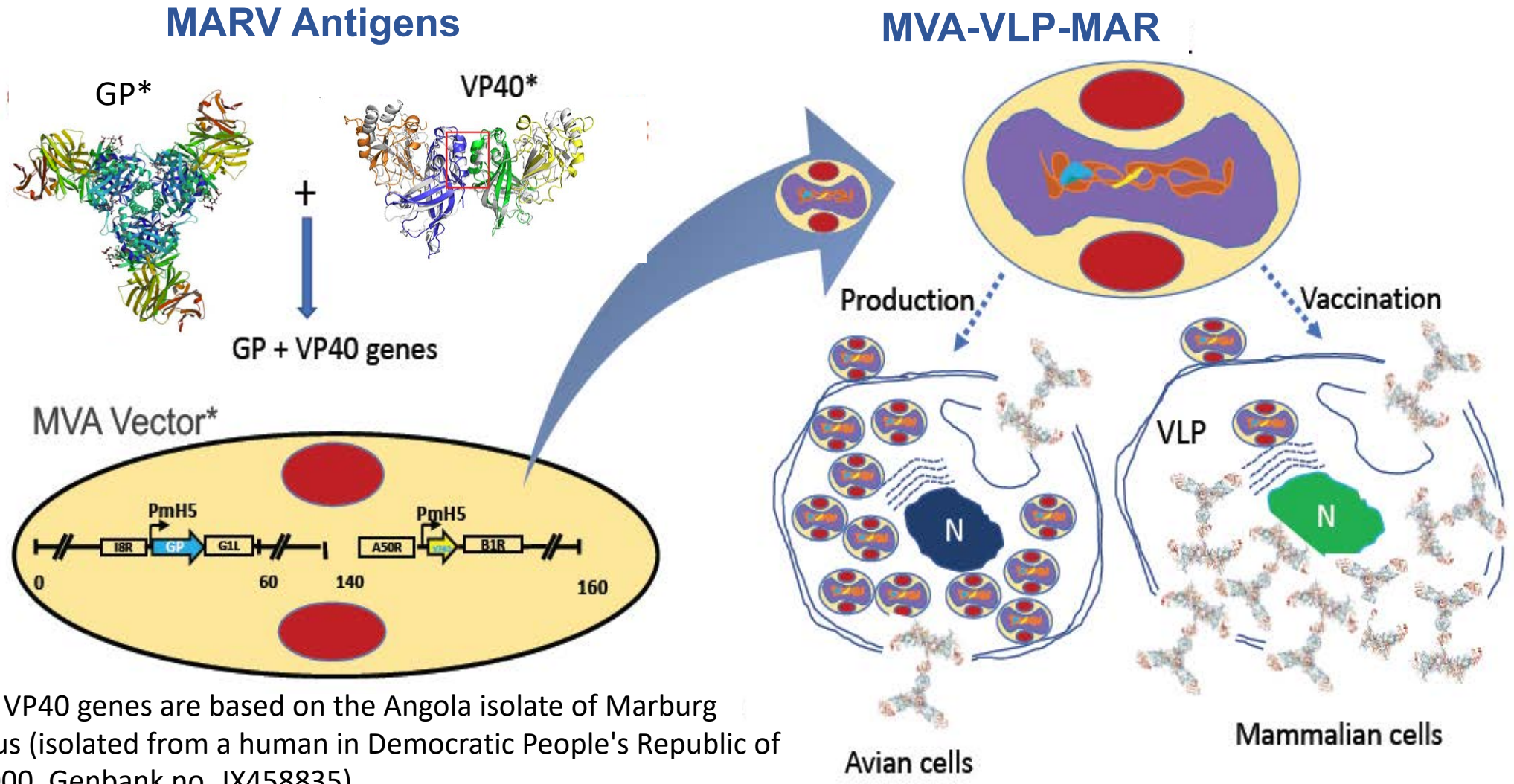
(*Domi et al, Nature's Scientific Reports 2018)

Development of MVA-VLP MAR vaccine Candidate

- **Disease:**
  - Marburg virus disease (MVD), first detected in 1967 after simultaneous outbreaks in Marburg and Frankfurt in Germany; and in Belgrade, Serbia
  - So far >12 outbreaks, most recent 2017, 3 cases in eastern Uganda, all have died
  - Virus causes a severe hemorrhagic fever, often fatal (CFR up to 88%), death occurs between 8 and 9 days after symptom onset, usually preceded by severe blood loss and shock
- **Virus:**
  - Marburg and Ebola viruses are both members of the Filoviridae family (filovirus)
  - Though caused by different viruses, the two diseases are clinically similar
  - Both diseases are Category A (high risk to national security, transmitted human to human, results in high mortality and potential to cause public panic)
- **Vector:**
  - Fruit bats considered as natural hosts
- **Human transmission:**
  - MV is transmitted to people from fruit bats and spreads among humans through human-to-human transmission (e.g. blood, secretions, organs/other bodily fluids, burial ceremonies, breast feeding, and sexual)
- **Vaccine and therapeutics:**
  - No proven treatment available (vaccine or therapeutics)
  - However, a range of potential treatments including blood products, immune therapies and drug therapies are currently being evaluated
  - Supportive care – rehydration with oral or intravenous fluids – and treatment of specific symptoms, improves survival



