Institut Pasteur

Unité de Biologie des Infections Virales Emergentes

Centre International de Recherche en Infectiologie

Review of Lassa fever host immune response and protective immunity

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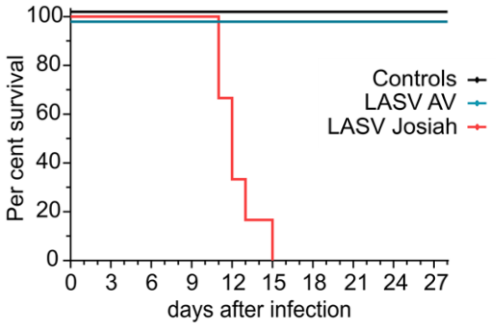
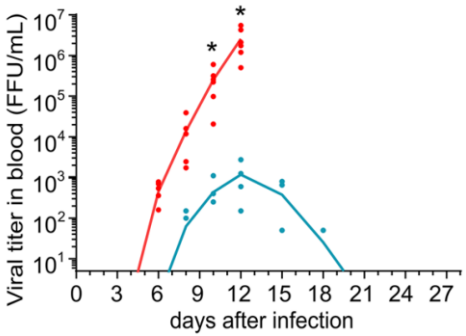
Accelerating the licensure of Lassa vaccines – Abuja, October 25-26, 2022

Pathogenesis and immune responses during Lassa fever

Relentless viral replication associated with fatal outcomes in cynomolgus monkeys

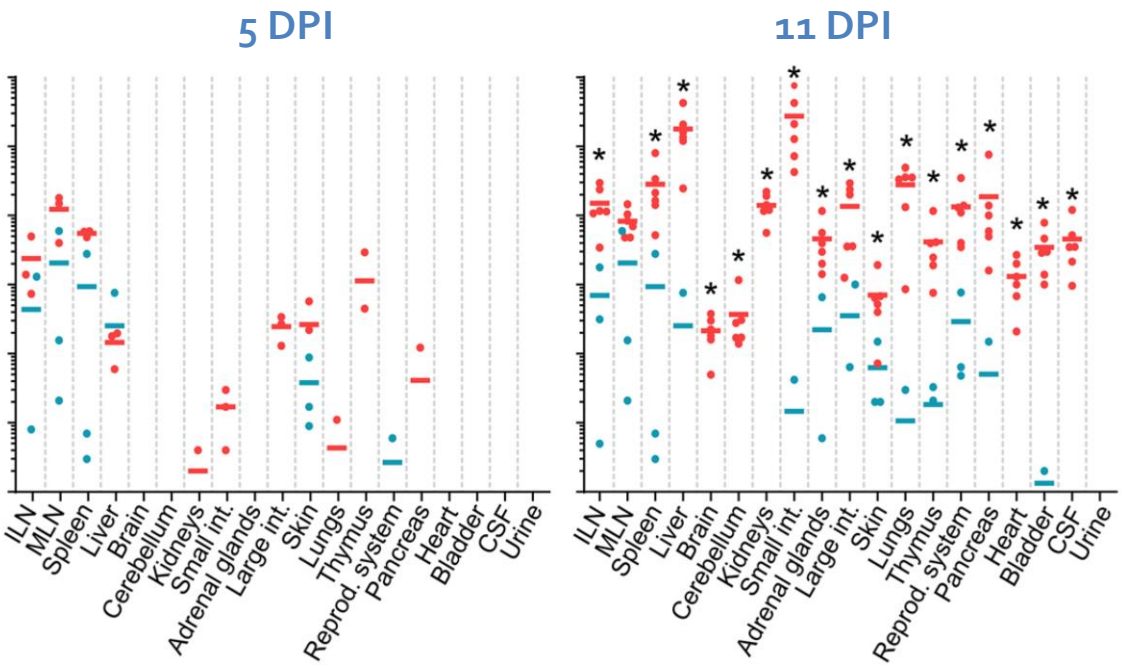




Systemic dissemination of **Josiah strain** in all organs and tissues with elevated titers in the terminal stages

AV strain does not significantly spread outside secondary lymphoid organs (SLO), and titers remain low during the course of the disease

