

Robust Protection Against Monkeypox Virus Mediated By a Novel Cell-Line-Derived MVA Vaccine (TG-MVA$_{CL}$)

Nathalie Silvestre, Head of the Vectorology Laboratory at Transgene

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Disclaimer

Data presented herein reflect preclinical analyses available as of the date of this presentation. These results are preliminary and intended for scientific discussion only. They are not predictive of future outcomes and should not be construed as a guarantee of the results, safety, or efficacy of any future preclinical or clinical studies.

OUTLINE

- Background
- TG-MVA : a proposed third generation vaccine for mpox and smallpox produced on cell line
- TG-MVA : immunogenicity and efficacy in animal models

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Monkeypox Virus (MPXV)

An orthopoxvirus belonging to the same family as the Variola virus causing smallpox



- **General features**
  - Large complex **enveloped virions** (360 x 250 x 200 nm) belonging to the Poxviridae family
  - Member of the orthopoxvirus genus, which includes **vaccinia virus** (VACV) and variola virus (VARV) and characterized by **well-conserved central core genes**
  - Double stranded linear DNA genome of **around 200 kb** encoding for approximately 250 genes
  - Pure **cytoplasmic** replication

- **Two main clades of MPXV**
  - Clade I (Central Africa): Clade Ia and Ib
  - Clade II (West Africa): Clade IIa and IIb

- **Epidemiology and transmission**
  - Historically associated with small-scale zoonotic outbreaks in endemic African countries, travel-related or importation of animals from endemic area

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Monkeypox (mpox) : a New Threat

Increase of global burden since 2022

Before 2022

- Mpox was an **emerging disease** circulating in limited regions in Africa with sporadic cases out of the continent

2022

- May: **Outbreak** caused by Clade IIb in Africa and in non endemic country (UK) and fast spread to EU and US
- July: The World Health Organization (WHO) declared the first **Public Health Emergency of International Concern** (PHEIC)
- More than 100,000 cases in 122 total countries, including 115 countries where mpox was not previously reported (Death rates < 1%)

2024

- Outbreak caused by Clade Ia and Ib in central Africa and 2nd PHEIC declaration by WHO. Over 20,000 cases reported in 2025
- Clade Ia: central and east Africa mostly reported in children (Death rates : 10%)
- Clade Ib: world-wide with evidence of human-to human transmission, with predominance of APOBEC3-type mutations (death rate< 4%)

2025

- September: lift of second PHEIC but still moderate risk due to ongoing circulation of the virus

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Orthopox-Related Diseases : a Global Threat

- **Mpox: a convergence of viral evolution, ecological changes, human behavior, and public health limitations**
  - Increased risk of health emergency due to climate change, emerging and engineered pathogens, global mobility, and geopolitical instability
  - Emergence of clade Ib with improved human transmissibility
  - **Decrease of global population immunity against orthopoxvirus following the cessation of smallpox vaccination**
  - Recurring outbreaks by endemic animal reservoirs in Sub-Saharan Africa, making eradication unrealistic
  - **Risk of global pandemic**

- **Smallpox : a potential bioterrorism agent**
  - **Highly contagious disease** caused **by variola virus** with a **mortality rate of 30-40%**
  - Declared **officially eradicated in 1980** following of the **WHO global vaccination campaign**
  - Sma**llpox** has been classified as **a Category A bioterrorism** agent by the CDC

Vaccines: a cornerstone in the prevention of smallpox and mpox

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Vaccines Against Smallpox and Mpox

Licensed second & third-generation smallpox / mpox vaccines

First generation vaccines

- Vaccines used during the smallpox eradication campaign based on live vaccinia virus (replication-competent)
- **Produced directly on the skin of live animals** (e.g: Dryvax®)
- **Highly effective vaccine** but rare serious adverse events and production not compliant with modern GMP standards

Second generation vaccines

❖ **ACAM2000®** (Emergent Biosolutions, USA)

- **Live replication-competent virus,** produced in cell culture on **African Green Monkey kidney (Vero) cells**
- Rare severe complications and contra-indicated in immunocompromised individuals or people with skin disorders
- Licensed in US: smallpox (2007), mpox (2024)

Third generation vaccines

❖ **LC16KMB** (KM Biologics, Japan)

- **Live attenuated, replication-competent but highly attenuated in human**, produced on **primary rabbit kidney cells**
- Contra-indicated in people immunocompromised receiving immunosuppressive treatment, pregnancy, people with epidemic skin disease
- Licensed in Japan: smallpox (1980), mpox (2022)

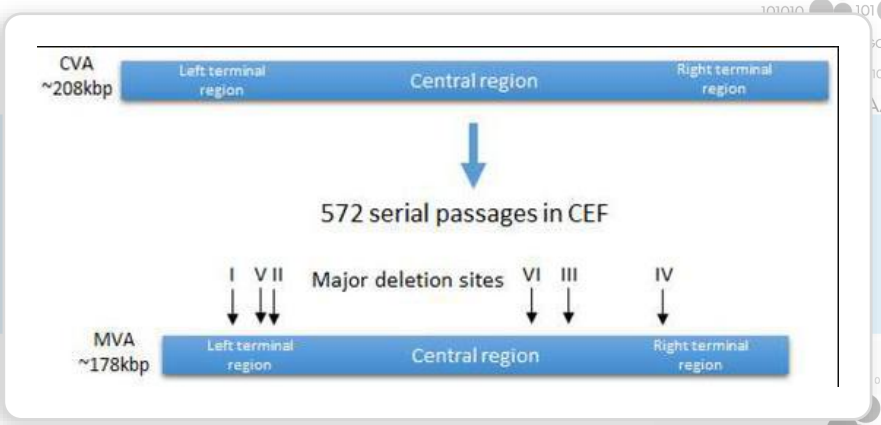
❖ **MVA-BN®** (Bavarian Nordic, Denmark)

- **Live attenuated, non-replication competent in human**, **produced on Chicken Embryo Fibroblasts (CEF)**
- Used in immunocompromised individuals
- Licensed in EU: smallpox (2013), mpox (2022) ; US : smallpox and mpox (2019) and other countries

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MVA (Modified Vaccinia Ankara) : a Potent Smallpox and Mpox Vaccine

- **MVA** was obtained from the CVA[1] vaccinia virus isolate by Pr. A. Mayr in late 70's after **572 passages** onto **chicken embryo fibroblasts (CEF)**
- Lost over 15% of the viral genome (6 major deletions), including host range restriction genes and immunoregulators such as chemokine soluble receptors and IFN soluble receptor
- Non replicative in mammalian cells
- Able to elicit **strong, durable** and specific immune response with establish safety profile
- Manufacturing of MVA on **Chicken Embryo Fibroblasts (CEF)**, prepared from specific pathogen free (SPF) embryonated eggs
- MVA-BN® induces strong protection against mpox
  - 70-90 % effectiveness against symptomatic mpox after full vaccination (2 doses)
  - Also reduces disease severity and hospitalization



1. Chorioallantois Vaccinia Virus Ankara

Orthopox-Related Threats : a Strategic Preparedness Challenge

- **Challenge as vaccine supply is fragile**
  - Current system depends on too few suppliers
  - Single supplier (monopoly) for MVA vaccine (Bavarian Nordic) with limited capacity and centralized production
  - Europe relies on a single approved mpox/smallpox vaccine (Bavarian Nordic), with development and manufacturing capacity largely aligned with U.S. funding and procurement priorities

- **Global unmet need estimated in the billions of doses**
  - Mpox: ~130 million doses across the EU and US, and exceeding 1 billion in Africa
  - Smallpox: Potential demand in the billions of doses, driven by a largely orthopox-naïve global population—particularly in Africa.

➢ **Need for second-source solutions enabling diversified and stockpile-friendly vaccine capacity**
➢ **Development of a new vaccine: TG-MVA**

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TG-MVA | Building Next Line of Biosecurity Against Pox-Diseases

- **TG-MVA : A Safe Third-Generation Vaccine**
  - **Non-replicating pox vaccine** built on a viral backbone identical to Bavarian Nordic's reference platform: shared MVA lineage (**100% Region of Interest (ROI) sequence identity**)
  - Designed to protect against mpox, smallpox and disease caused by vaccinia virus

- **An innovative cell-line based production process**
  - Overcoming **ethical and industrial limit of CEF**[1] production
  - Eliminates reliance on animal-derived materials and enabling consistent, **reproducible manufacturing**
  - Scalable manufacturing approach
  - Designed to **rapidly expand capacity in response to public health needs**, including pandemic scenarios
  - Dedicated EU-based manufacturing facilities but **easily transferable manufacturing enabling regional production (e.g. in Africa)**

1. Chicken Embryo Fibroblats,

TG-MVA | Pre-Clinical Studies

Generated non-clinical evidence of TG-MVA efficacy, immunogenicity & safety

Objective: to compare the efficacy, immunogenicity & safety of TG-MVA and MVA-BN® in established Non-human primates and murine animal models

Immunogenicity study in mice

Objective: compare the prophylactic immunogenicity of TG-MVA and MVA-BN® in wild type mice (e.g. Balb/c , ...).

