

# Therapeutic Vaccines moving forward

HBV Forum Jan 17 2022

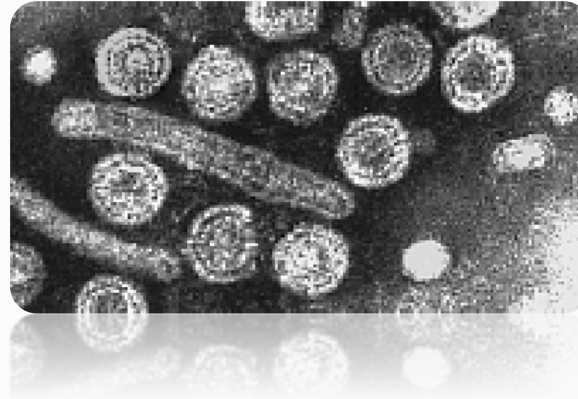
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# Immune control determines the course of hepatitis B

HBV



**strong antibody and  
effector T cell response**



**self-limiting infection**

**immune control**

**therapeutic  
vaccine**

**no neutralizing antibodies  
T cells are scarce,**

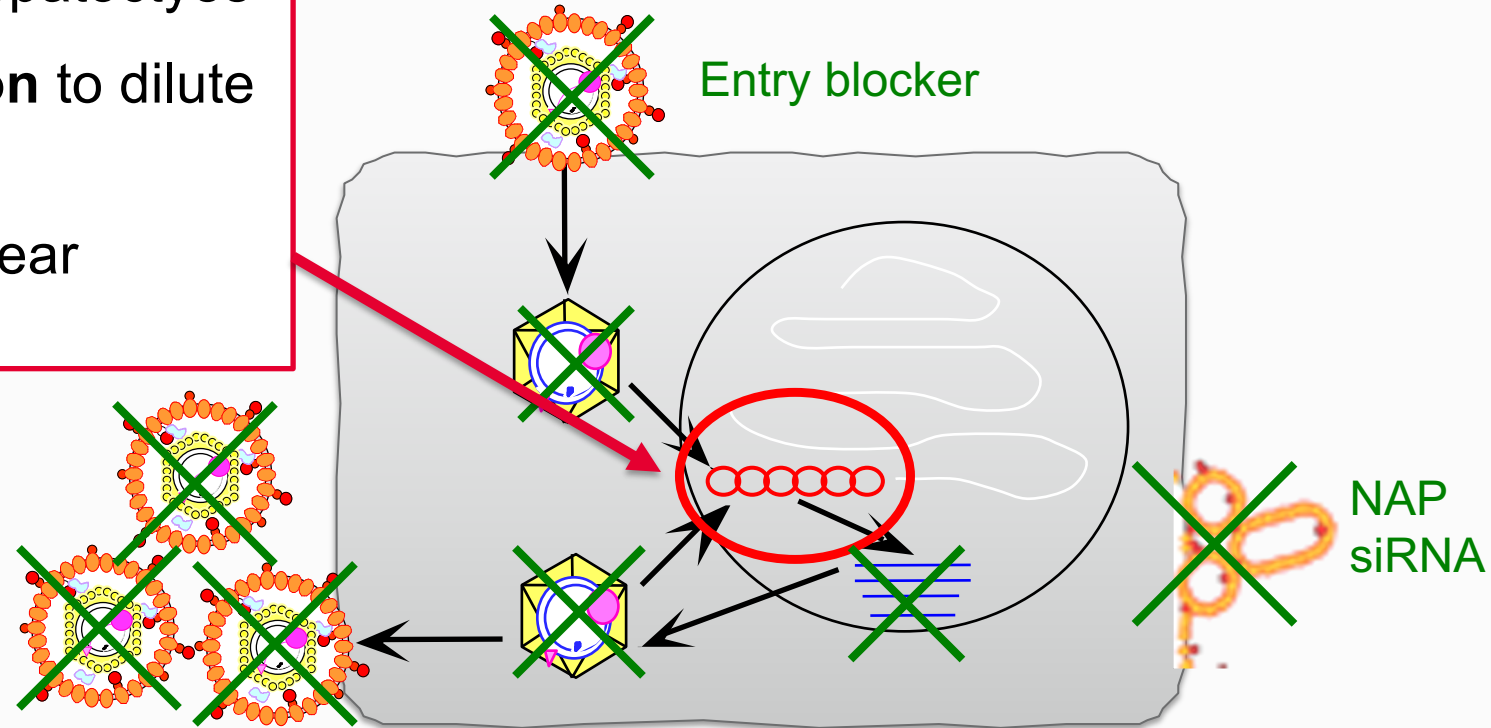


**chronic infection**

**immune tolerance**

# How can hepatitis B be cured?

1. **killing** of infected hepatocytes