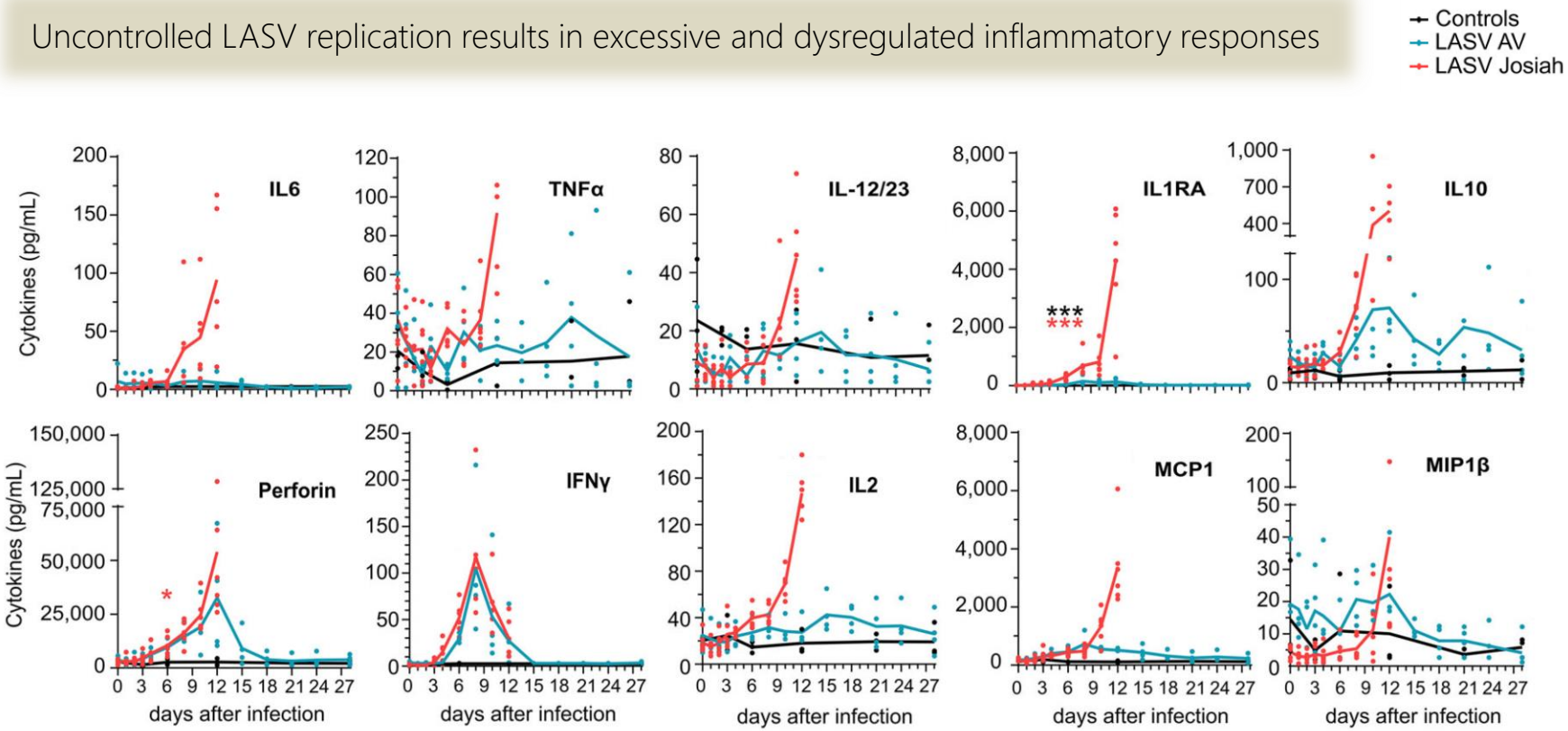
LASV replication is rapidly controlled during non-fatal LF



Baillet 2021, Comm Biol

Pathogenesis and immune responses during Lassa fever

Uncontrolled LASV replication results in excessive and dysregulated inflammatory responses

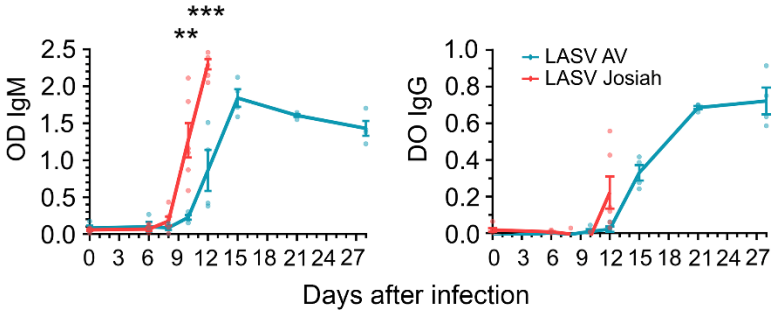


A cytokine / chemokine storm occurs in fatally-infected cynomolgus monkeys, with pathogenesis similar to septic shock syndrom

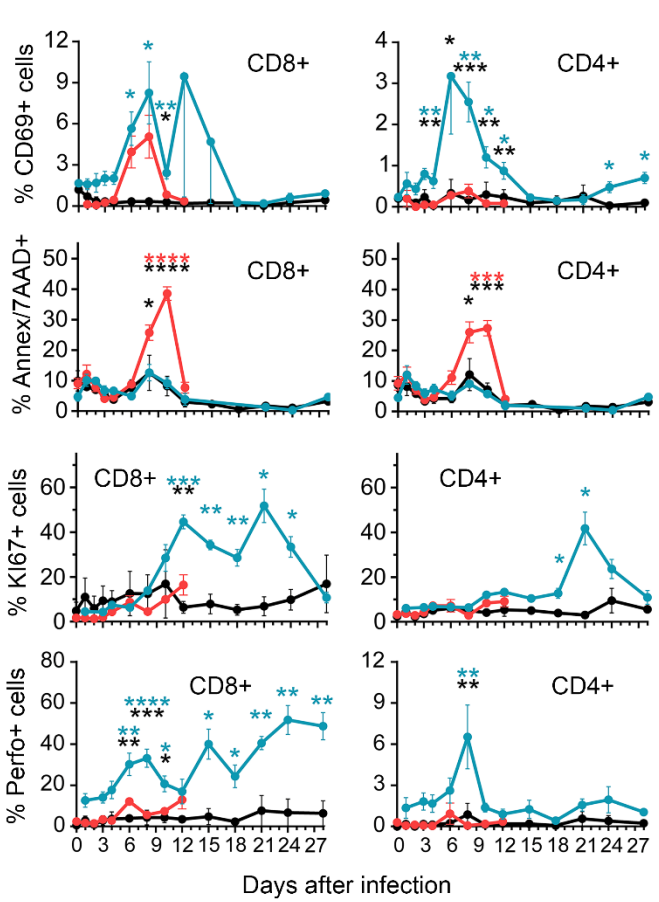
→ Multi-organ failure, hypovolemic shock, bleeding, neurological signs