Parameters evaluated:
- Immune readouts



mpox lethal-challenge study in mice

Objective: compare the prophylactic efficacy & immunogenicity of TG-MVA and MVA-BN® in CAST/EI mice challenged by MPXV clade 1a by intra-nasal route

Parameters evaluated:
- Survival
- Immune readouts



mpox lethal-challenge study in NHP[2]

Objective: compare the prophylactic efficacy, immunogenicity & safety of TG-MVA and MVA-BN® in NHP challenged by mpox virus (MPXV) clade 1a by intra-tracheal route.

Parameters evaluated:
- Survival
- Immune readouts
- Viral load
- Safety

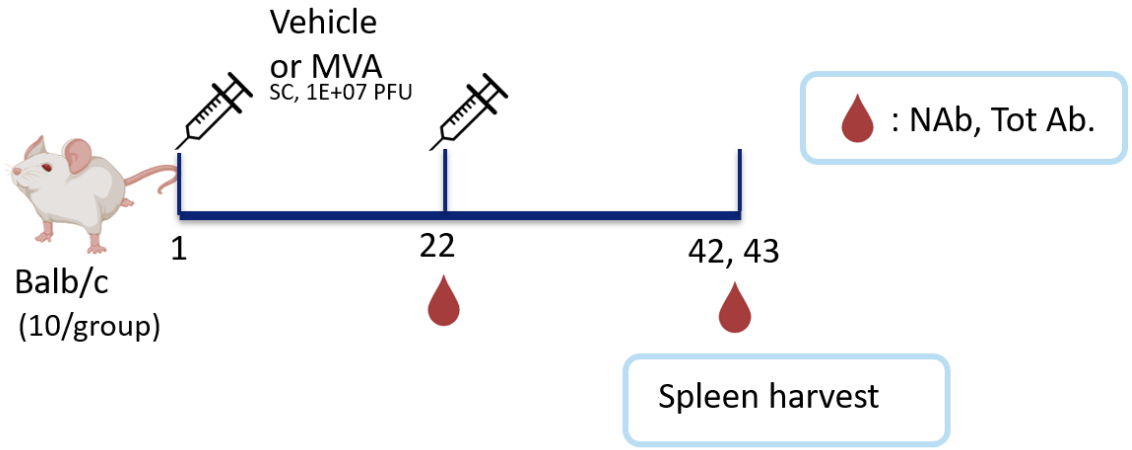


1. Non-Human Primates

Immunogenicity in BALB/c Mice: Study Design

- **Tested items**
  - **MVA-BN® (Jynneos®)** : registered as a prophylactic vaccine against Mpox and smallpox, **produced on CEF**
  - **TG-MVA$_{CEF}$ (TG4080)** : TG-MVA **produced on CEF**
  - **TG-MVA$_{CL}$ (TG4090)** : TG-MVA **produced on avian cell line**
  - Vehicule: formulation buffer

Objective: Demonstrate that **TG-MVA** and **MVA-BN®** have **similar immunogenicity** and that **change of manufacturing process** has no impact on **immunotoxic potential compared to manufacturing on CEF**

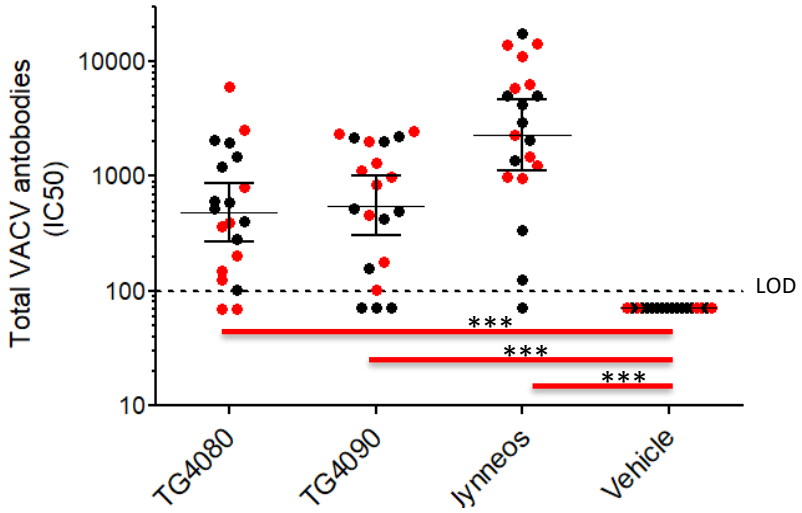


Immunogenicity in BALB/c Mice: Antibodies Response

TG-MVA induce Total and Neutralizing VACV Ab comparable to MVA-BN®

MVA-BN® : Jynneos®
TG4080 (TG-MVA$_{CEF}$)
TG4090 (TG-MVA$_{CL}$)

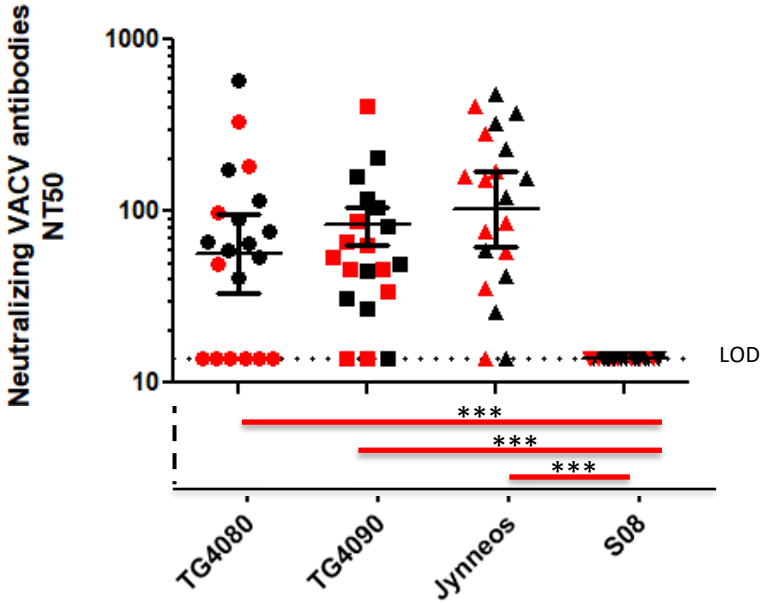
Total Ab detected at D42/D43



*** p<0.001, **p<0.01, * p<0.05

Total Anti-VAVC titers expressed as IC50 for individual animals with bars representing the geometric mean +/- 95% CI of each group
Black dot: N=1 experiment; red not: N=2 experiment

Neutralizing Ab detected at D42/D43



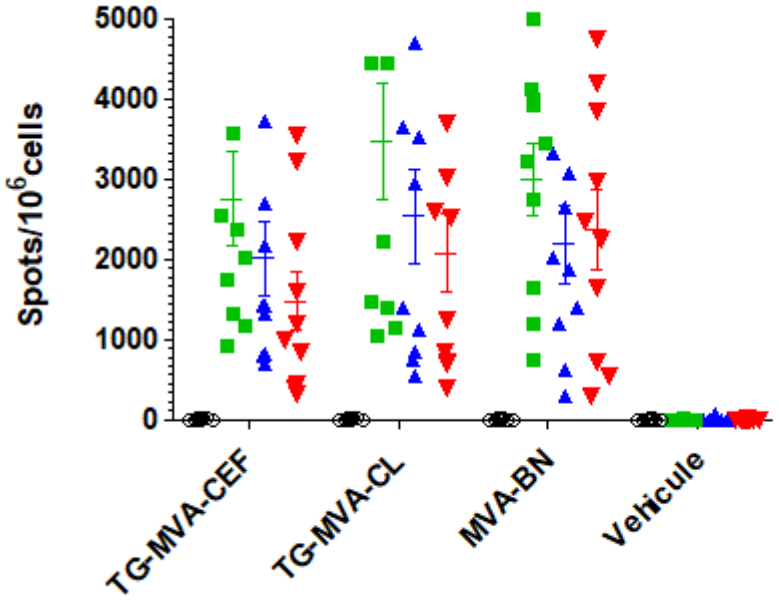
Anti-VAVC neutralization titers expressed as NT50 for individual animals with bars representing the geometric mean +/- 95% CI of each group
Black dot: N=1 experiment; red not: N=2 experiment