2. inducing **cell division** to dilute cccDNA over time
3. **degradation** of nuclear cccDNA



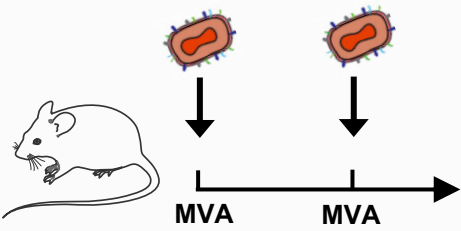
**Nucleos(t)ide analogues**  
Capsid Assembly inhibitors

**Interferons**  
TLR agonists  
siRNA

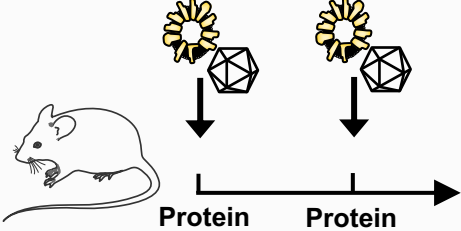
NAP  
siRNA

Therapeutic hepatitis B vaccine  
activating T cells

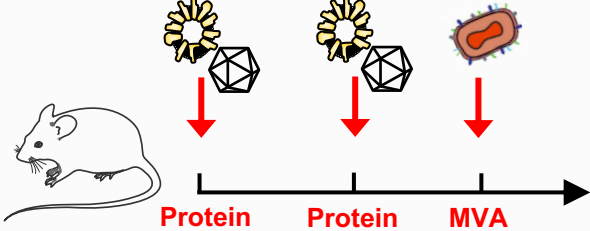
# Rational for the heterologous prime-boost *TherVac B* strategy



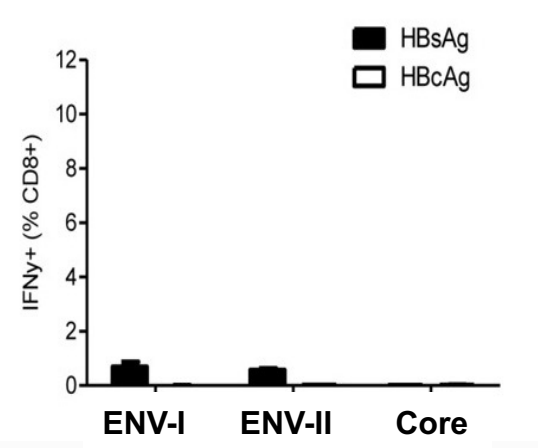
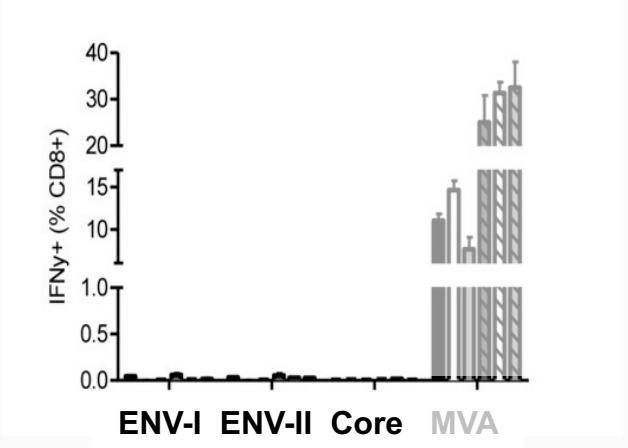
**MVA → MVA**