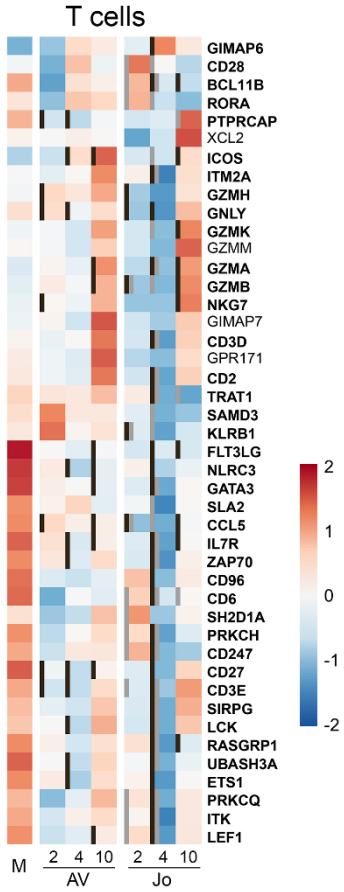
Baillet 2021, Comm Biol

Immune responses associated with the outcome of LASV



- No difference in terms of humoral responses between fatal and non-fatal outcomes (no NAb in both cases)





- Robust T-cell activation during non-fatal Lassa fever (*PBMC, spleen, lymph nodes*)

- No activation during fatal LASV infection, massive apoptosis of T cells in PBMC

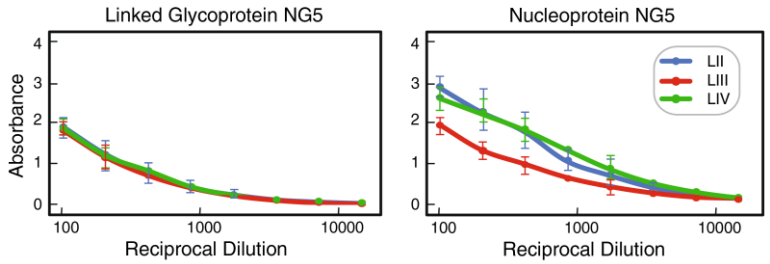
Control of LASV probably mainly mediated by T lymphocytes

No involvement of NAb in the natural control of Lassa fever

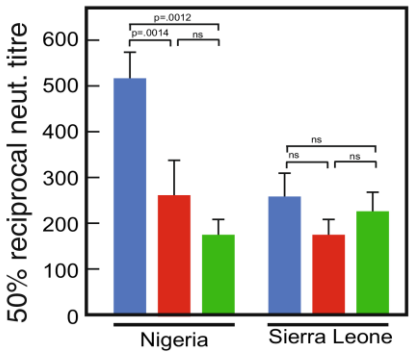
Baillet 2021, Comm Biol

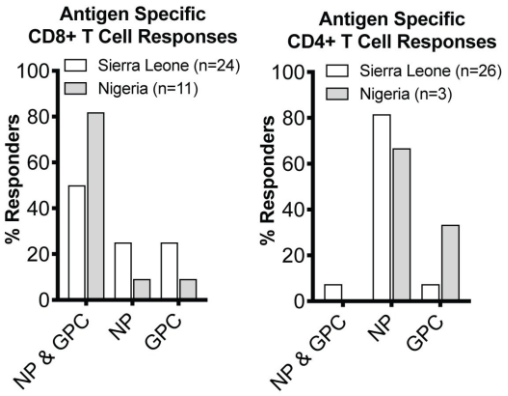
Correlates of protection in human Lassa fever

- Cross-reacting GP- and NP-specific IgG with neutralizing properties in Lassa fever survivors



Heinrich 2020, Sci Rep



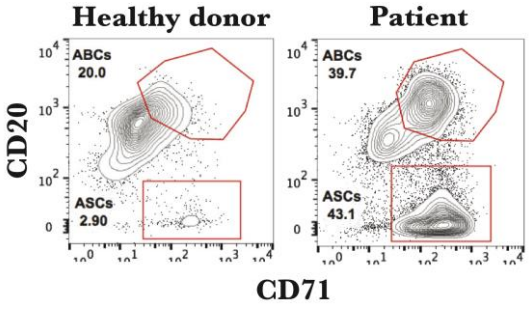


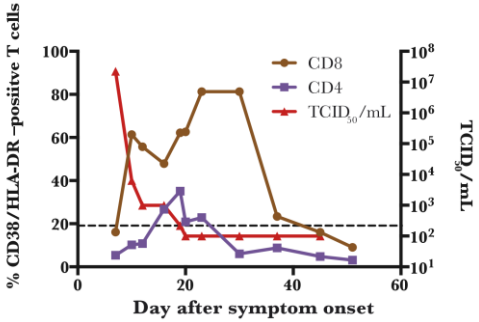
- Cross-reactive CD4+ and CD8+ T cells specific for GPC and NP in survivors

