mRNA vaccine; CCHFV

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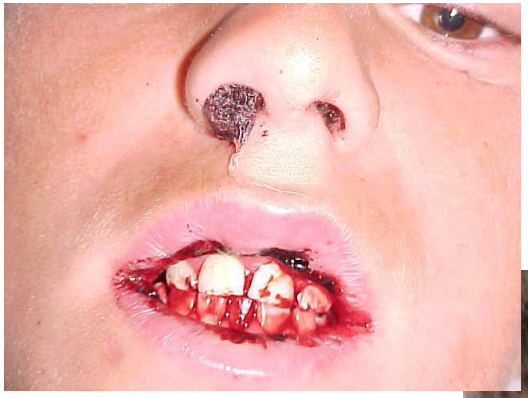
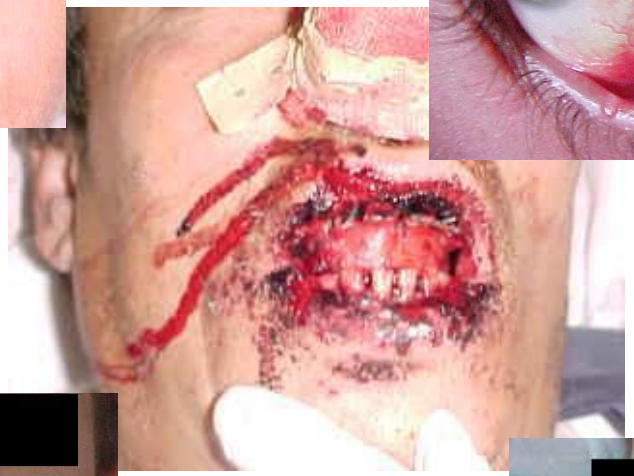
Crimean – Congo Haemorrhagic fever- Is in the blue Print list of WHO (highlight the emergency of vaccine and Antiviral for this disease)

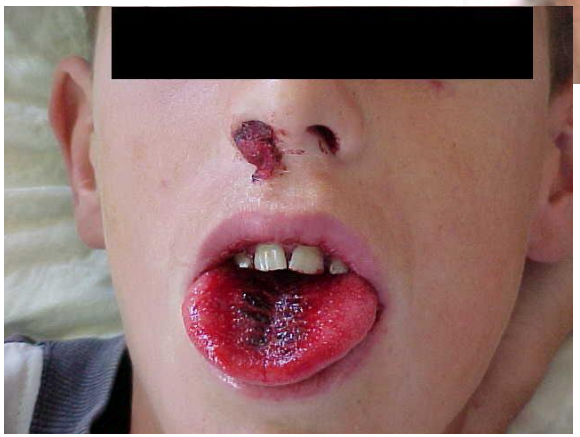
CCHFV is one of the formidable viral haemorrhagic fevers.

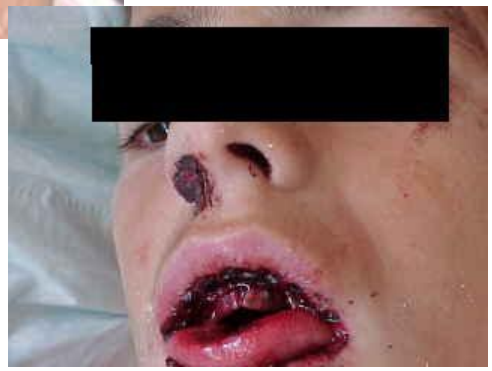
- Cases reported from 40 countries.
- Ticks has been found even in North Europe such as Sweden sience 2 years ago

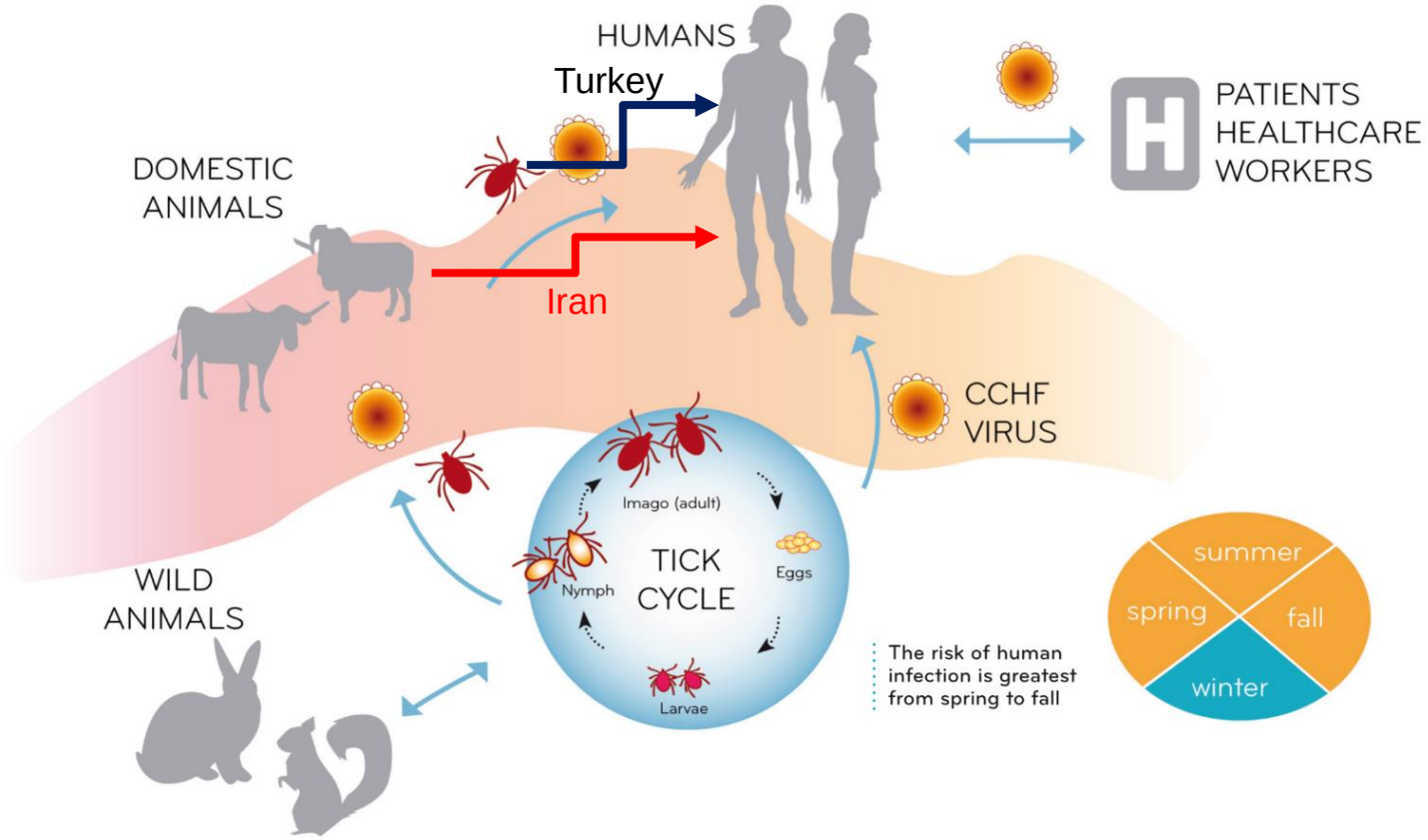
Distribution of CCHF correlates with principal vector of virus, ticks belonging to genus Hyalomma