- ✓ **Total Ab detected in 70 -100 % of MVA vaccinated mice**
- ✓ **Neutralizing Ab detected in 90-100 % of MVA vaccinated mice**

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Immunogenicity in BALB/c Mice : Cellular Response Assessed by ELISpot

TG-MVA and MVA-BN® induce similar cellular immune response



Stimulation

- P815 NI : Not infected P815 cells
- P815 WR : P815 cells infected with VACV strain Western Reserve
- Pool MVA : mix of 3 specific MVA peptides
- Pool WR : mix of 3 specific WR peptides

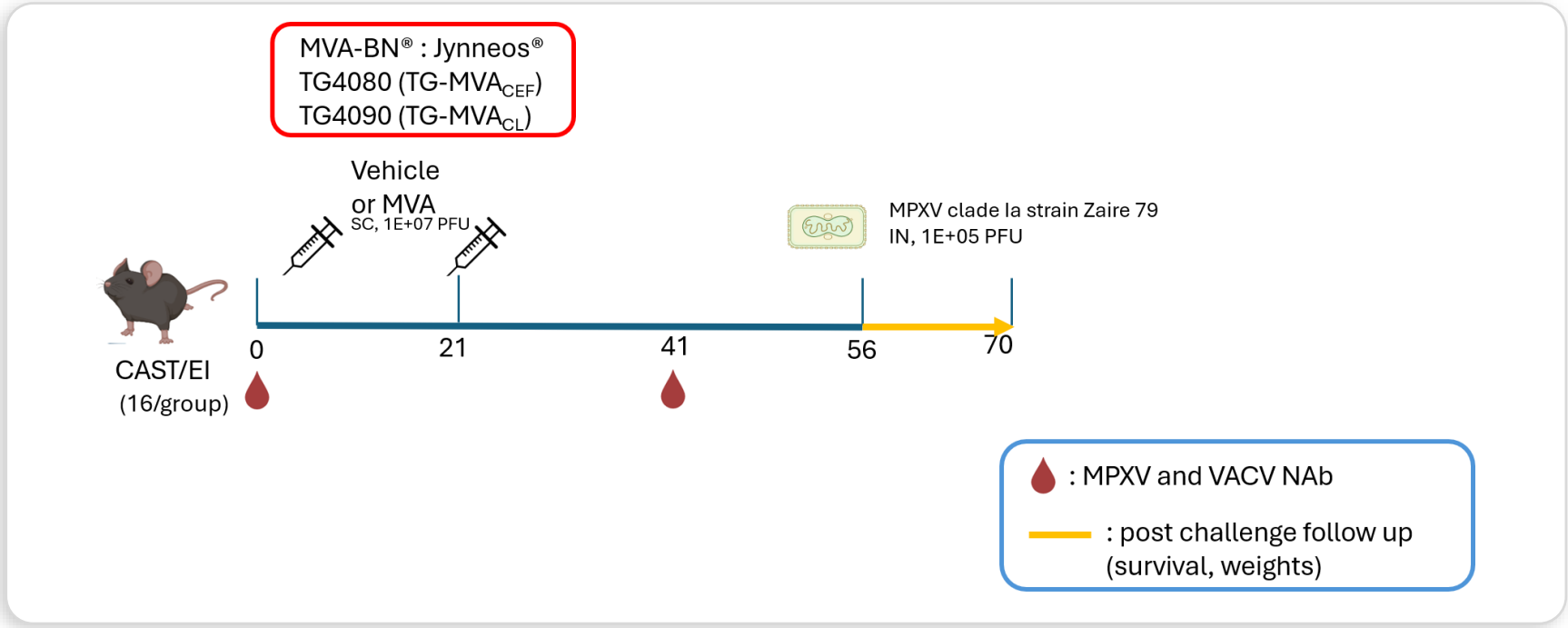
Detection of IFN-gamma producing cells. The background-subtracted SFC per million PBMC is reported.
Shown are the individual responses (dots) as well as the group mean (bar) with variation (SEM)

Detection of antigen-specific cellular immune responses following stimulation with VACV-infected P815 cells or with MVA- and WR-specific peptides

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Mpox Lethal-Challenge Study in CAST/Ei Mice: Study Design

Objective: Demonstrate that **TG-MVA** and **MVA-BN®** have **similar immunogenicity** and that **change of manufacturing process** has no impact on **immunotoxic potential compared to manufacturing on CEF**



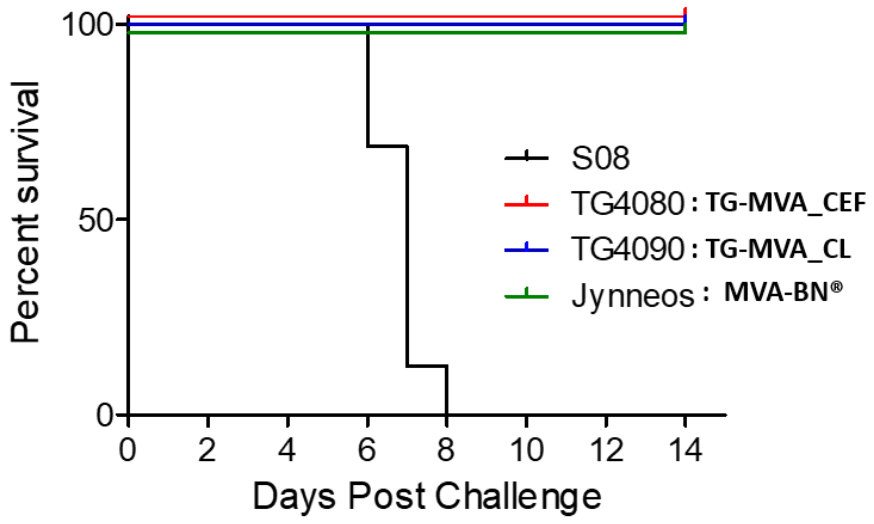
- CAST/Ei mice* is a strain of mice for which MPXV challenge is lethal (physiological low IFNy response)

*: Americo et al, 2010 DOI: 10.1128/JVI.00621-10

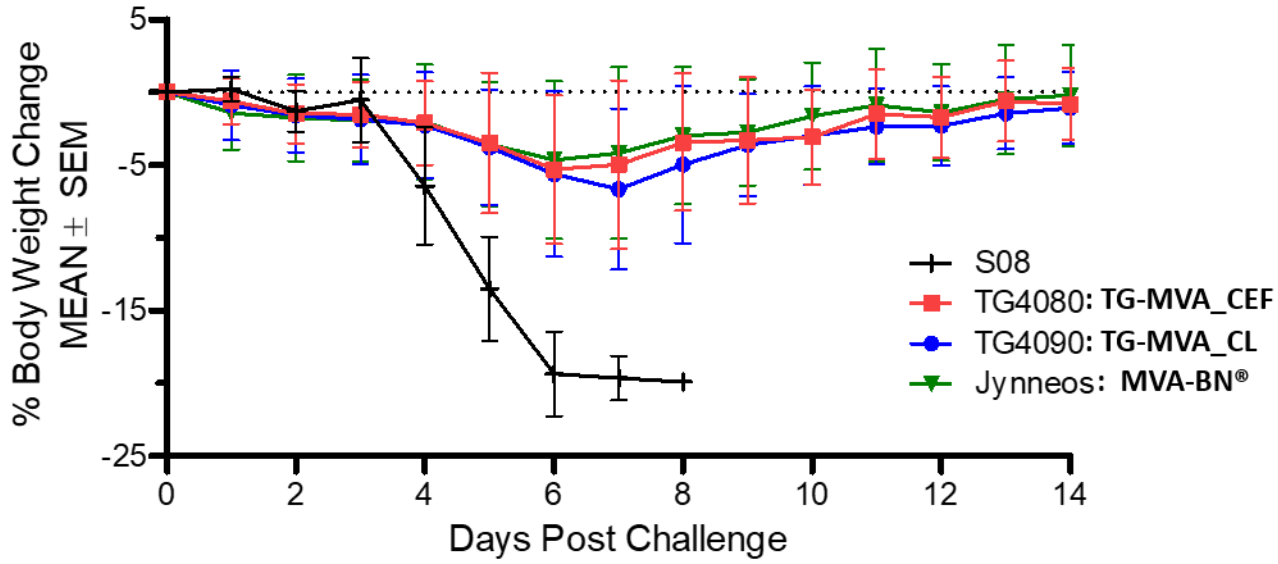
Mpox Lethal-Challenge Study in CAST/Ei Mice : Survival and Weight Loss

TG-MVA and MVA-BN® provide equivalent protection against MPXV challenge

Survival



Weight loss



- **No lethality in all MVA-vaccinated group**
- **Minor weight loss in MVA-vaccinated mice**