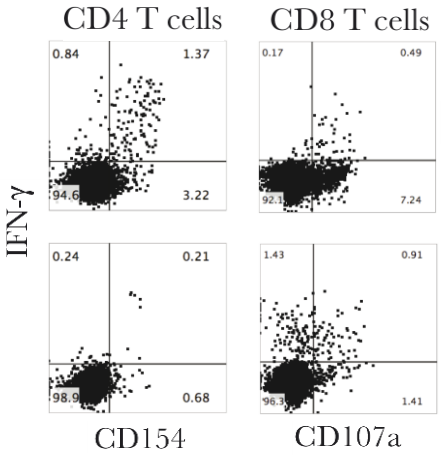
Sullivan 2020, PLoS Pathog

Sakabe 2020, J Virol

- Robust B- and T-cell activation in a Lassa fever case who survived







Day 20

Day 129

McElroy 2017 J Infect Dis

Conclusions on protective immune responses

- IgG responses are induced whatever the outcome

  ➡ *May be important but not sufficient for control*

- Neutralizing Ab are induced late during the course of infection

  ➡ *Probably not involved in the control of acute infection in primary LASV infection*

- CD4+ and CD8+ T cells specific for GPC and NP are induced during non-fatal infection

  ➡ *Cellular adaptive immunity is crucial for the control of LASV*

- Innate immunity could play an essential role in the early control of LASV dissemination

  ➡ *Avoid overwhelming release of viral material before induction of adaptive immunity*

What we learned from vaccine studies

Neutralizing Ab titers after immunization are not a good marker of efficacy

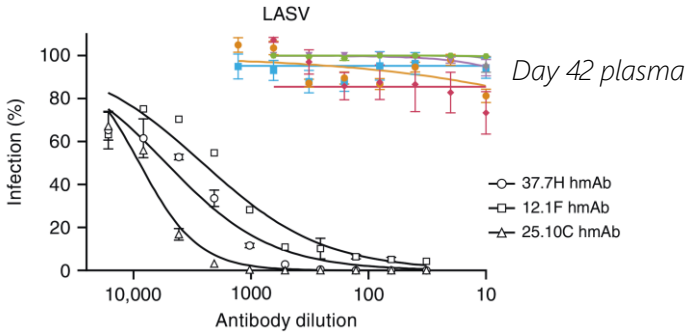
- Some vaccines are highly efficient without induction of NAbs after immunization or challenge

Vaccinia vectors expressing GP1 and GP2 w or w/o NP protect NHP but NAbs were never detected

Fisher-Hoch 2000, J Virol

Recombinant **rabies vaccine** expressing LASV GPC protects guinea pigs without inducing NAbs

Abreu-Mota 2018, Nature Comm



LASV viral replicon particles are efficient as a pre- and post-challenge vaccine without inducing NAbs

Kainulainen 2018 &2019 J Infect Dis

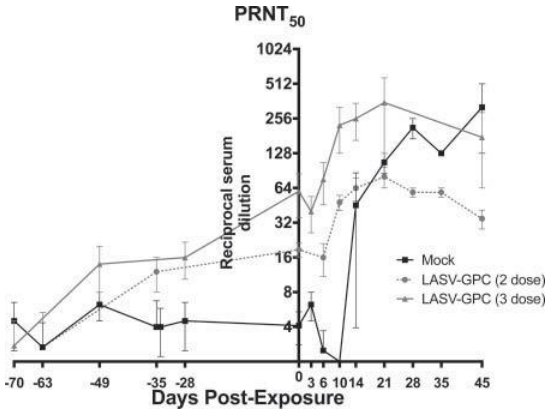
- Most vaccines work with only low titers of NAbs before the challenge

A **DNA vaccine** induced only very low titers before challenge, even after 3 doses

Cashman 2017, Hum Vacc Immun

A **ChAdOx1 vector** expressing LASV GPC protects guinea pigs without detectable NAbs

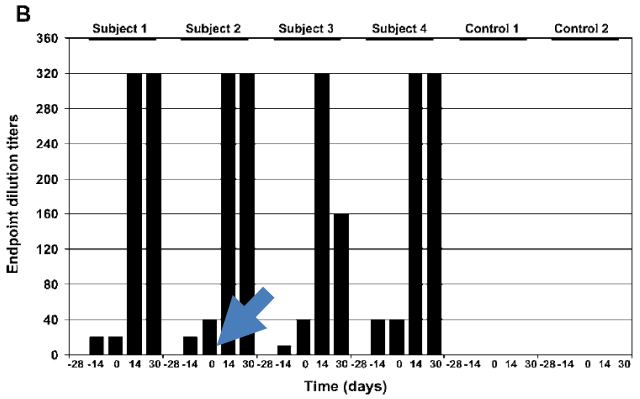
Fischer 2021, NPJ Vacc



Neutralizing Ab titers after immunization are not a good marker of efficacy

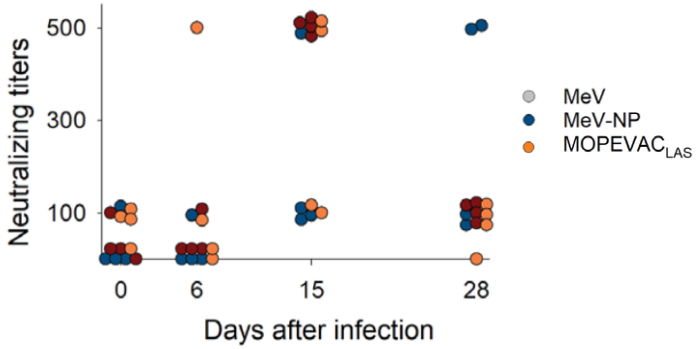
The **VSV-GPC vaccine** is efficient in NHP with only low titers of NAbs before the challenge

Geisbert 2005, PLoS Med *Cross 2020, JCI*



The **VSV-GPC vaccine** is efficient when administered 7 and 3 days before challenge