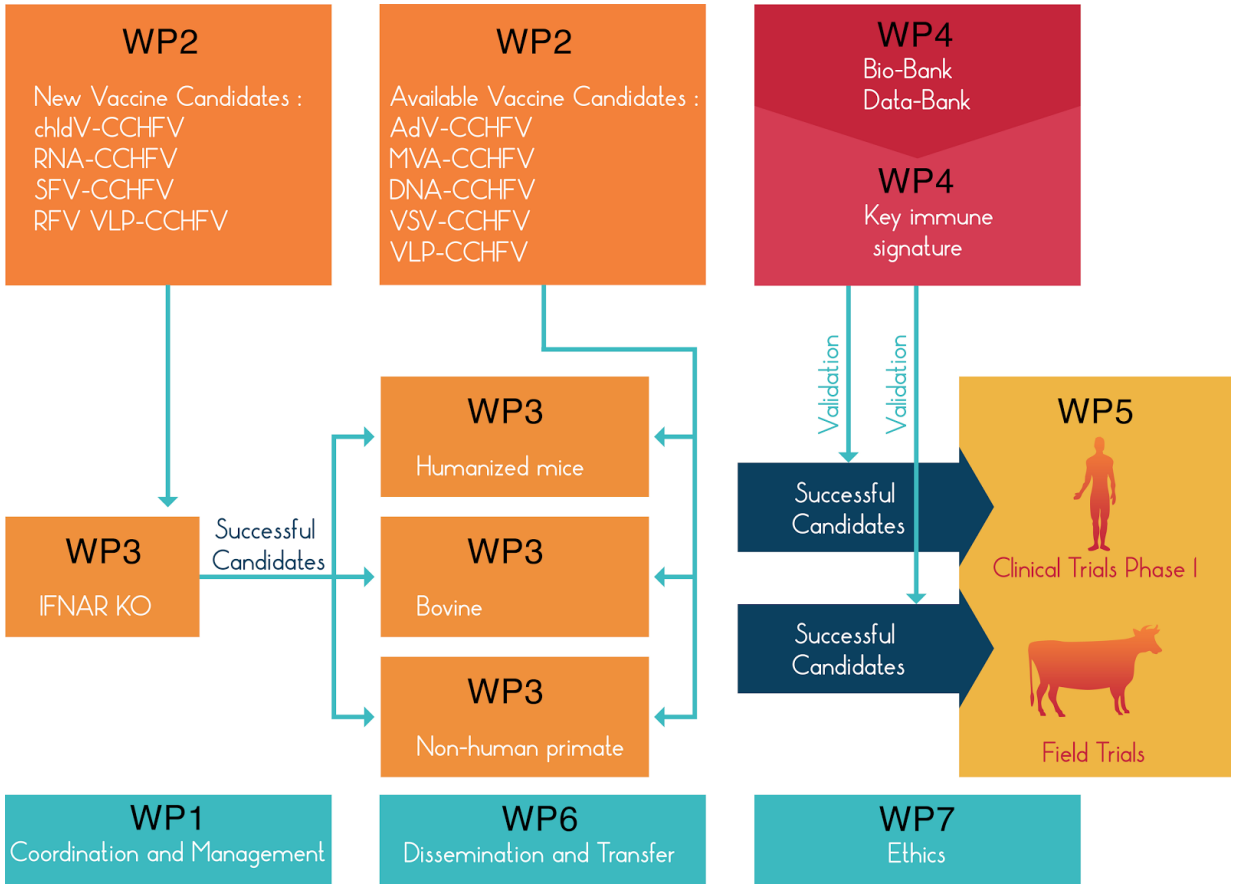







HUMANS
Turkey
DOMESTIC ANIMALS
Iran
PATIENTS HEALTHCARE WORKERS
CCHF VIRUS
WILD ANIMALS
Imago (adult)
Eggs
Larvae
Nymph
TICK CYCLE
The risk of human infection is greatest from spring to fall
summer
fall
winter
spring

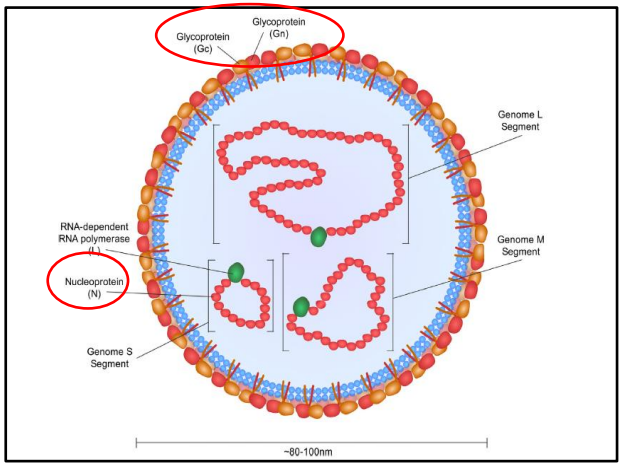
***Hyalomma marginatum*, are "two-host" ticks**
***Hyalomma* are "hunting" ticks, which can quest up to 400 m to find their hosts (including humans).**


WP2
New Vaccine Candidates :
chIdV-CCHFV
RNA-CCHFV
SFV-CCHFV
RFV VLP-CCHFV
WP2
Available Vaccine Candidates :
AdV-CCHFV
MVA-CCHFV
DNA-CCHFV
VSV-CCHFV
VLP-CCHFV
WP4
Bio-Bank
Data-Bank
WP4
Key immune signature
Validation
Validation
WP3
Humanized mice
WP3
IFNAR KO
Successful Candidates
WP3
Bovine
WP3
Non-human primate
Successful Candidates
Successful Candidates
WP5
Clinical Trials Phase I
Field Trials
WP1
Coordination and Management
WP6
Dissemination and Transfer
WP7
Ethics

WP 3 – DNA based vaccine

DNA plasmids coding for different CCHFV proteins.