TG-MVA | Conclusions in Mice Models

- **Primary end-point**: **Protection** is reached (CAST/Ei mice) for all three MVAs and with identical efficacy (100% for all groups)

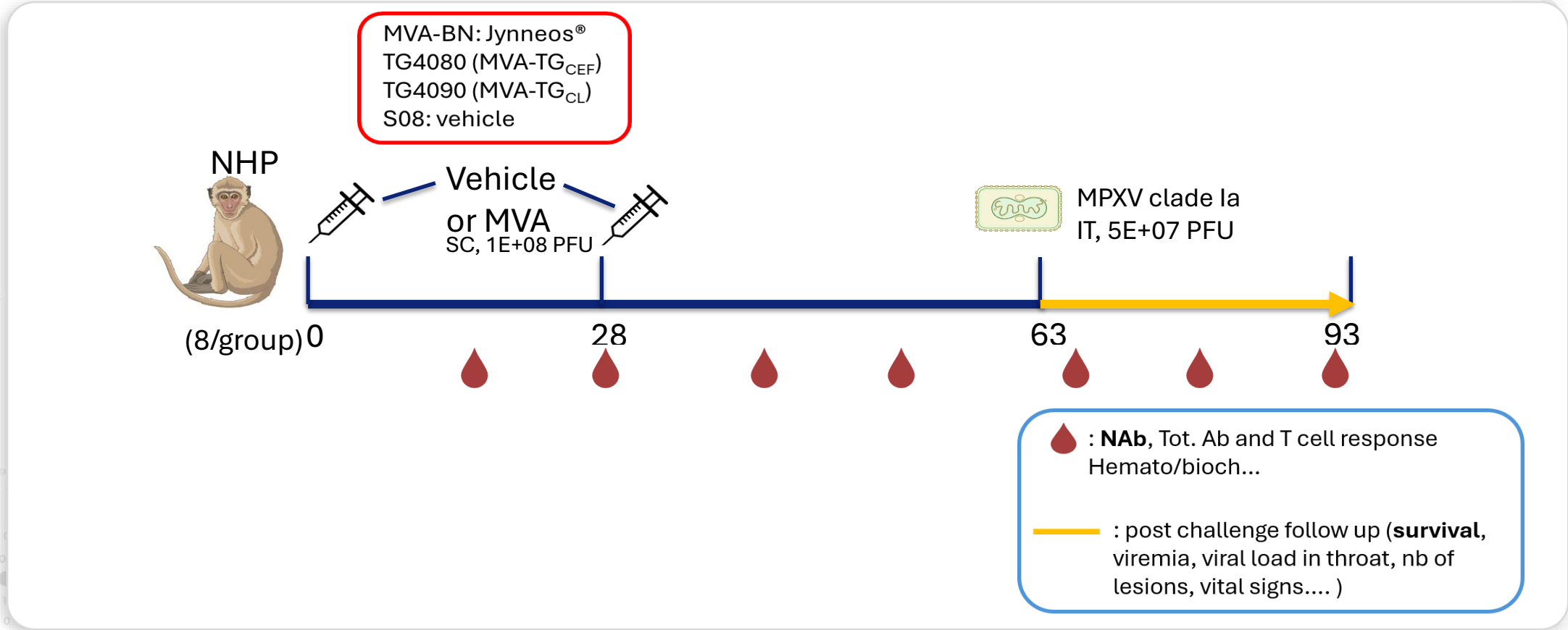
- **Secondary end-points: Morbidity/Immunogenicity**
  - Weight Loss : minimal and same weight loss for the three MVA vaccines groups
  - MPXV neutralizing Abs (CAST/Ei), VACV Neutralizing Abs (BALB/c) and Total VACV Abs (BALB/c): detected only for the three vaccinated groups
  - Means of Ab titers, for all 3 types of Abs tested, are comparable for the 3 MVAs

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Mpox Lethal-Challenge Study in NHP: Study Design

A gold-standard for anti-Mpox vaccine evaluation

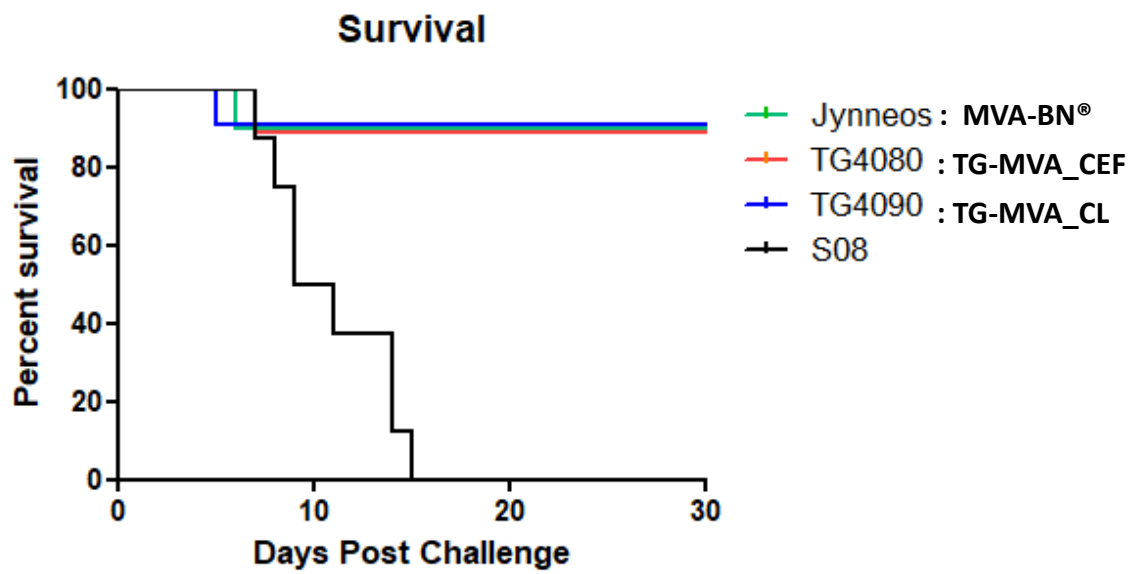
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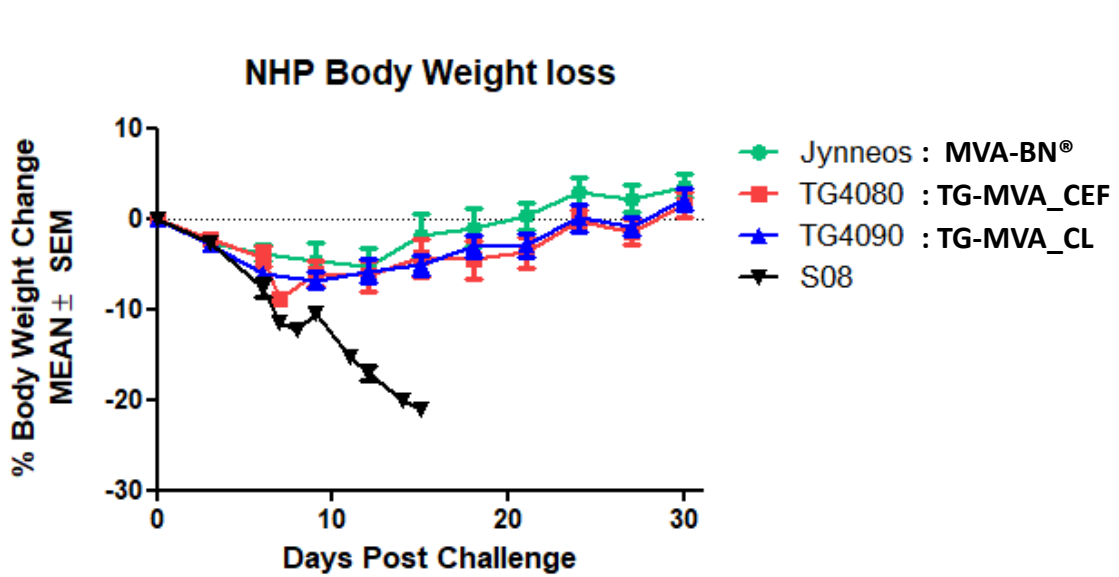


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Mpox Lethal-Challenge Study in NHP : Survival and Weight Loss