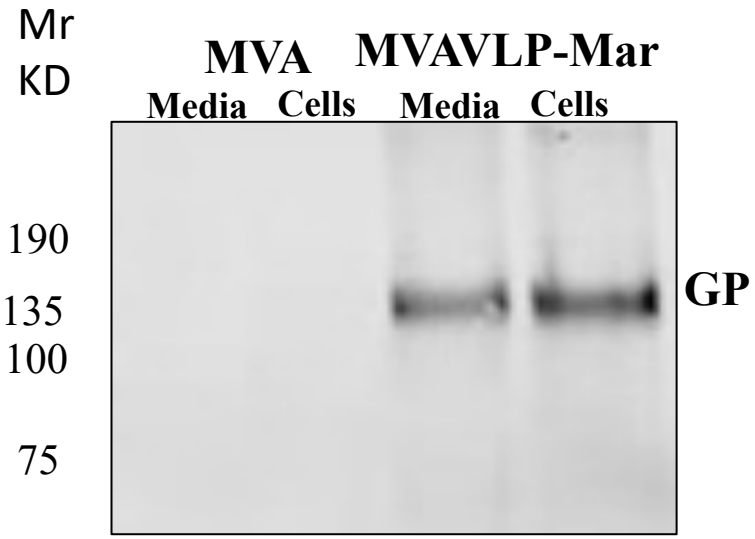
MVA-VLP Marburg Vaccine



The GP and VP40 genes are based on the Angola isolate of Marburg marburgvirus (isolated from a human in Democratic People's Republic of Congo in 2000, Genbank no. JX458835)

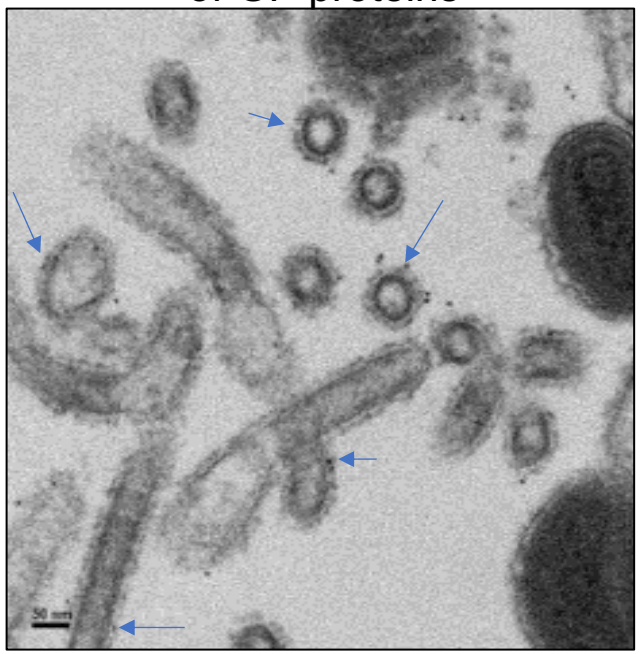
In Vitro Characterization of MVA-VLP-MAR and Immunogenicity In C57Bl/6 Mice