- Nucleoprotein
- Precursor glycoprotein M (include non-structural proteins)
- Glycoprotein Gc
- Glycoprotein Gn



Partner 1, FOHM

WP 3 – A DNA-based vaccine protects against Crimean-Congo haemorrhagic fever virus disease in a Cynomolgus macaque model.

Nature Microbiology | VOL 6 | February 2021 | 187–195 | www.nature.com/naturemicrobiology

Group	1	2
Plasmid(s)	M + N	Control

1st immunization and blood sample

2nd immunization and blood sample

3rd immunization and blood sample

4th blood sample

CCHFV Hoti challenge

3 weeks

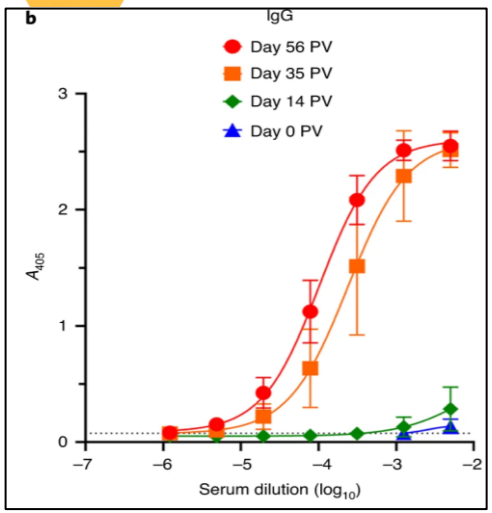
3 weeks

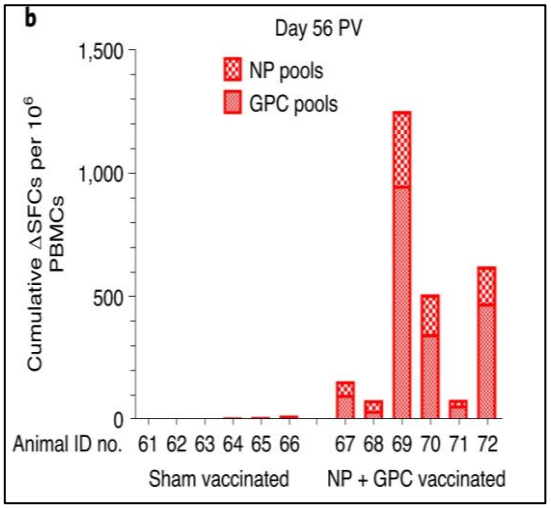
3 weeks

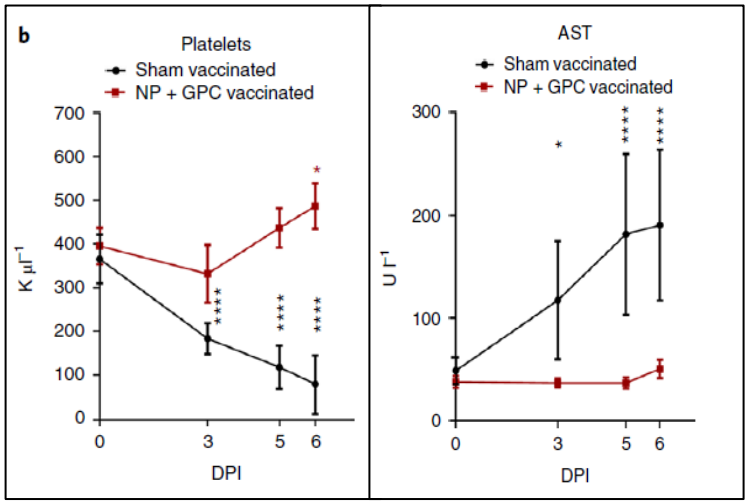
- Non Human Primates (NHP)
- 6 per group, 2 groups
- 3 immunizations
- Total of 2 mg DNA/animal at each immunization (1 mg M and 1 mg N)
- End point – 6 days post challenge

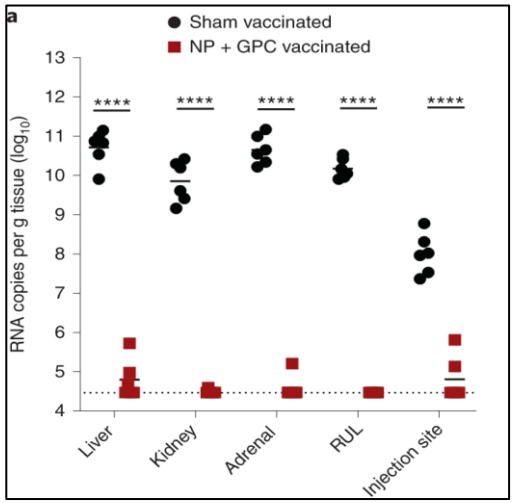
Partner 1, FoHM; partner 7, KI, NIH

WP 3 – A DNA-based vaccine protects against Crimean-Congo haemorrhagic fever virus disease in a Cynomolgus macaque model.