TG-MVA and MVA-BN® provide equivalent protection against MPXV challenge



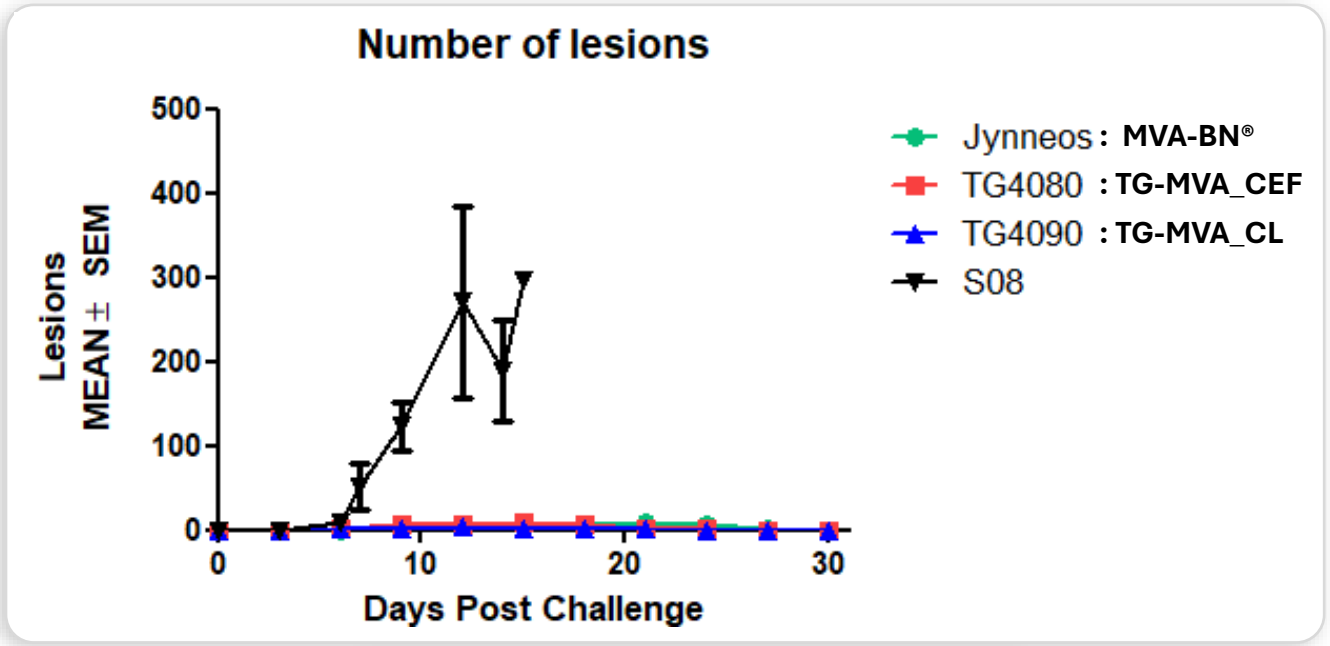


- **7/8 animals survived in all MVA-vaccinated group**
- **Minor weight loss in MVA-vaccinated NHP**

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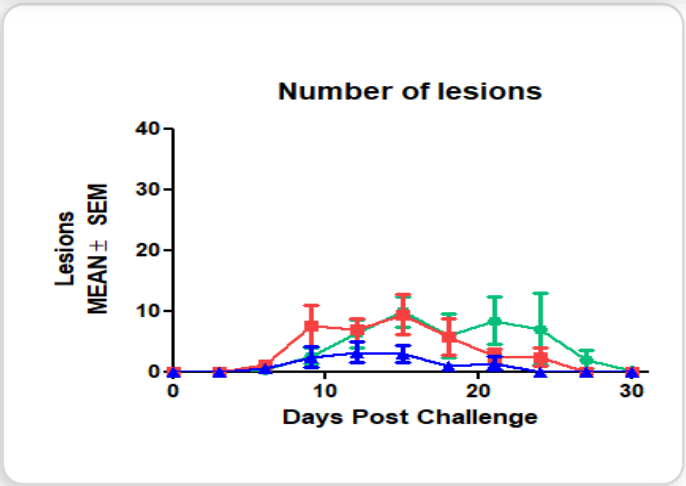
Mpox Lethal-Challenge Study in NHP: Lesion Counts

TG-MVA and MVA-BN® strongly protect against MPXV-induced lesion development



	Number of animal	
	With lesions*	Without lesions
MVA-BN®	7 (87,5%)	1(12,5%)
TG-MVA$_{CEF}$	8 (100.0%)	0 (0%)
TG-MVA$_{CL}$	5 (62.5%)	3 (37.5%)
Vehicle	8 (100%)	0 (0%)

* : Lesions detected at least at one time point

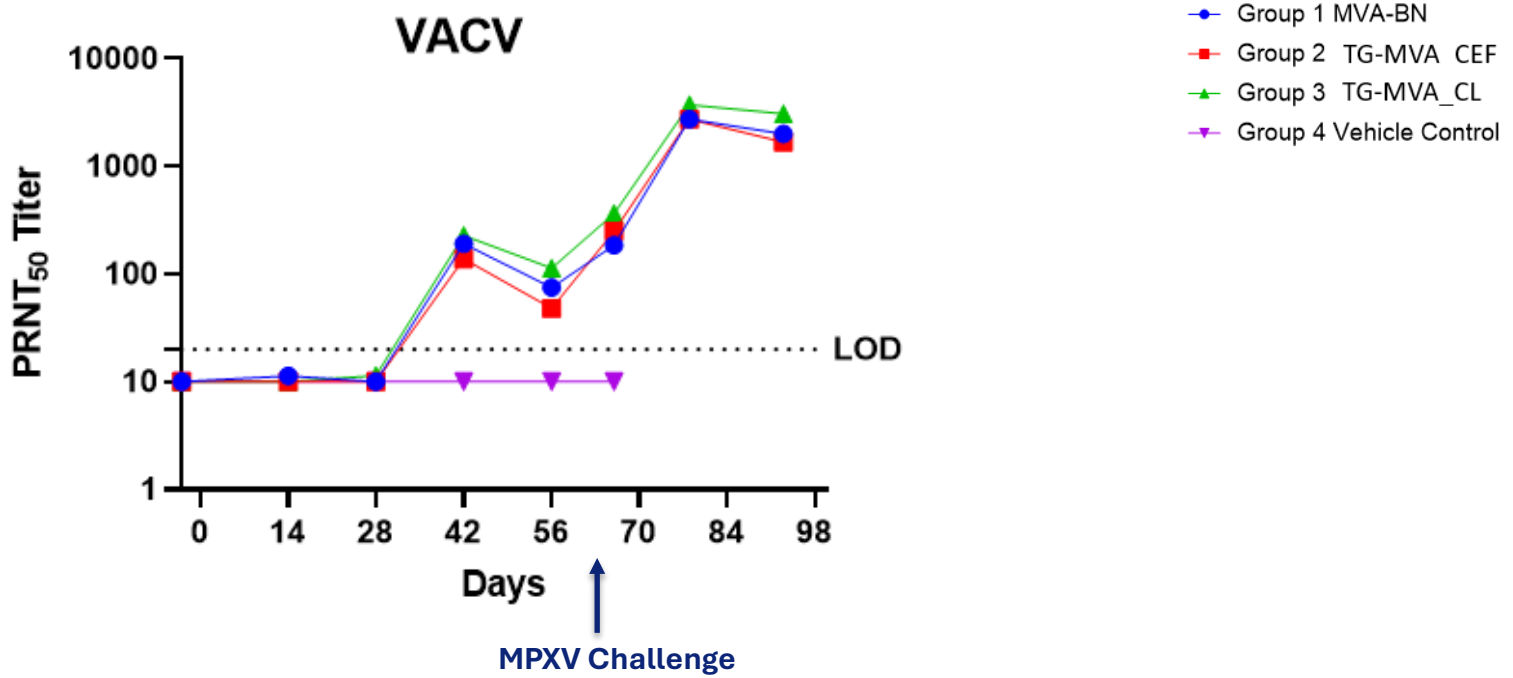


Few lesions in MVA-vaccinated animals

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Mpox Lethal-Challenge Study in NHP: Neutralizing anti-VACV Ab