WB showing expression of MARV GP in infected cells*

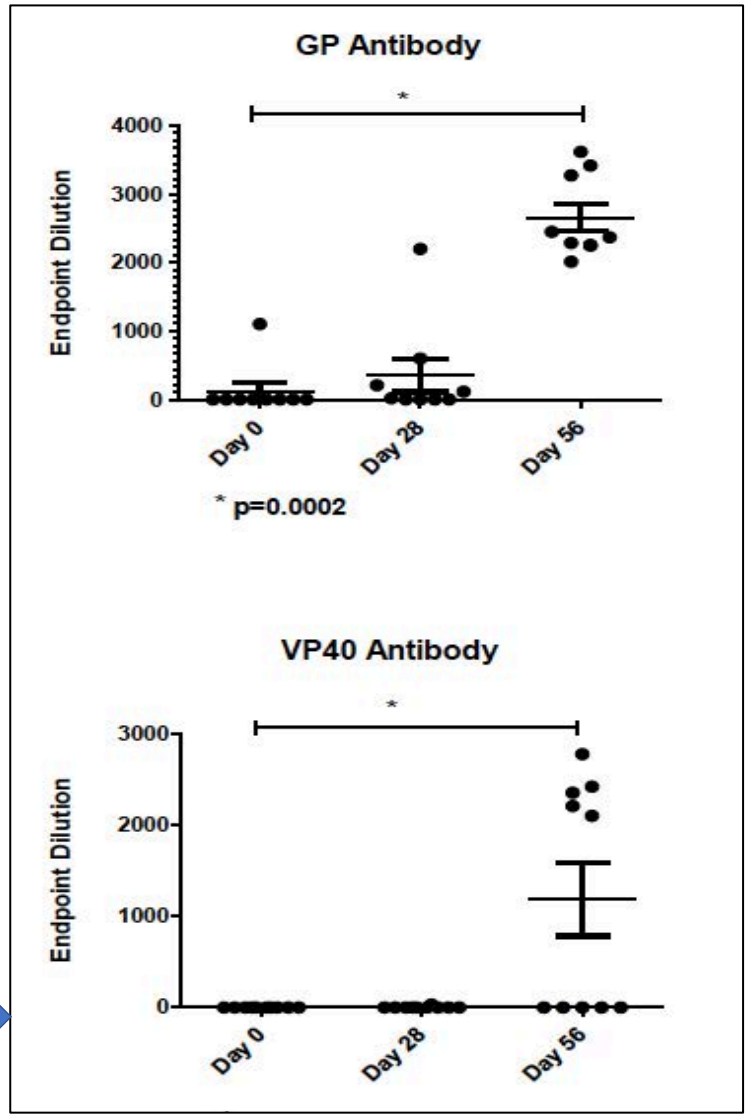


*: DF1 cells infected with an m.o.i. of 0.5 of MVA parental (MVA) or MVA-GPVP40 (MVA-VLP-MarV).
Anti-MAR GP Ab: IBT Bioservices, cat# 0303-007

EM showing MARV-VLP in infected cells. Arrows; immunogold staining of GP proteins



Immunogenicity of MVA-VLP-MARV in mice (N=10)
Vaccine Dose: 1x10e7 $TCID_{50}$
Schedule: Day 0, 28
Route: IM

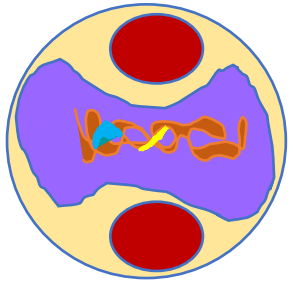


Efficacy Testing of MVA-VLP-MAR Vaccine in Hartley Guinea Pig Challenge Model

Design

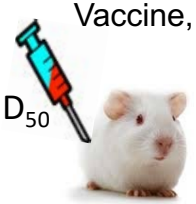
Groups	n
GEO-EM05 (vaccine) Prime/Boost	5
Saline	5