Cross 2022, Cell Rep



The **MV-LASV** and **MOPEVAC$_{LASV}$** vaccines are efficient in NHP despite low/no NAbs before challenge

Mateo 2019 Science Transl Med

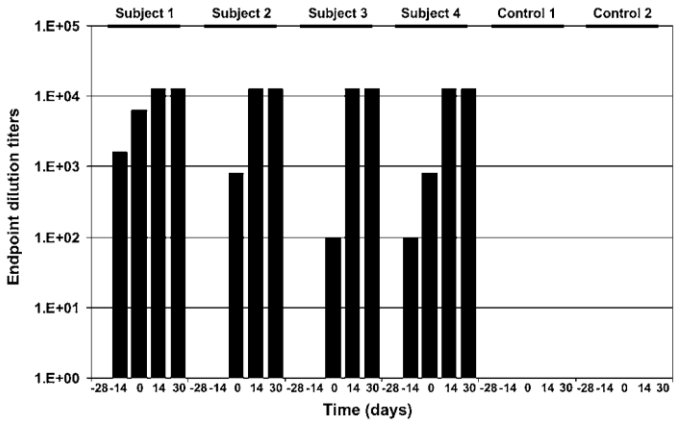
The **MV-LASV** and **MOPEVAC$_{LASV}$** vaccines are efficient in NHP when administered 8 days before challenge (*no NAbs before challenge*)

NAbs appeared rapidly after the challenge with most vaccines, suggesting that they were generated before the challenge, but at too low levels to be detectable after immunization

NAbs may play a role in the control of LASV but are not a reliable post-immunization marker of vaccine efficacy

Non-neutralizing LASV IgG are a good marker of efficacy, but are not sufficient

LASV IgG are detected at high levels after immunization with efficient vaccines

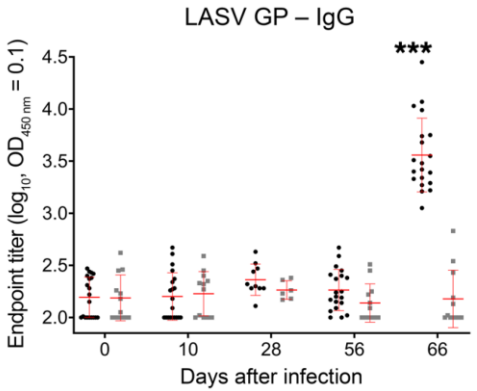


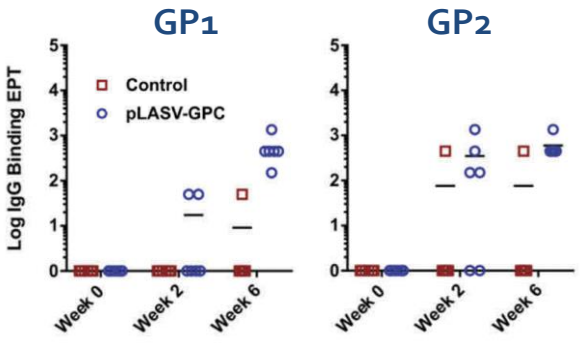
VSV-GPC vaccine, single immunization

Geisbert 2005, PLoS Med

VSV-GPC vaccine, prime-boost immunization (*quadrivalent*)

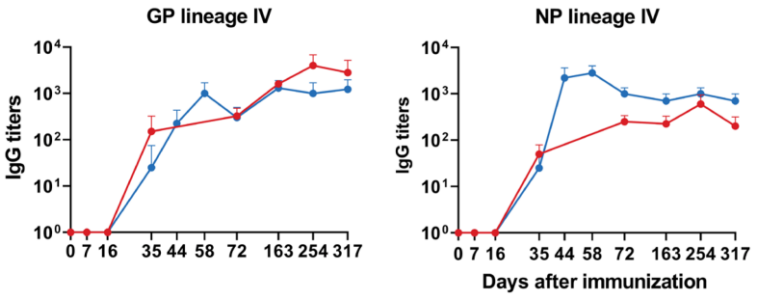
Cross 2020, JCI





DNA vaccine, prime-boost immunization

Jiang 2019, Hum Vacc Immun



Mateo 2021 Science Transl Med

MV-LASV vaccine, IgG cross-react with lineage 2 and 7

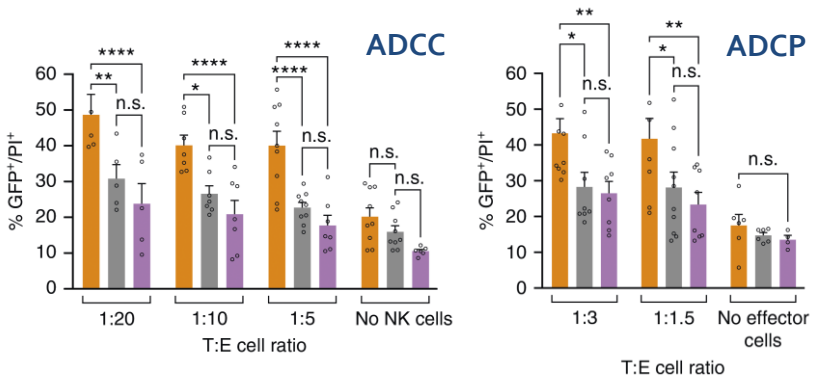
MOPEVAC$_{LASV}$ vaccine, single immunization