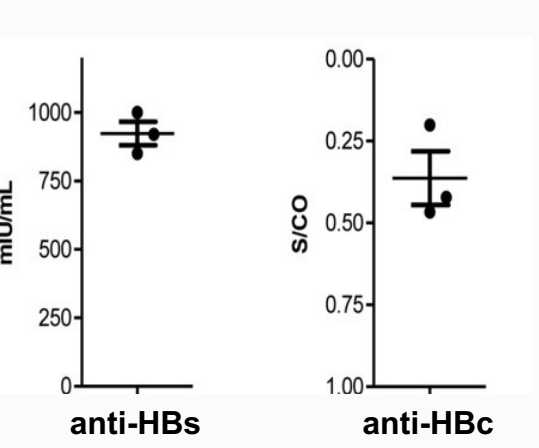
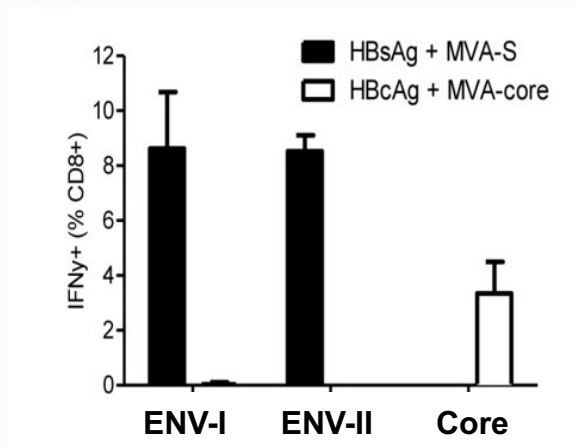
**Protein → Protein**



**Protein prime → MVA boost**



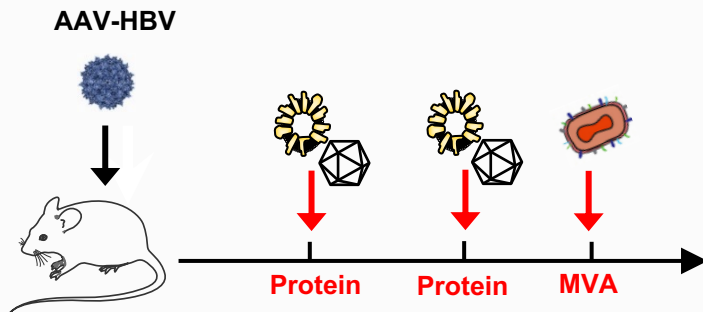
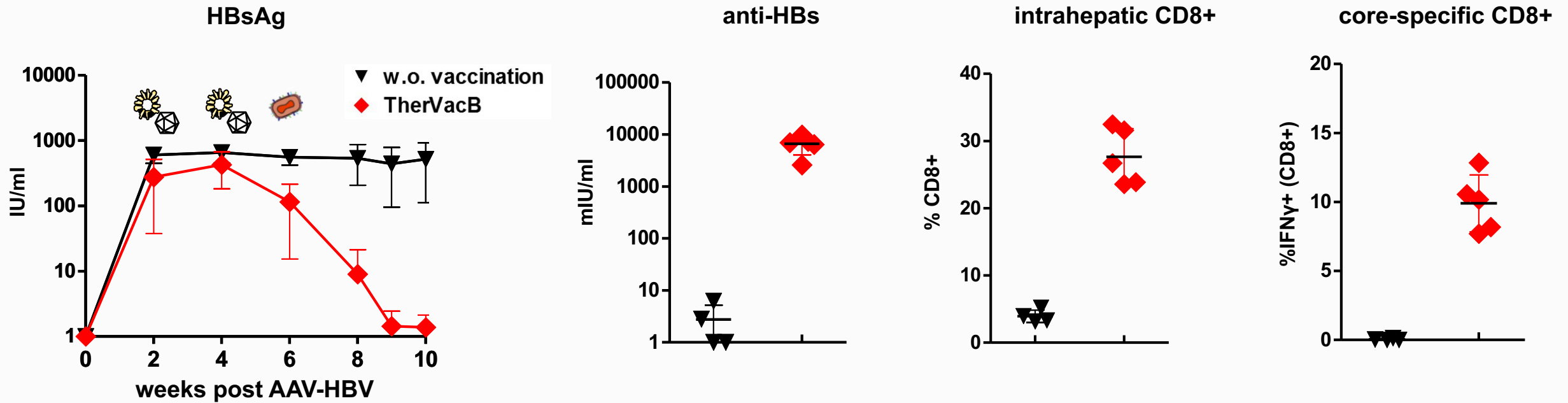
**HBV-specific T-cells**