MVA-VLP-MARV



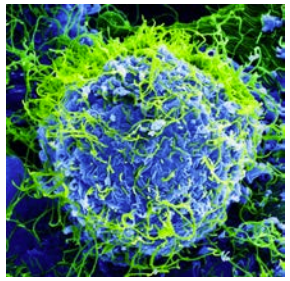
Vaccine, IM, prime/boost

1x10^8 $TCID_{50}$



MARV GP adapted Angola strain

Disease, including body weight, and survival monitored throughout 28d



Challenge, 1000 PFU

28 Days

- Weight loss
- Death

Day

0 14 28 42 56 58-66 84

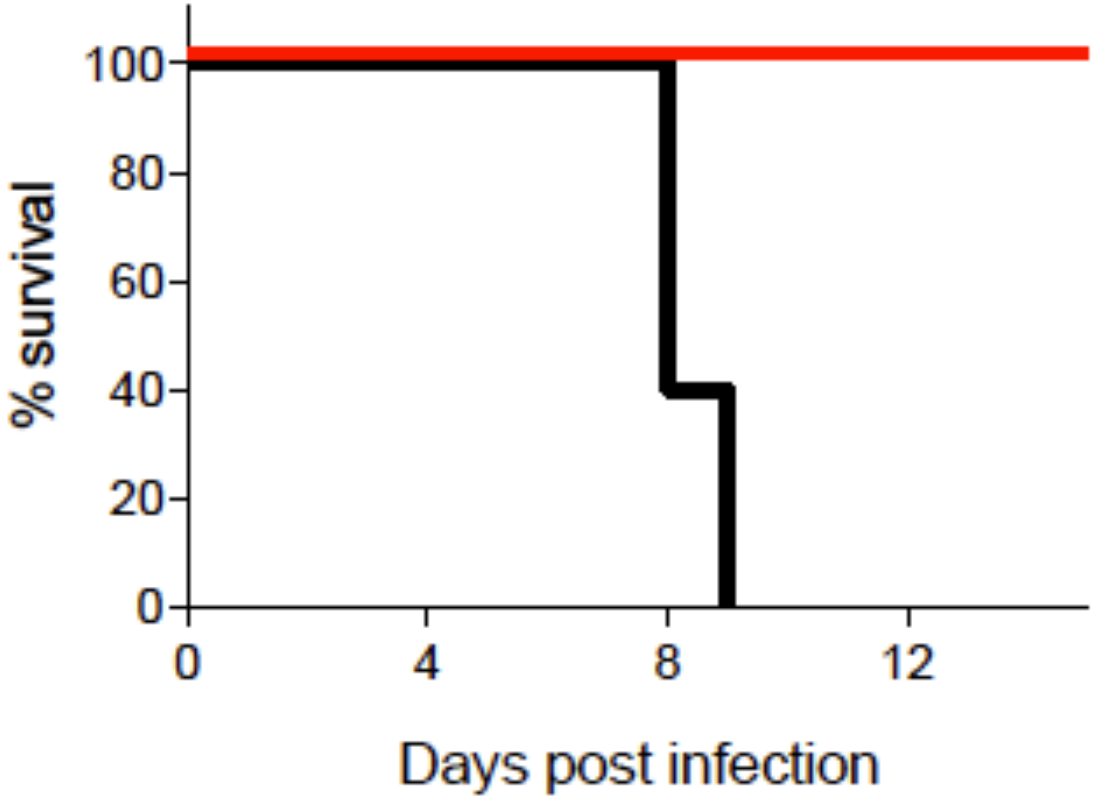
Collection

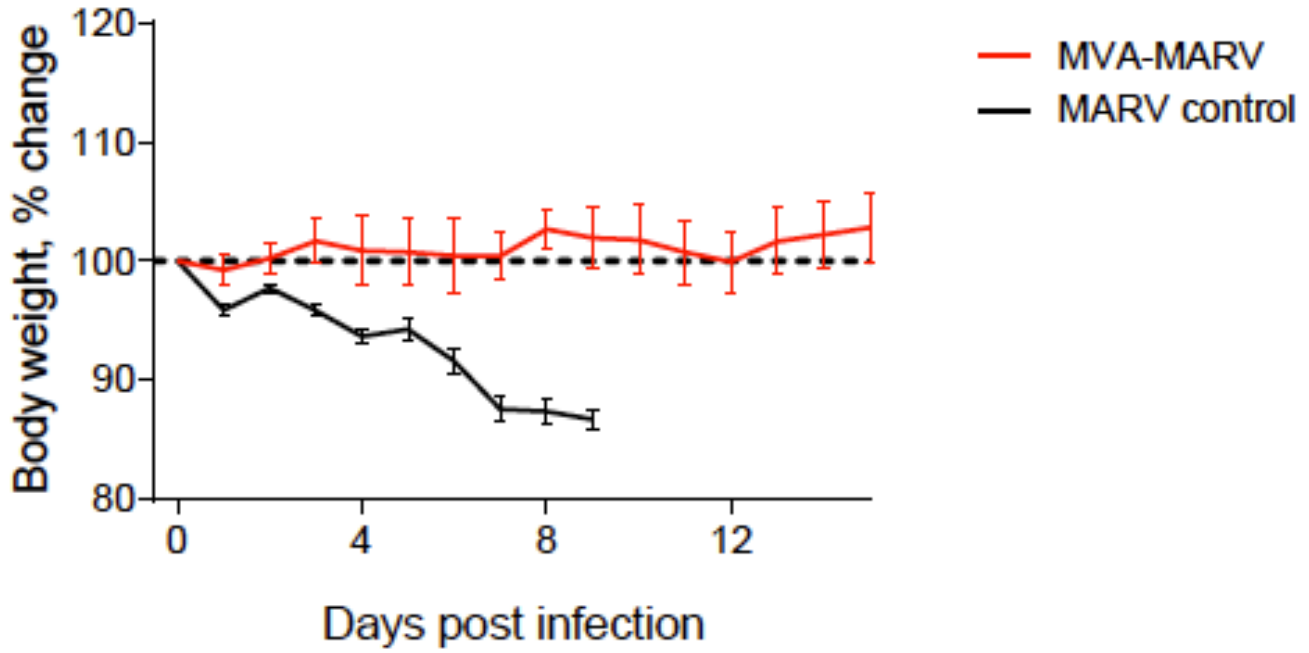
D0-56 Serum pre challenge

D58-66 viremia post challenge

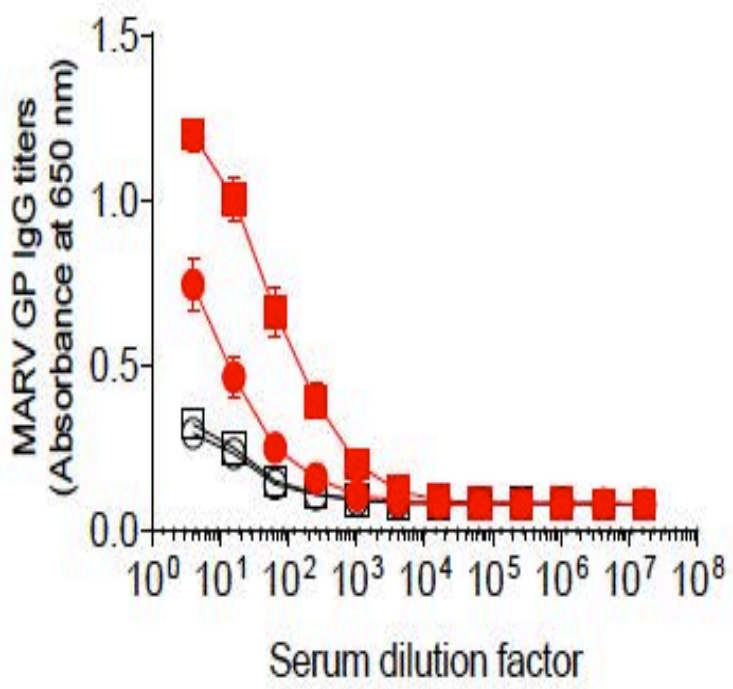
Terminal bleed

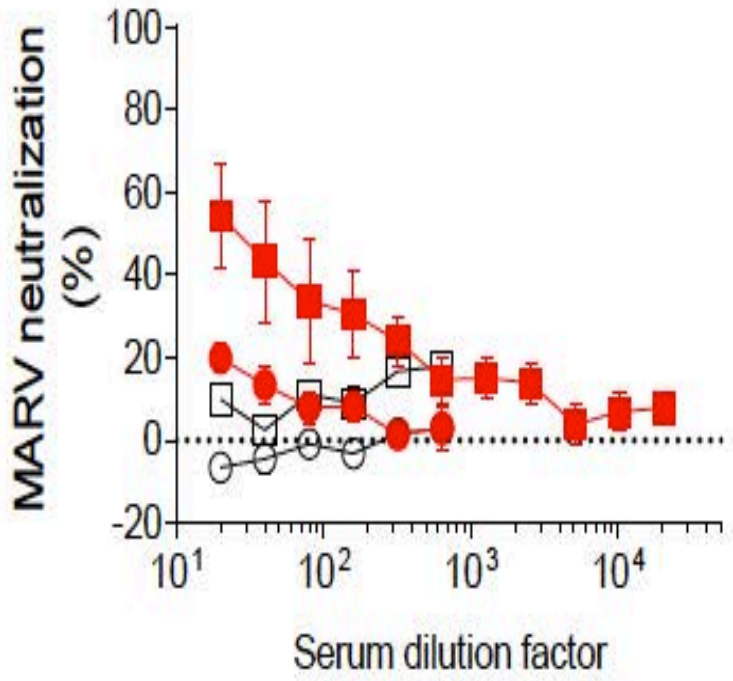
Measurements of Body Weights and Survival Post Challenge