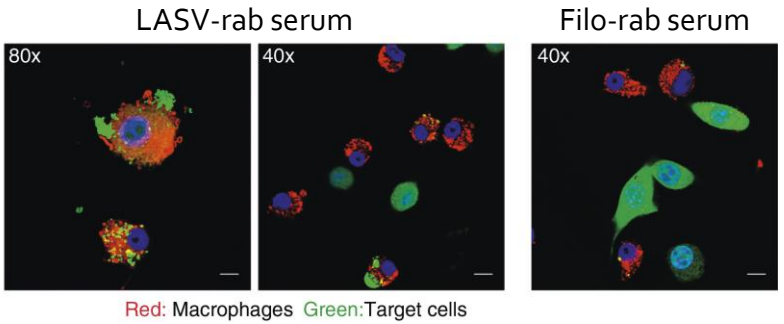
LASV IgG titers at day 37 = 250, 250, 250 and 1,000

Mateo 2019, Science Transl Med

Non-neutralizing LASV IgG are a good marker of efficacy, but are not sufficient

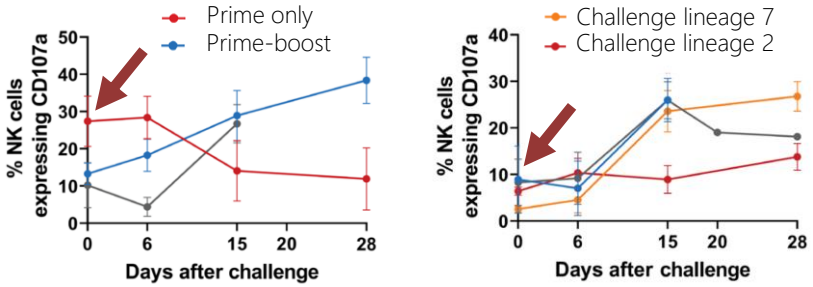
LASV IgG non-neutralizing properties may play a role in the protection





ADCC and ADCP seem to be involved in the protection induced by a rabies-LASV vaccine

Abreu-Mota 2018, Nature Comm



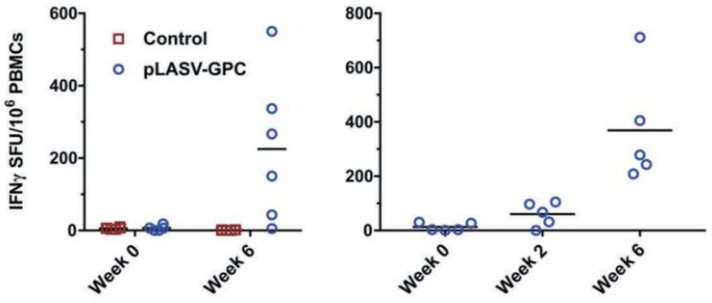
LASV IgG induced by the MV-LASV vaccine (*Josiah strain*) are able to mediate ADCC (*still present one year after immunization*) against different lineages

Mateo 2021, Science Transl Med

However, some inactivated vaccines failed to protect despite robust IgG responses

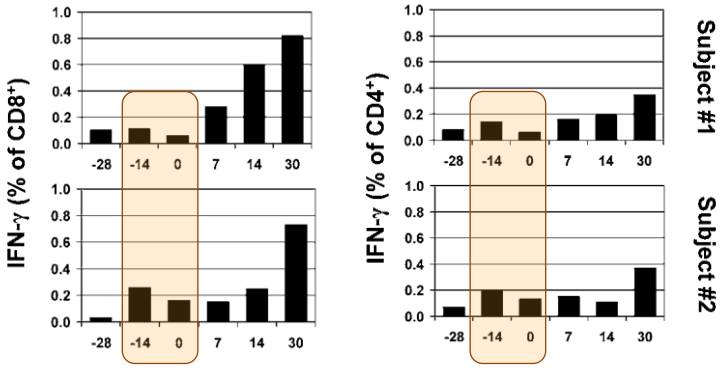
Non-neutralizing LASV IgG and their functional properties are important, but not sufficient, markers of vaccine efficacy

T-cell responses, a mandatory component of vaccine-induced LASV immunity



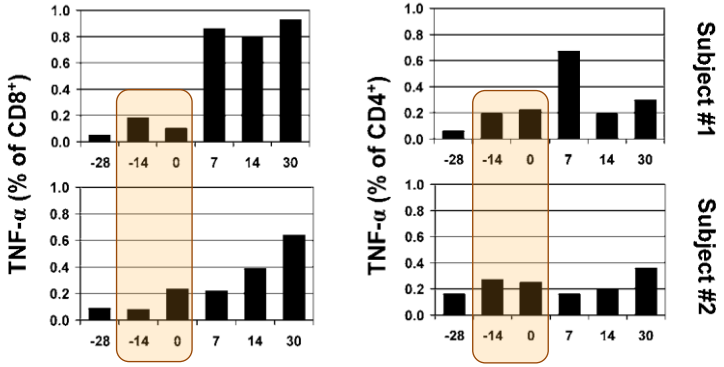
Post-immunization T-cell responses, **DNA vaccine**