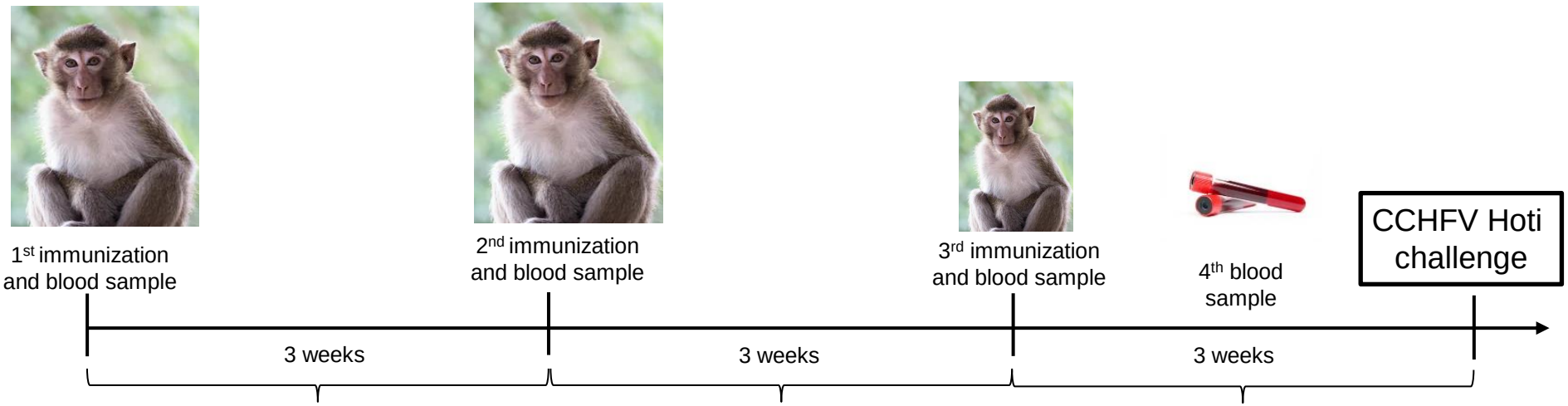
- Immunological results
  - Vaccination induced CCHFV specific antibodies after 2 immunizations
  - CCHFV-specific T-cell responses against N and G
- Clinical results
  - Vaccination prevented changes in blood chemistry often associated with poor outcome of CCHF in humans
  - Vaccination significantly reduced CCHFV viral shedding and viral burden in several tissues tested.

Partner 1, FoHM; partner 7, KI, NIH

WP 3 – DNA based vaccine protects NHP against CCHF.

Confidentiellt

Group	1	2	3	4
Plasmid(s)	M + N	N	M	Control



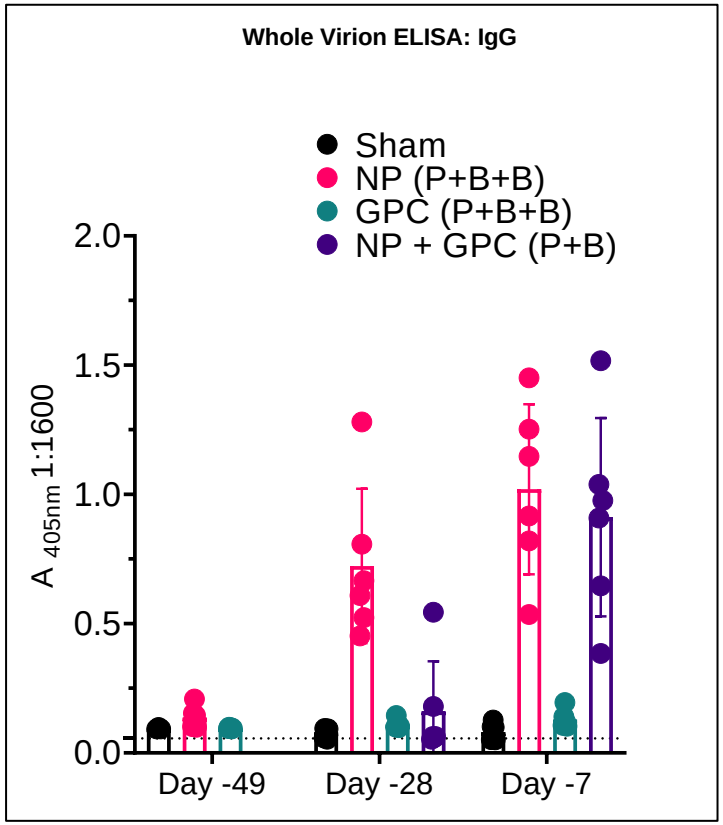
- Non Human Primates (NHP)
- 6 per group
- 2 OR 3 immunizations
- Total of 2 mg DNA/animal at each immunization
- End point – 6 days post challenge

Partner 1, FoHM; partner 7, KI, NIH

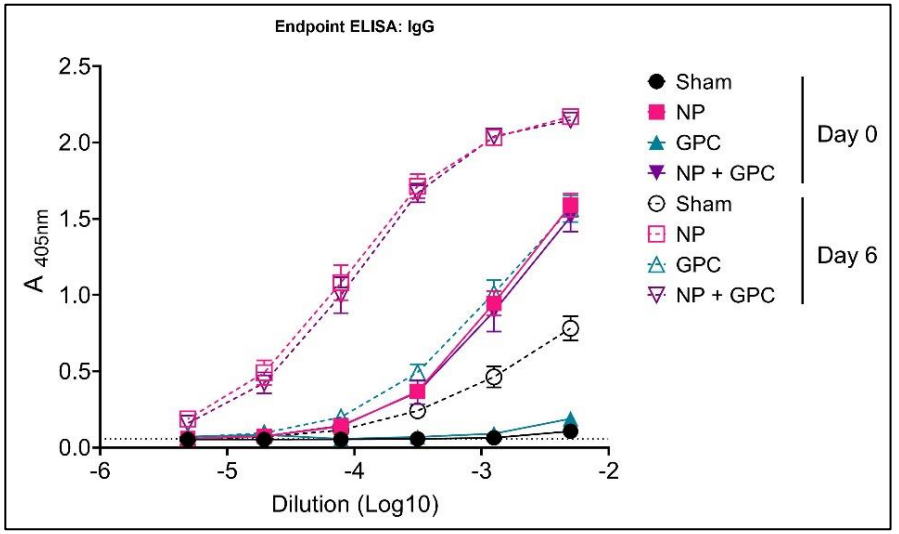
WP 3 – DNA based vaccine protects NHP against CCHF