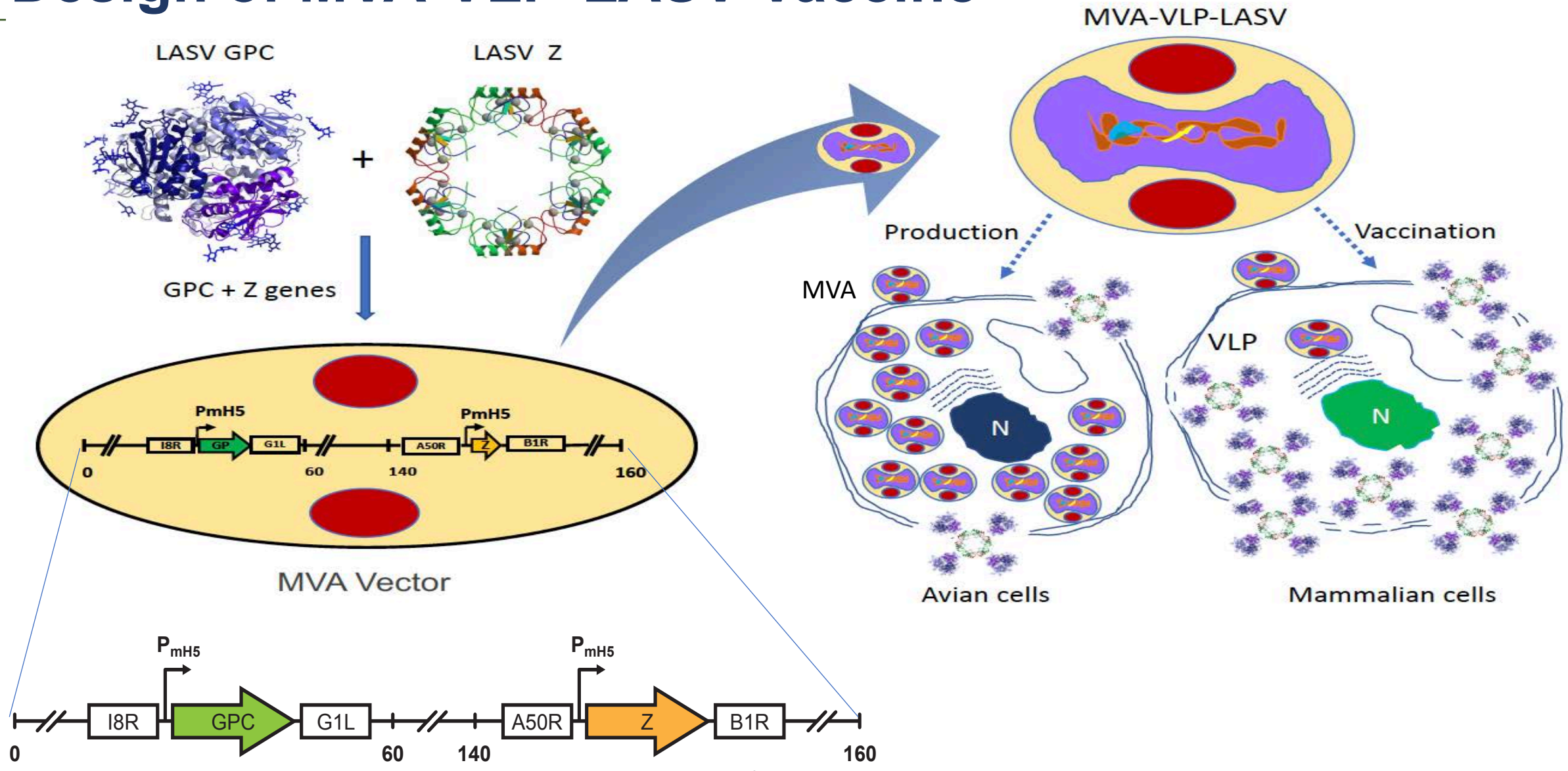


Measurements of Binding and Neutralizing Antibodies Post Vaccinations





Design of MVA-VLP-LASV Vaccine



In Vitro Characterization of MVA-VLP-LASV Vaccine Candidate

VLP expressed in Human 293 cells

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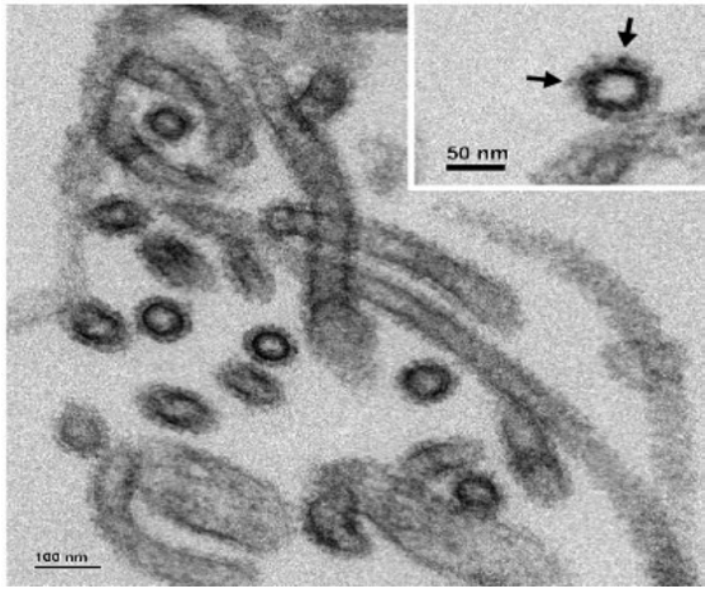

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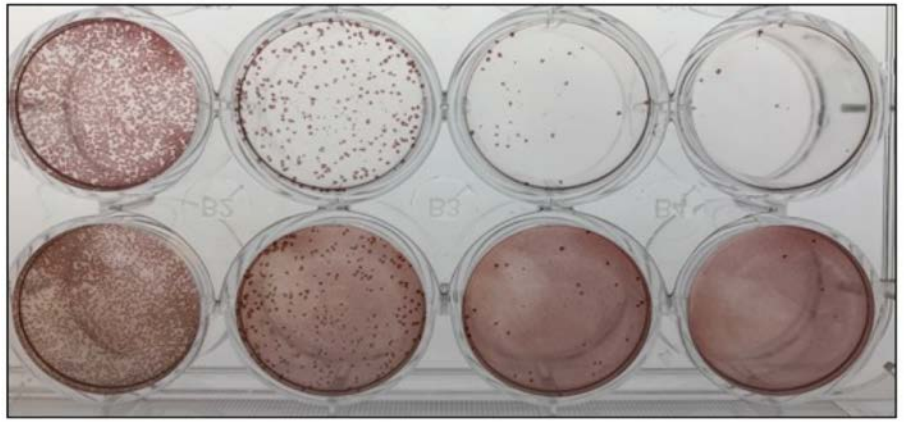
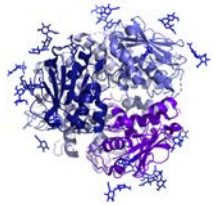


Immunostain of MVA-VLP-LASV with anti GPC (Top) or anti Z Mabs (bottom)

WB of MVA-VLP-LASV showing processing of GPC to GP1 (receptor binding domain) and GP2 (fusion domain) of GPC, 1. Cell lysate, 2 Sup



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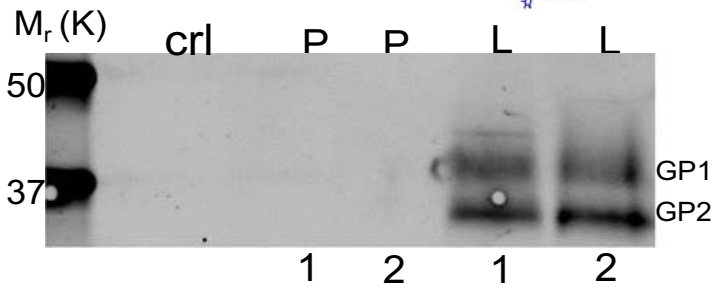