TG-MVA and MVA-BN® provide similar immunogenicity against VACV

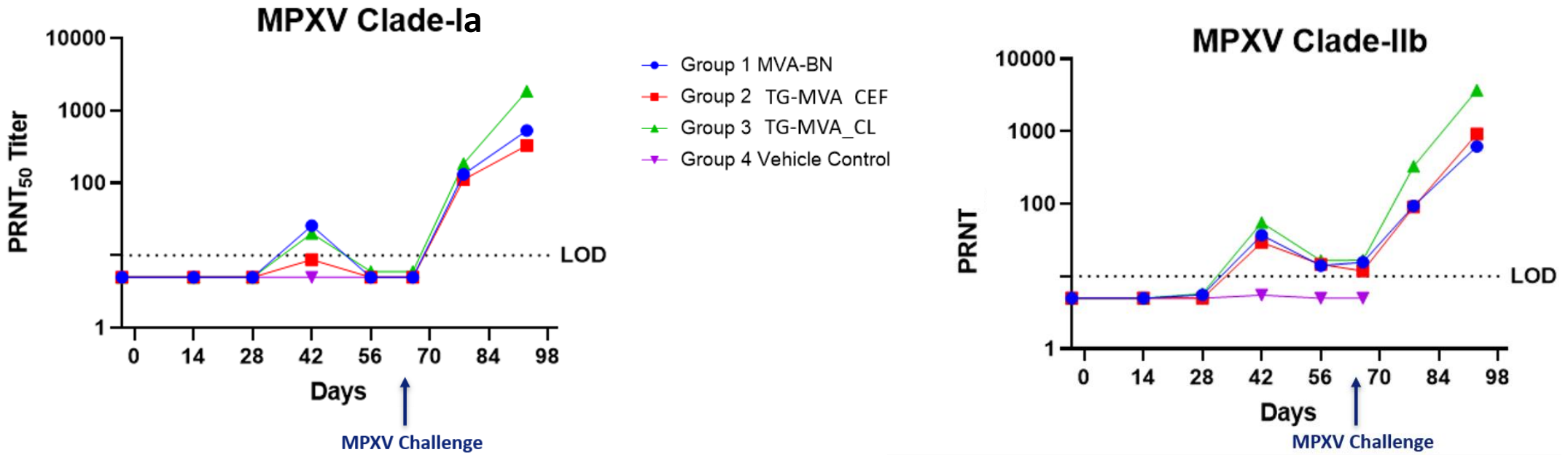


Anti-VAVC neutralization titers expressed as NT50. Data represents geometric mean for each group.

- **Prior to challenge, peak of response at D42**
- **Comparable Titer for all the MVA-vaccinated groups**

Mpox Lethal-Challenge Study in NHP: Neutralizing anti-MPXV

TG-MVA and MVA-BN® provide similar immunogenicity against MPXV



Anti-MPXV neutralization titers expressed as NT50. Data represents geometric mean for each group.

- **Prior to challenge, peak of response at D42**
- **Comparable Titer for animals vaccinated with TG-MVA$_{CL}$ and MVA-BN®**

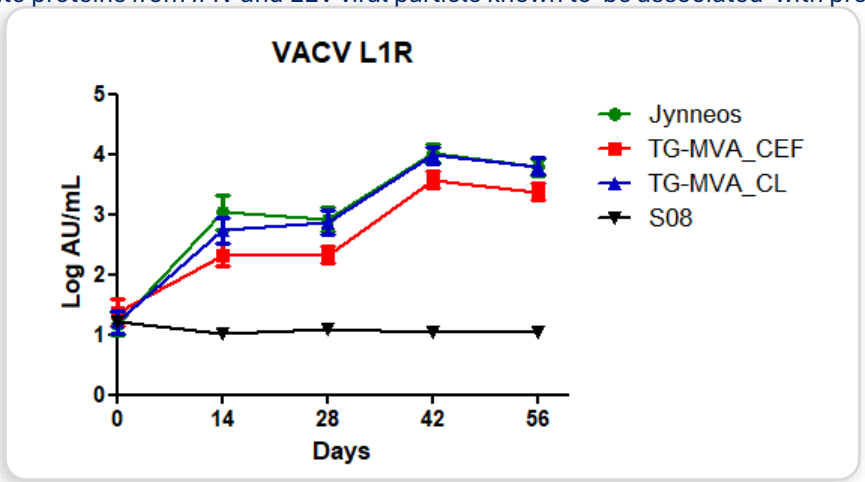
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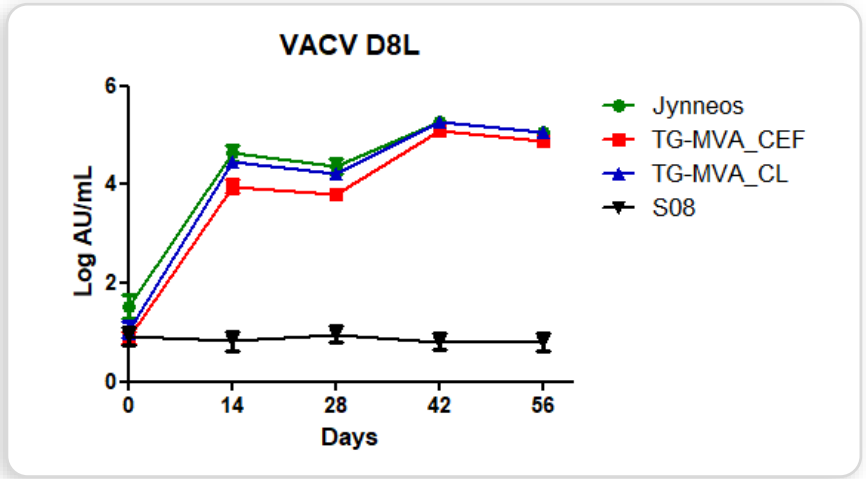
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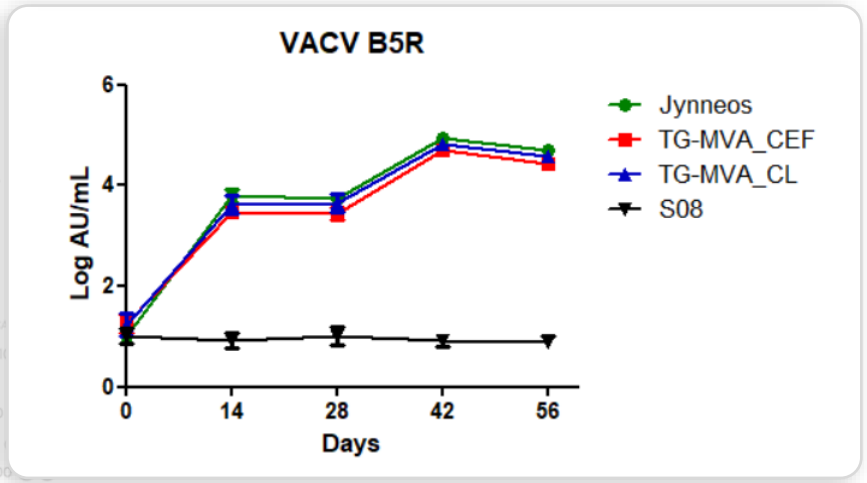
Mpox Lethal-Challenge Study in NHP: Total Antibodies Against VACV Proteins*

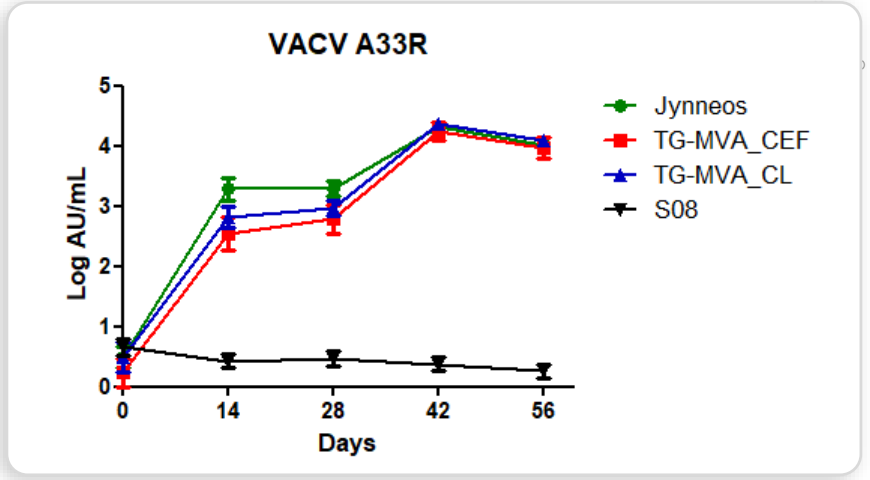
TG-MVA and MVA-BN® provide similar immunogenicity against VACV proteins

* : Orthologous late proteins from IMV and EEV viral particle known to be associated with protection