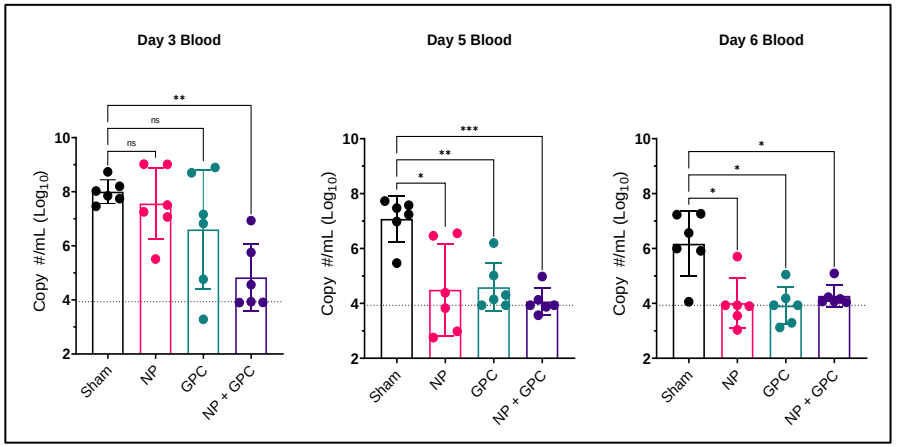
Confidentiellt

Before challenge



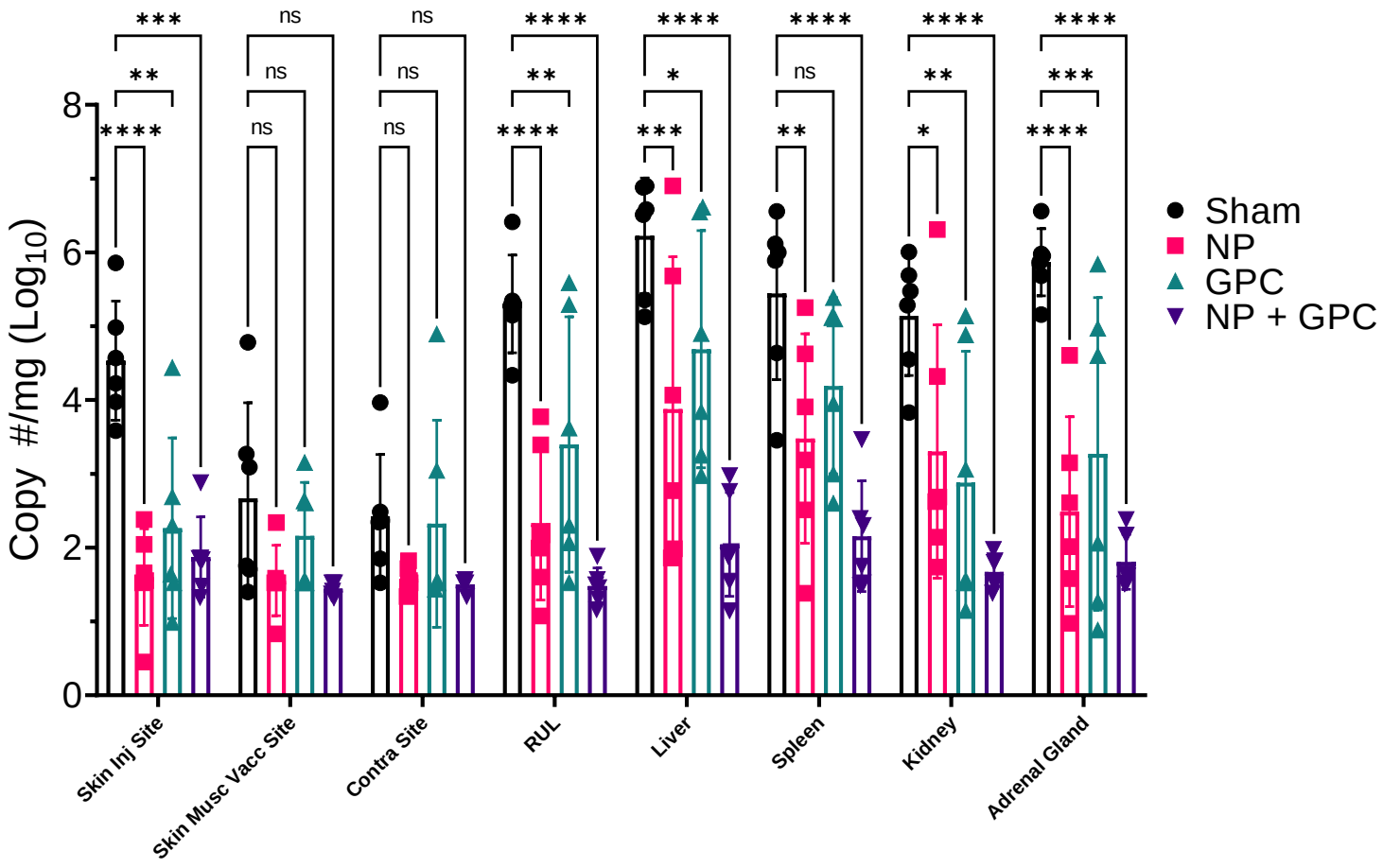
After challenge





Partner 1, FoHM; partner 7, KI, NIH

Day 6 Tissues Difference compared to sham

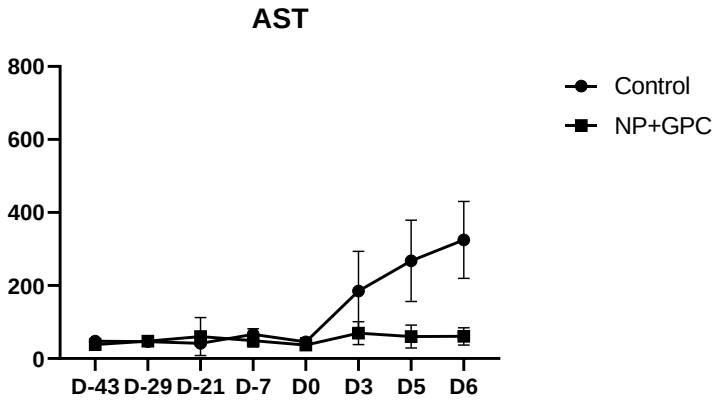


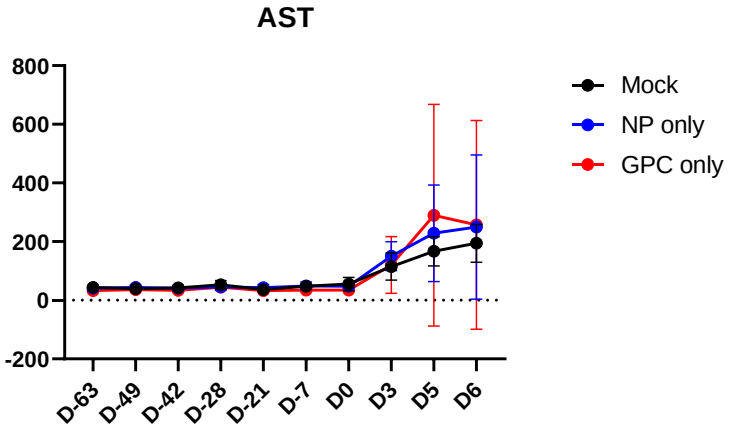
Partner 1, FoHM; partner 7, KI, NIH

WP 3 – DNA based vaccine protects NHP against CCHF

Confidentiellt

Biochemistry data





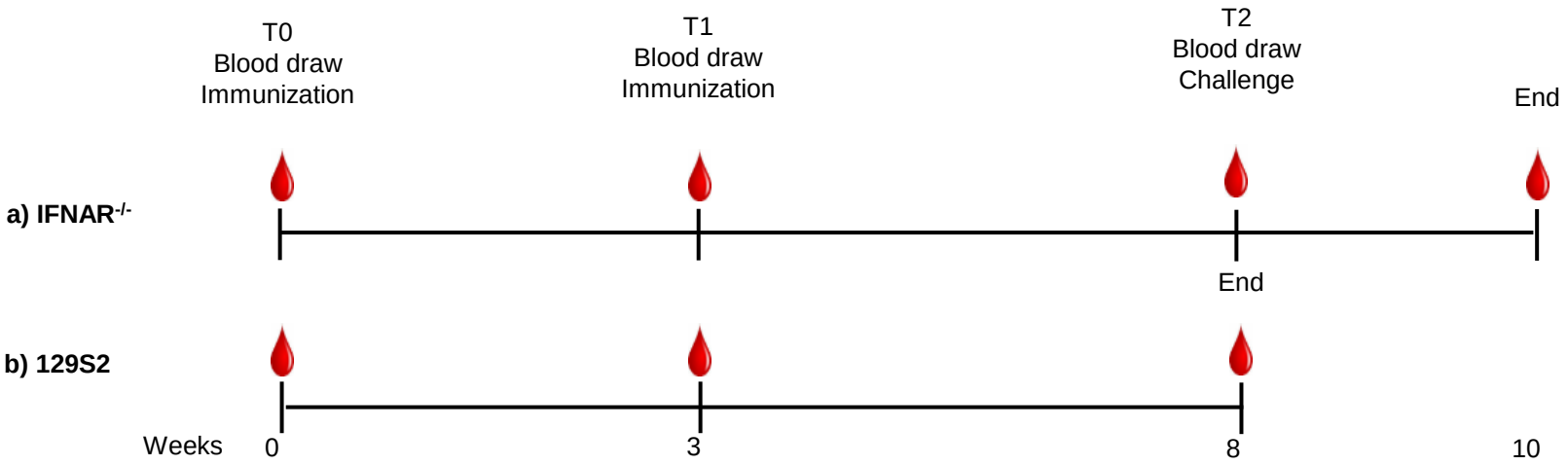
NP+GPC	NP or GPC
Hepatic functions (ALP, ALT, AST, and T bilirubin) in vaccinated group were normal during the study. **The control animals elevated ALT and AST after inoculation**	**Hepatic functions (ALP and AST) in all groups were elevated after inoculation**

- Major conclusions is that double antigen conferred the most protection while single antigen was not as effective.