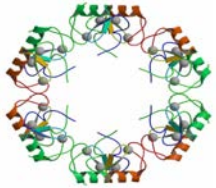

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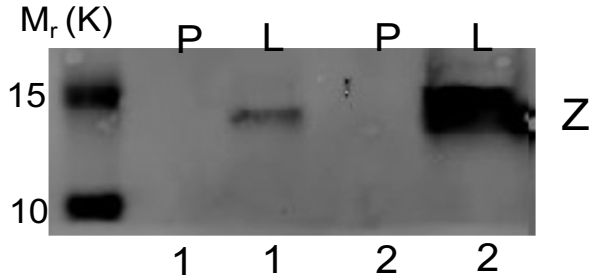
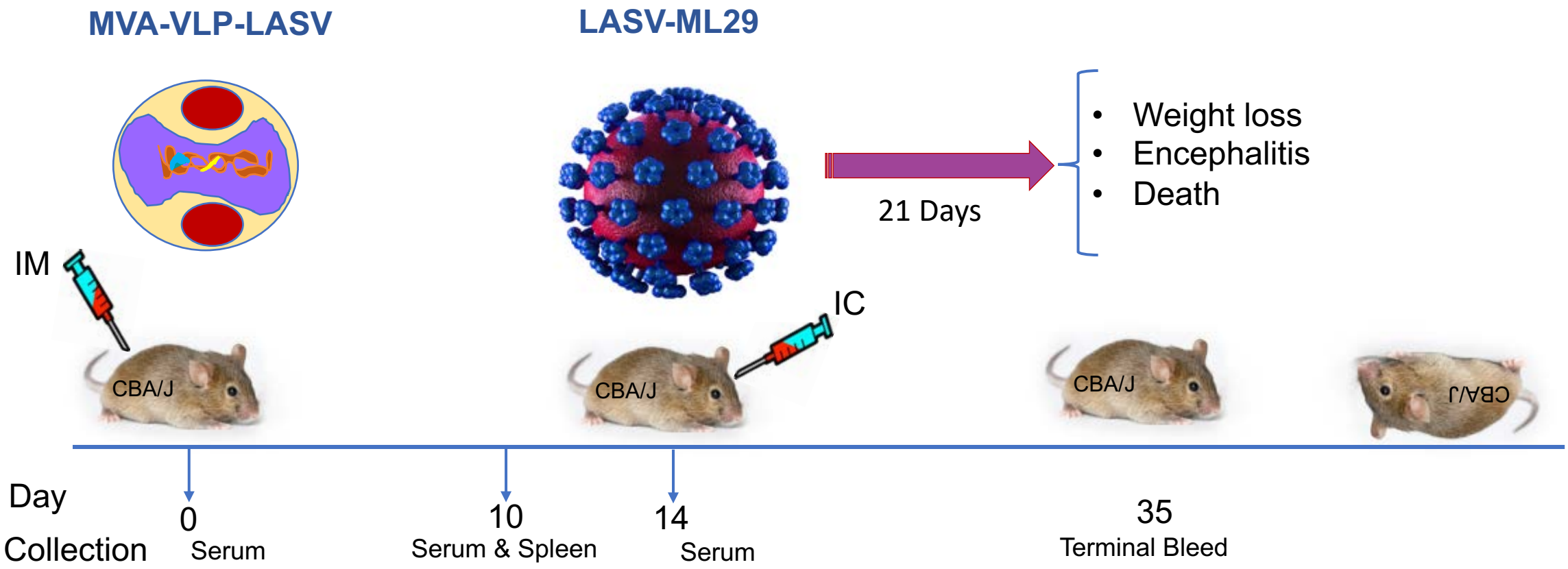
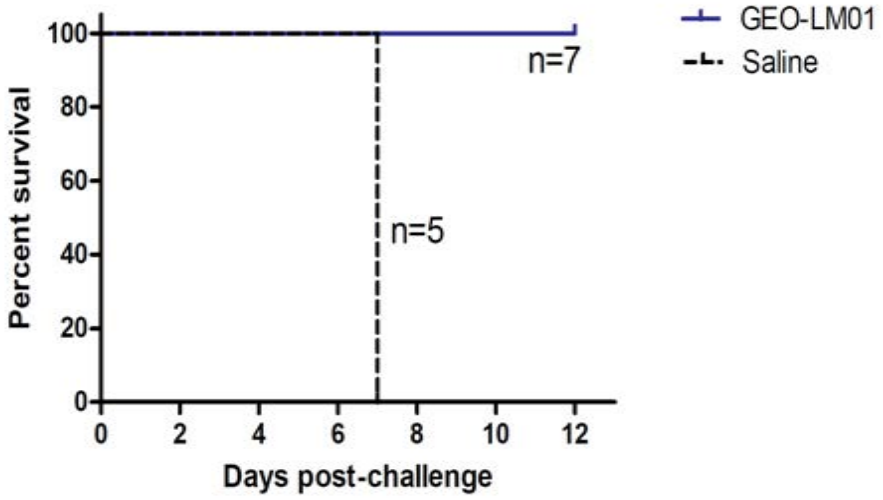
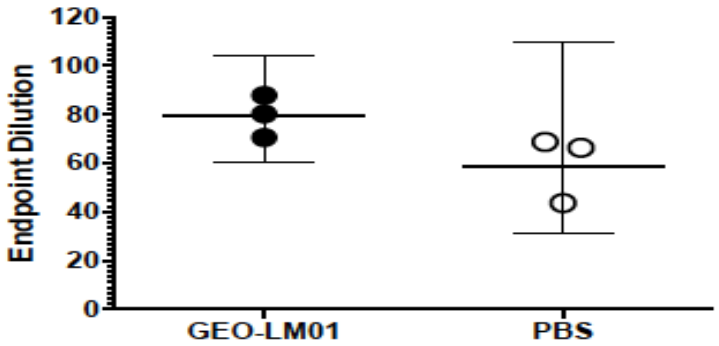