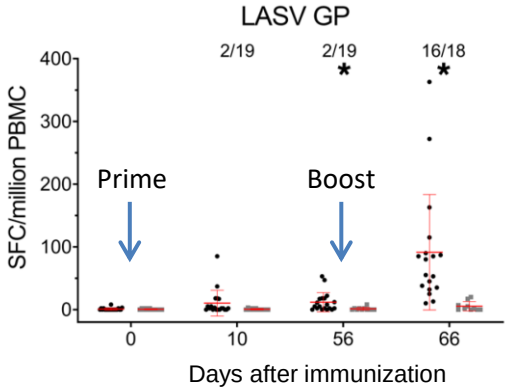
Jiang 2019, Hum Vacc Immun



The **VSV-GPC vaccine** induces CD4+ and CD8+ T cells specific for LASV GPC

Geisbert 2005 PLoS Med



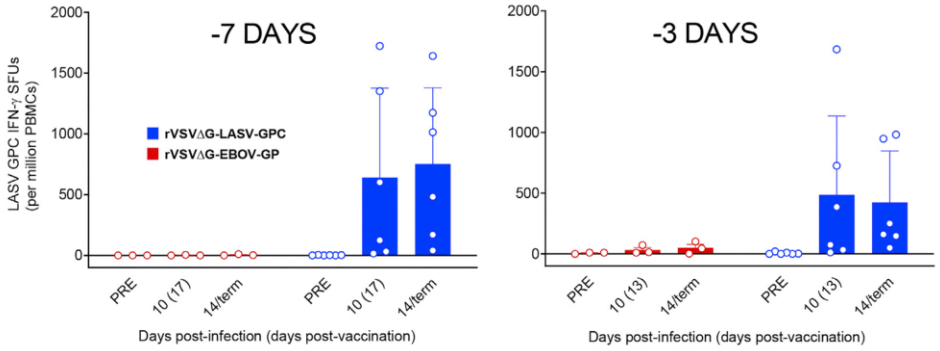


The response is increased by a boost immunization

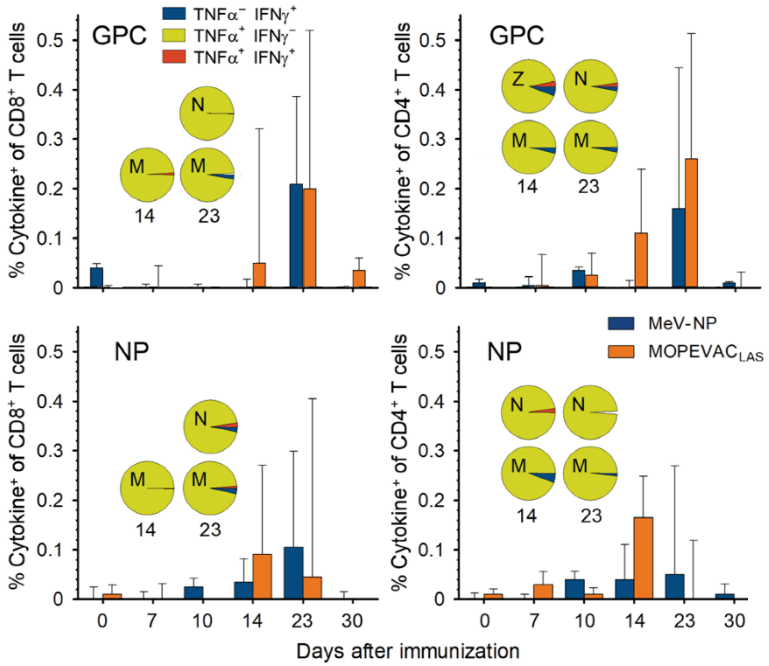
Cross 2020, JCI

T cells appeared about two weeks after immunization after a short-term single shot