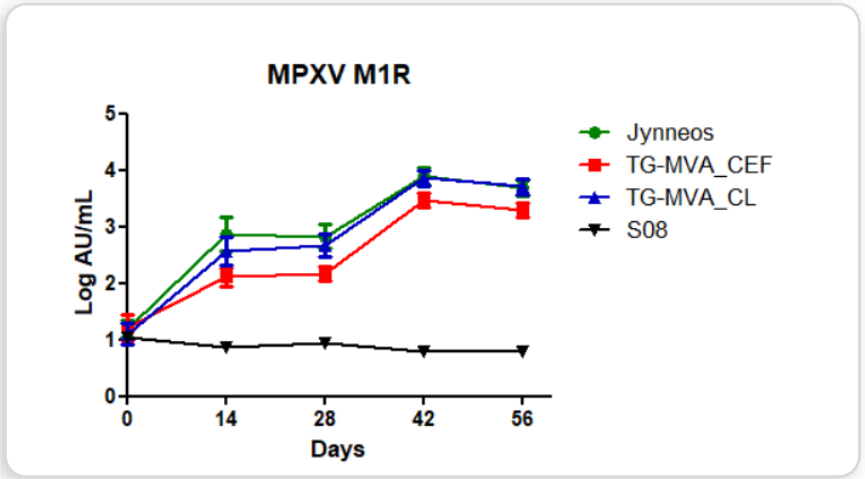
Mean of log concentration of VACV protein-binding IgG (expressed in arbitrary unit (AU)/mL)), measured by MSD technology

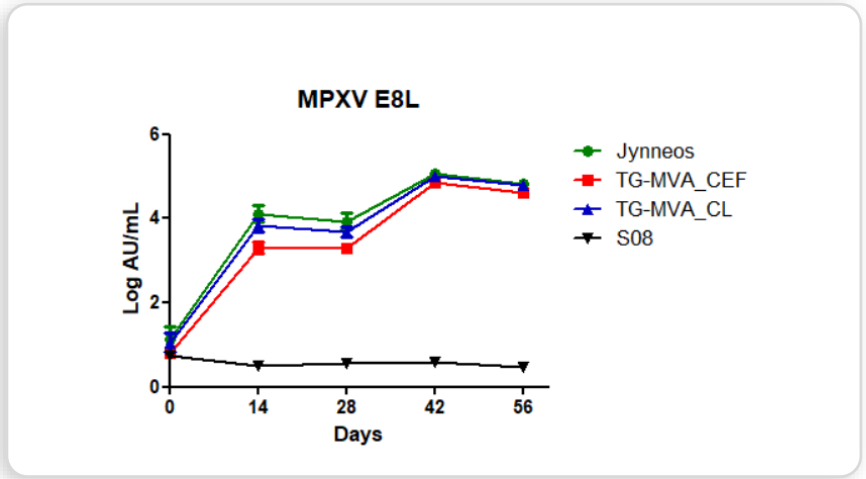
Seroconversion was observed in all vaccinated animals, with peak response at D42

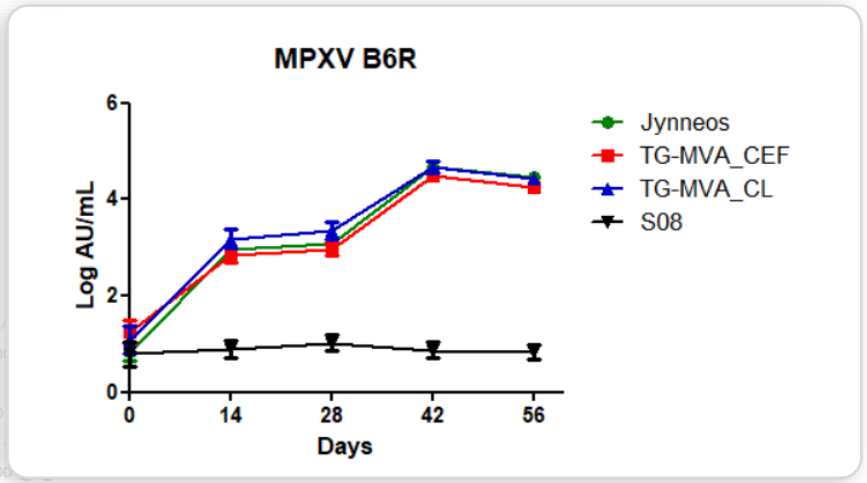
Mpox Lethal-Challenge Study in NHP : Total Antibodies Against MPXV Proteins*

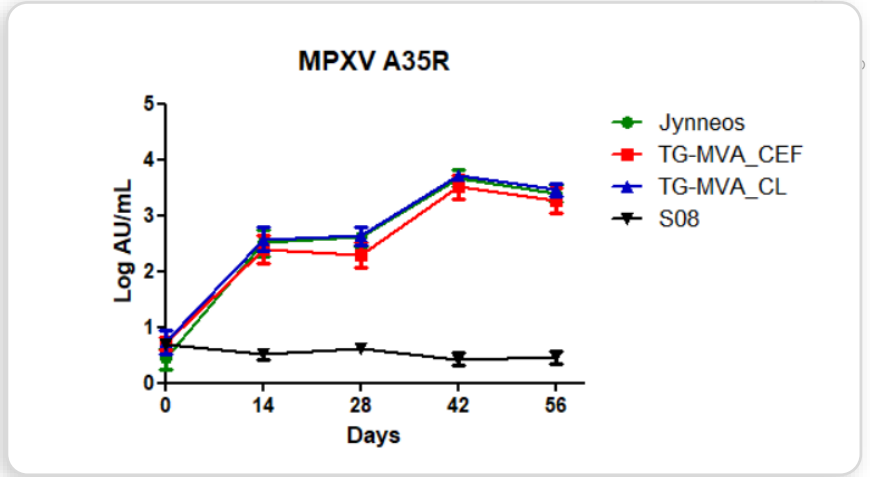
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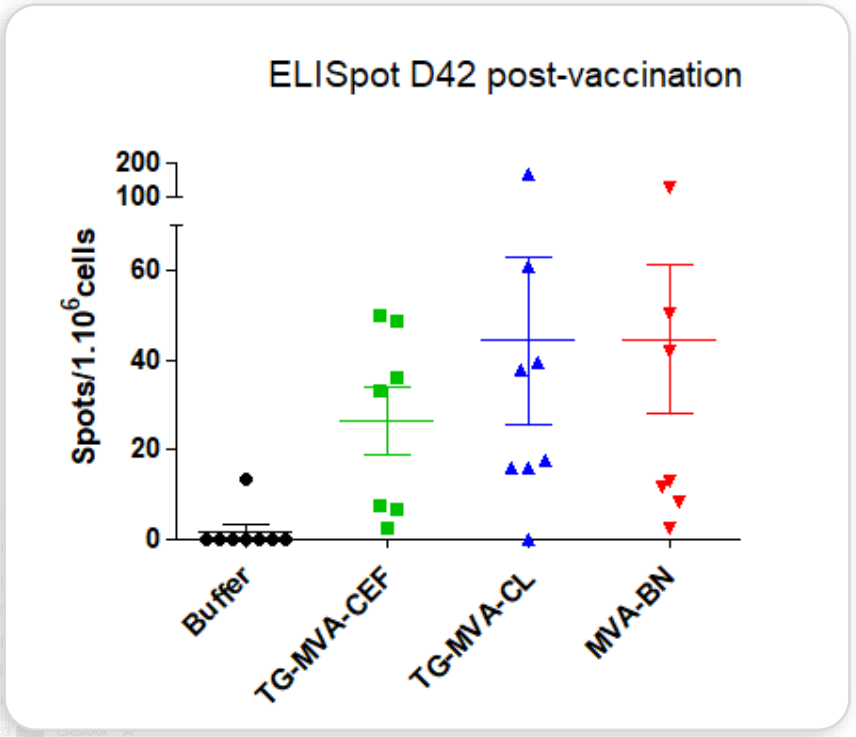
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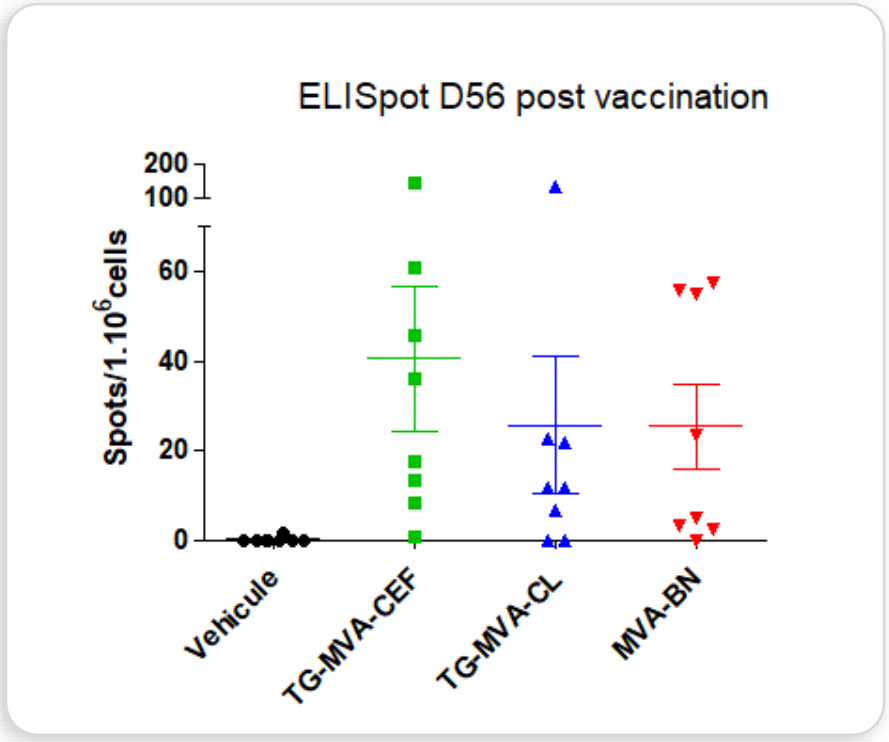
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Mpox Lethal-Challenge Study in NHP: Cellular Response Assessed by ELISpot