Partner 1, FoHM; partner 7, KI, NIH

Nucleoside-modified mRNA vaccines protect IFNAR$^{-/-}$ mice against Crimean Congo hemorrhagic fever virus infection

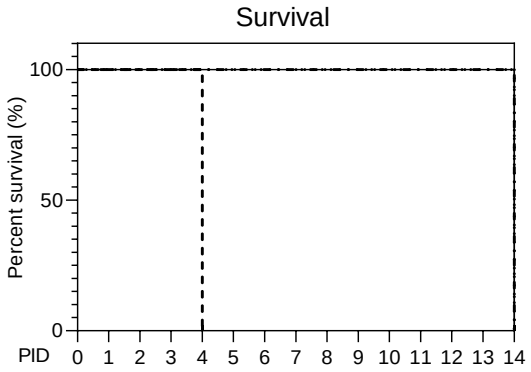
Appelberg et al 2022. J Virol.

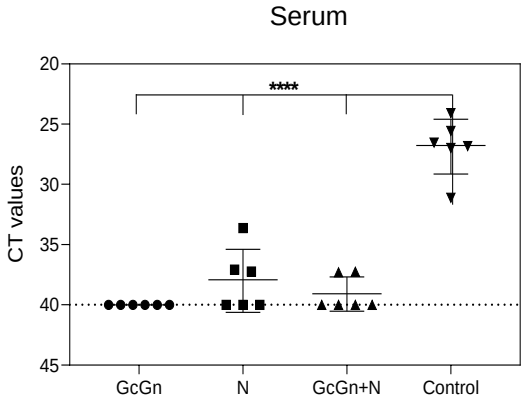


- IFNAR$^{-/-}$ mice lacking type I inerferon receptor and immunocompetent mice
- 4 different immunition groups: 1: GcGn; 2: N; 3: GcGn+N and 4: Control
- Intradermal injections of mRNA-LNP
- Immunocompetent mice euthanized 5 weeks after last immunization
- IFNAR$^{-/-}$ mice was challenged with 400 pfu CCHFV IbAr10200 (i.p)

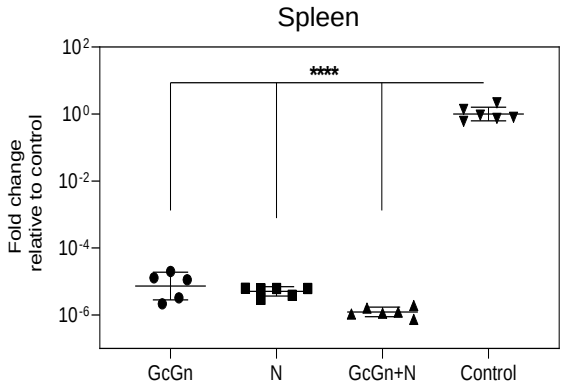
Survival and viremia

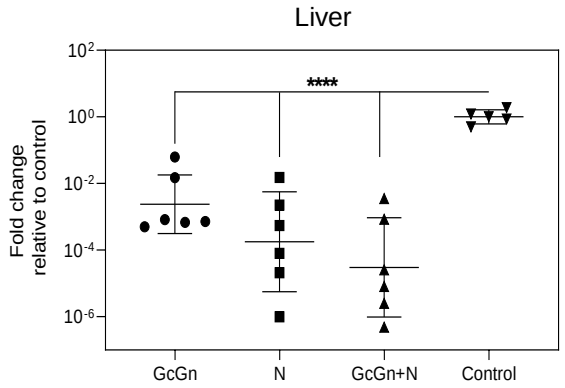
- Immunization, independent of vaccine candidate, induced 100% protection against CCHFV infection