Efficacy Testing of MVA-VLP-LASV Vaccine in CBA/J Lethal Challenge Model

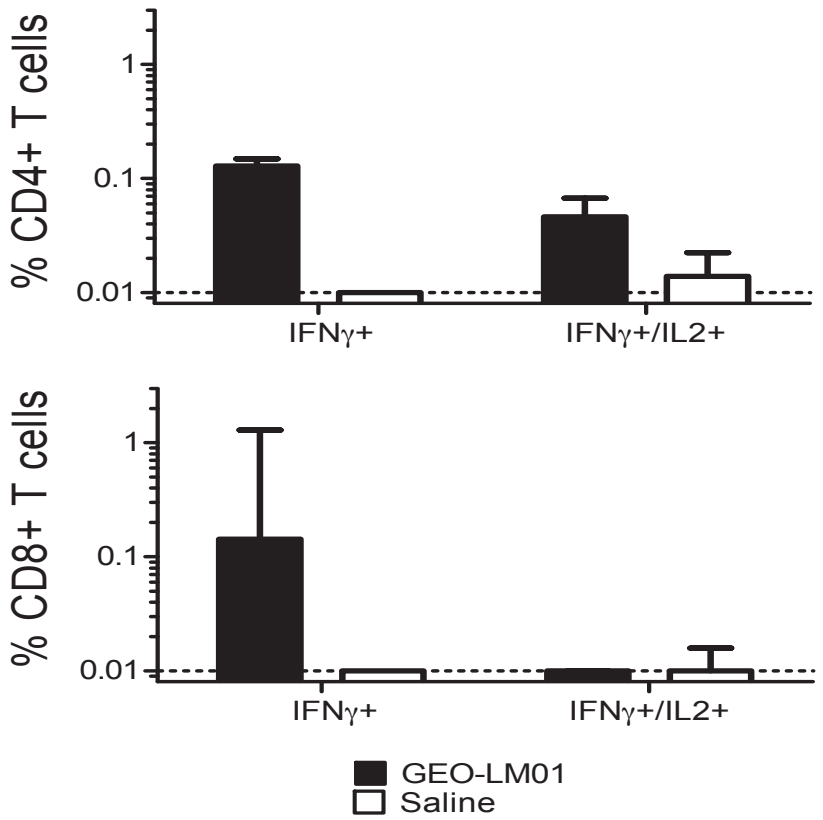


Immunogenicity and Efficacy of MVA-VLP-LASV in Mice after a Single-Dose Immunization





T cell response Day 10 post vaccination



- Abundant GPC-specific $CD4^+$ and $CD8^+$ T cells in spleens
- Double $IFN\gamma^+$ and $IL2^+$ $CD4^+$ T cells suggest an expanding population

Summary, Single Dose Vaccines

- **Ebola Vaccine (BSL4)**
  - 100% protection in 2 rodent models
  - 100% protection after single dose in NHP
  - Protective levels of antibody by ≤ 2 weeks after primary immunization
  - Near sterile immunity, no viremia in single or prime-boost groups
    - Suggesting the prime-only immunization was as effective as the prime/boost at controlling the infection
- **Marburg Vaccine (BSL4**
  - **Immunogenic in normal mice**
  - **100% protection in lethal guinea pig model**
  - **100% death in unvaccinated animals**
  - **Production of binding and neutralizing antibodies**
  - **No weight loss in vaccinated animals after challenge**
- **Lassa Vaccine (BSL3)**
  - 100% single-dose protection in a lethal (**IC inoculation**) challenge mouse model
  - 100% death in unvaccinated animals
  - Strong $CD4^+$ and $CD8^+$ T cell responses 10 days post-single vaccination
  - No vaccine currently in clinic