TG-MVA and MVA-BN® induce similar cellular immune response





Stimulation: PepMix™ Pan-Poxviridae Select 127 peptides class I & II restricted T-cells epitopes)
- 122 found in MPXV
- 126 found in VACV WR

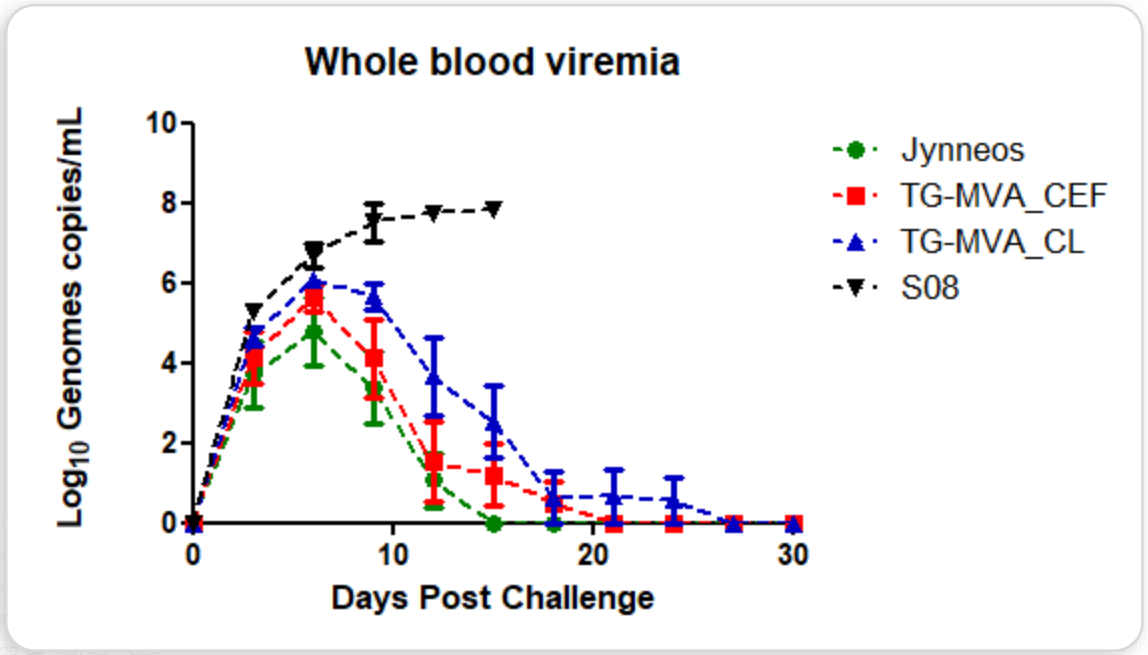
Detection of IFN-gamma producing cells. The background-subtracted SFC per million PBMC is reported.
Shown are the individual responses (dots) as well as the group mean (bar) with variation (SEM).

- **Induction of detectable T-cell immunity by all 3 vaccines**
- **High spread of response within vaccinated groups**

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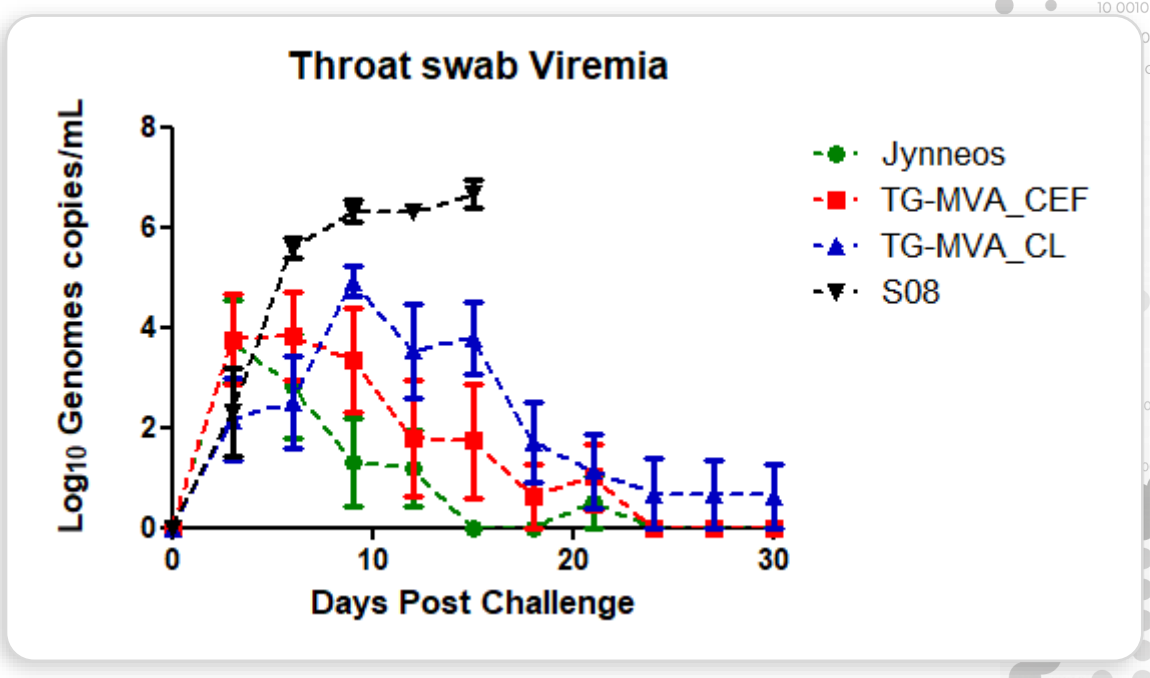
Mpox Lethal-Challenge Study in NHP: Viremia in Blood and Throat Swab

TG-MVA and MVA-BN® provide markedly attenuated systemic viral burden



Log_{10} MPXV genome copy numbers. Data represents mean +/-SEM

TG-MVA_CL : Only 1 positive NHP from J18



Log_{10} MPXV genome copy numbers. Data represents mean +/-SEM

- **Whole blood : peak viremia levels similar between vaccine groups while duration of detection shortest in Jynneos-vaccinated animals**
- **Throat swab : greater variability in each group (due to swab collection)**

Safety Assessment

Similar safety profile among all three vaccines

Safety end-points were incorporated in the NHP efficacy study :

- Hematology/biochemistry :
  - Variations observed after MPXV exposure consistent with viral infection (increased WBC, slight increased of liver enzymes and globulin concentrations)
- Slight to mild local reactogenicity 2 or 3 days post-vaccination in all vaccinated groups
- Pathology upon necropsy:
  - Organs gross lesions recorded mostly in lungs (discolored), lymph nodes (enlarged, discolored), liver (discolored) and spleen (enlarged) consistent with historical data in this model
  - Despite multi-organ involvement, most vaccinated animals survived (7/8 in all vaccinated groups)

Side-by-side comparison of MVA manufactured either on CEF (TG-MVA$_{CEF}$ and MVA-BN®) or cell line (TG-MVA$_{CL}$) showed similar safety profile and immunogenicity supporting the safe use of TG-MVA$_{CL}$

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TG-MVA | Conclusions

- **TG-MVA$_{CEF}$ and TG-MVA$_{CL}$ demonstrate efficacy, immunogenicity and safety comparable to MVA-BN®**
  - **Protection** for severe mpox morbidity and mortality
  - Induction of **comparable level of Neutralizing anti-VACV antibody**
  - **Comparable peak viremia levels** observed in blood and throat swab
  - **Comparable antibody responses** against VACV and MPXV with similar magnitude and production kinetics
  - **Similar safety profile**

- **Change of manufacturing process to cell line did not impair vaccine potency and has no impact on immunotoxic potential compared to manufacturing on CEF**

➢ **TG-MVA$_{CL}$: a next generation candidate for future clinical development**

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Acknowledgments

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Thank you for your attention

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