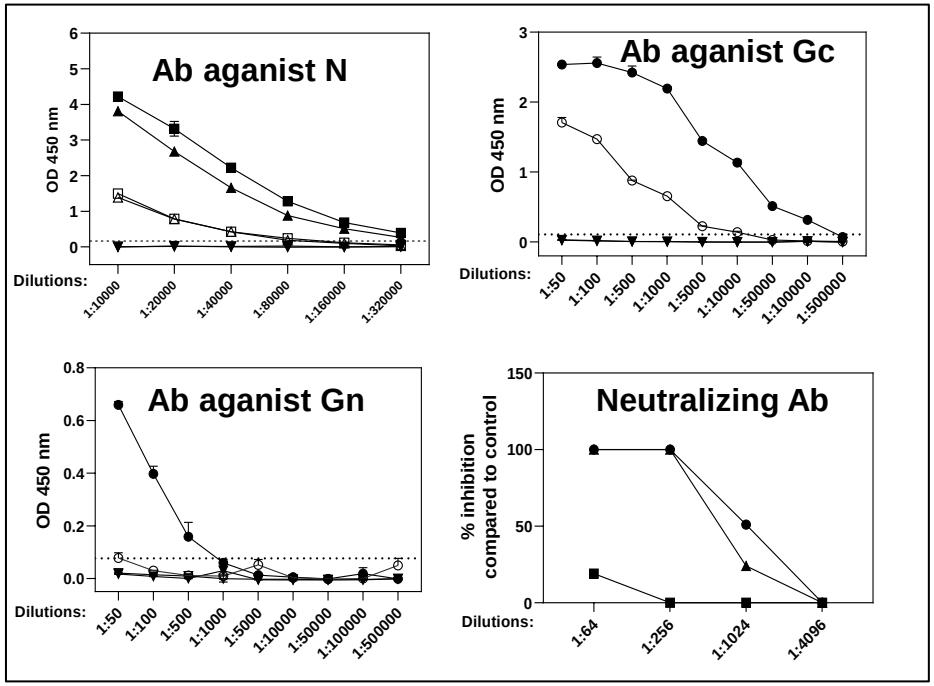
- Significant more viral RNA in serum, spleen and liver from control mice compared to immunized