Cross 2022, Cell Rep

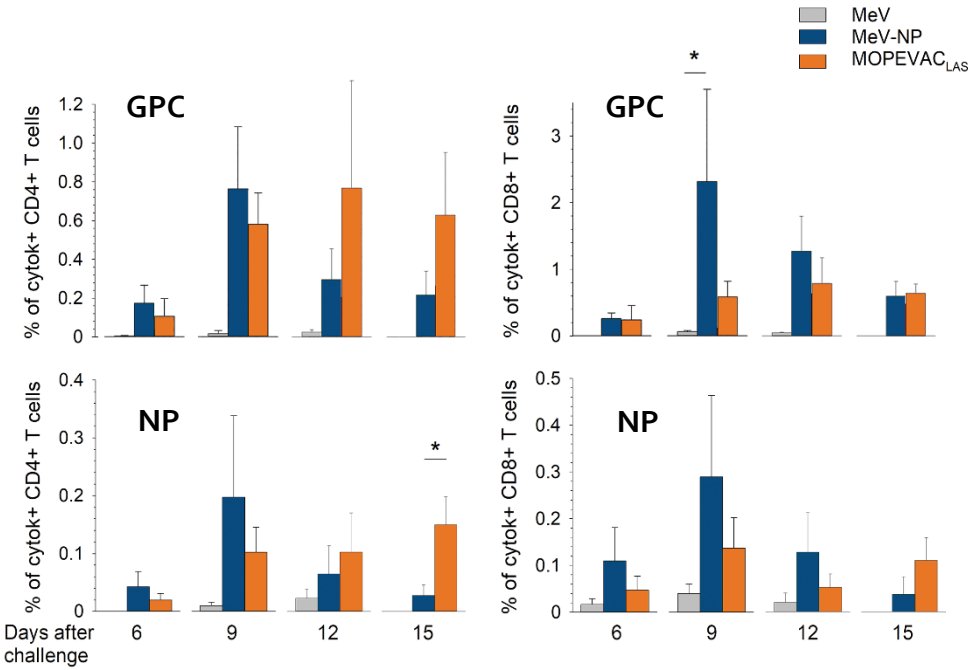


T-cell responses, a mandatory component of vaccine-induced LASV immunity



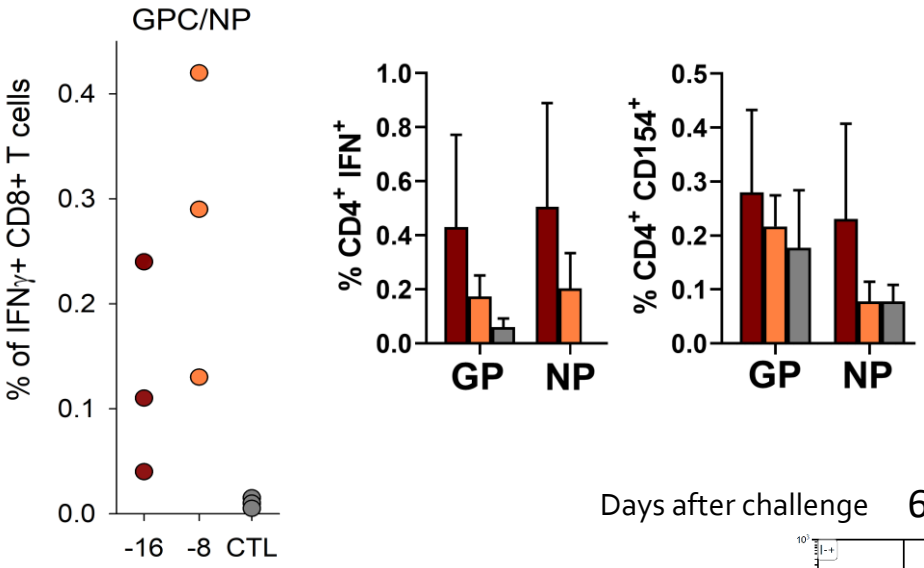
A single injection of **MV-LASV** or **MOPEVAC$_{LASV}$** induces CD4+ and CD8+ T cells specific for LASV GPC and NP in PNH

The T-cell responses are more intense after the challenge



T-cell responses, a mandatory component of vaccine-induced LASV immunity

- Protection after short-term immunization is associated with robust CD8+ and CD4+ T-cell responses

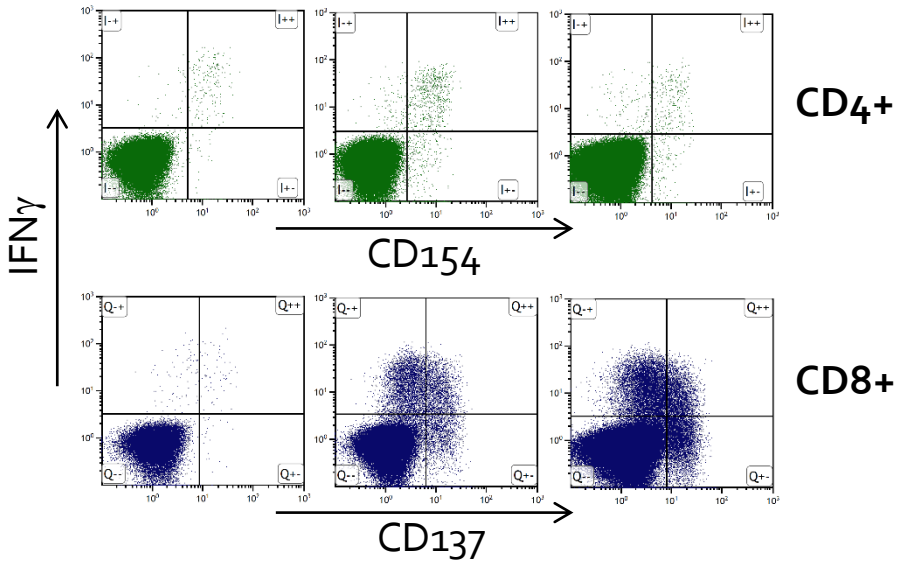


No LASV IgG or NAb at the time of challenge when immunization was performed at day -8

MV-LASV 9 days after challenge

MOPEVAC$_{LASV}$

Days after challenge 6 9 12

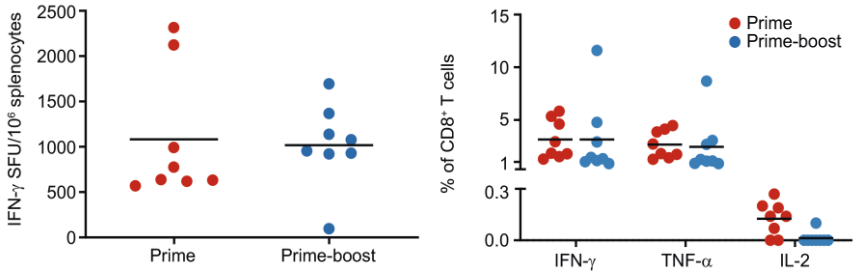


Immunomonitoring and prediction of vaccine candidate efficacy

- Non-neutralizing LASV IgG responses
- Functional properties of LASV IgG (*ADCC, ADCP*)
- CD8+ and CD_4+ T-cell responses against LASV (*ELISPOT, ICS*)

Low % of specific T cells expected in PBMC after immunization

LASV-specific T cells in spleen of mice immunized with ***ChAdOx1-LASV***



Fischer 2021 NPJ Vacc

Also important to check the cross-reactivity with other lineages and the long-term persistence of humoral and cellular immune responses

1. Evaluate the immunogenicity in a relevant pre-clinical model (*macaque*)
2. Obtain the same immunogenicity (*qualitatively and quantitatively*) in clinical trials

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