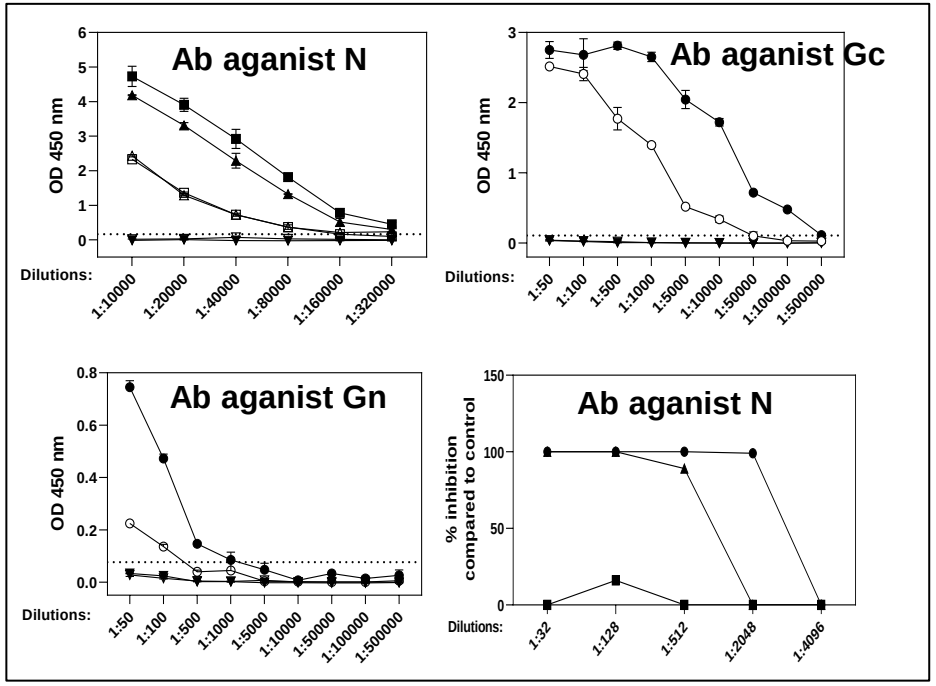


mRNA-LNP induced antibody titers and NT antibodies

IFNAR$^{-/-}$ mice



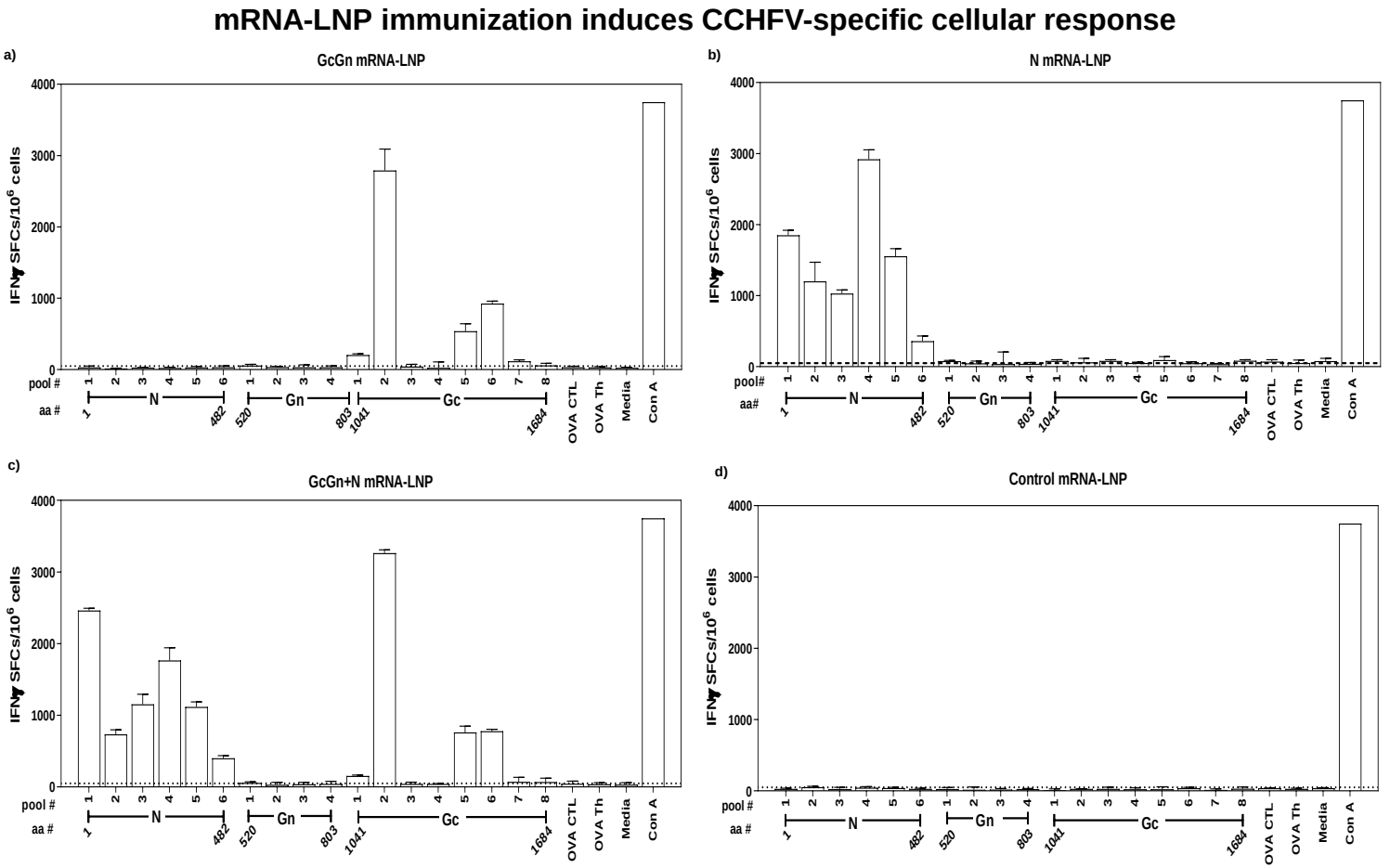
Immunocompetent mice



T1: □ N △ GcGn+N ○ GcGn ▽ Control

T2: ■ N ▲ GcGn+N ● GcGn ▼ Control

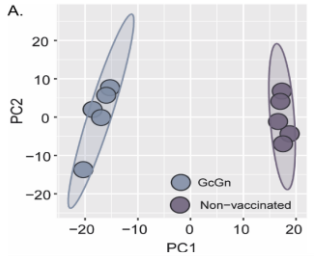
mRNA-LNP activated T cells in WT mice

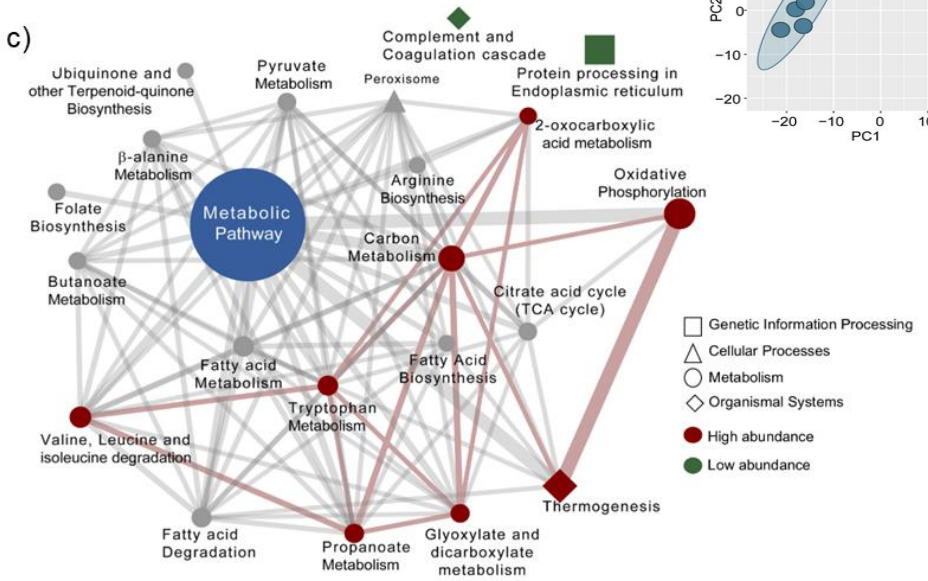


- Spleens from immunized immunocompetent mice was homogenized
- Cells counted and mixed with pools of peptides based on the CCHFV N, Gc or Gc proteins

mRNA-LNP vaccine induced proteomic changes

- To identify and better understand more large-scale potential differences between the two candidates and, in addition, compare to unvaccinated mice after CCHFV infection
- Liver samples from GcGn, N and control immunized mice after CCHFV infection
- No difference in protein expression between GcGn and N vaccinated mice.
- Clear separation between control and GcGn or N vaccinated mice.
- Most of the effected proteins were associated to “metabolic pathways.”
  For example:
  - oxidative phosphorylation,
  - propanoate metabolism
  - valine leucine and isoleucine degradation
  - carbon metabolism
- The results indicate a metabolic recovery in the liver of vaccinated mice.





Summary and conclusion

- Two immunizations with mRNA vaccine encoding for only CCHFV GcGn or N, or the combination of the two, induces a 100% protection of IFNAR$^{-/-}$ mice against CCHF.

- Both vaccine candidates induce:
  - high antibody levels (anti-N and anti-Gc).
  - cellular immunity. Result indicate that a large part of N can act as an antigen, while only a specific part of the glycoprotein induces a cellular response.

- No difference in the protein profile between the two vaccine candidates, but a distinct shift in metabolism compared to unvaccinated mice.

- Survival of mice immunized with only N mRNA-LNP strongly indicate that neutralizing antibodies is not necessary.

Next Step

- Doseing (Ongoing)
- Durability (ongoing)
- NHP Data
- Clinical Phase I

Thank you

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