**Antibody responses**

**A heterologous protein-prime / MVA-boost is superior to single component vaccine**

# Preclinical PoC: “HBV cure” in AAV-HBV mice

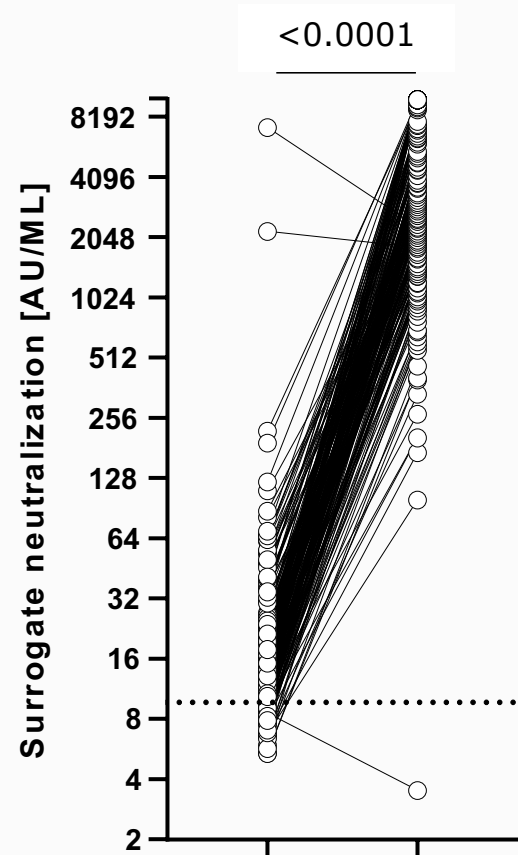


## Clinical endpoints of “functional HBV cure”:

- ✓ HBsAg loss
- ✓ (Ideally) anti-HBs seroconversion

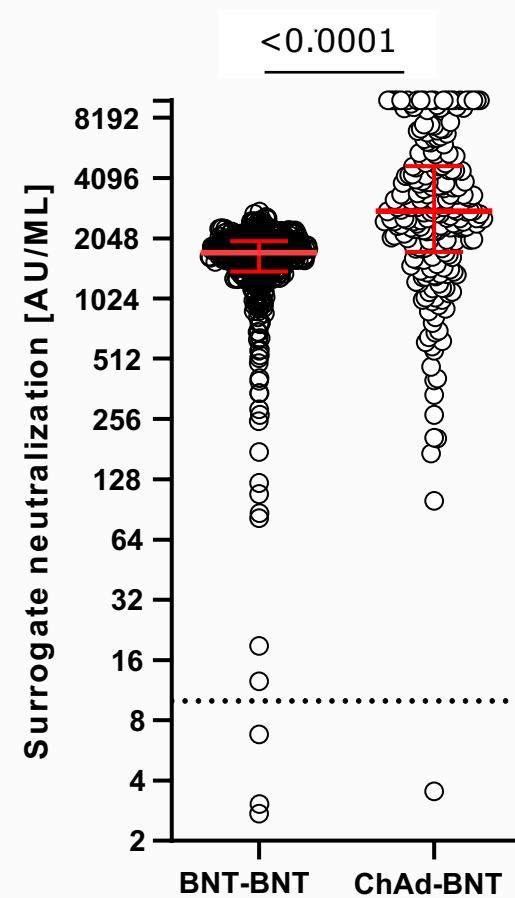
# Heterologous Prime-Boost in COVID-19 Vaccination: ChAd - mRNA

A



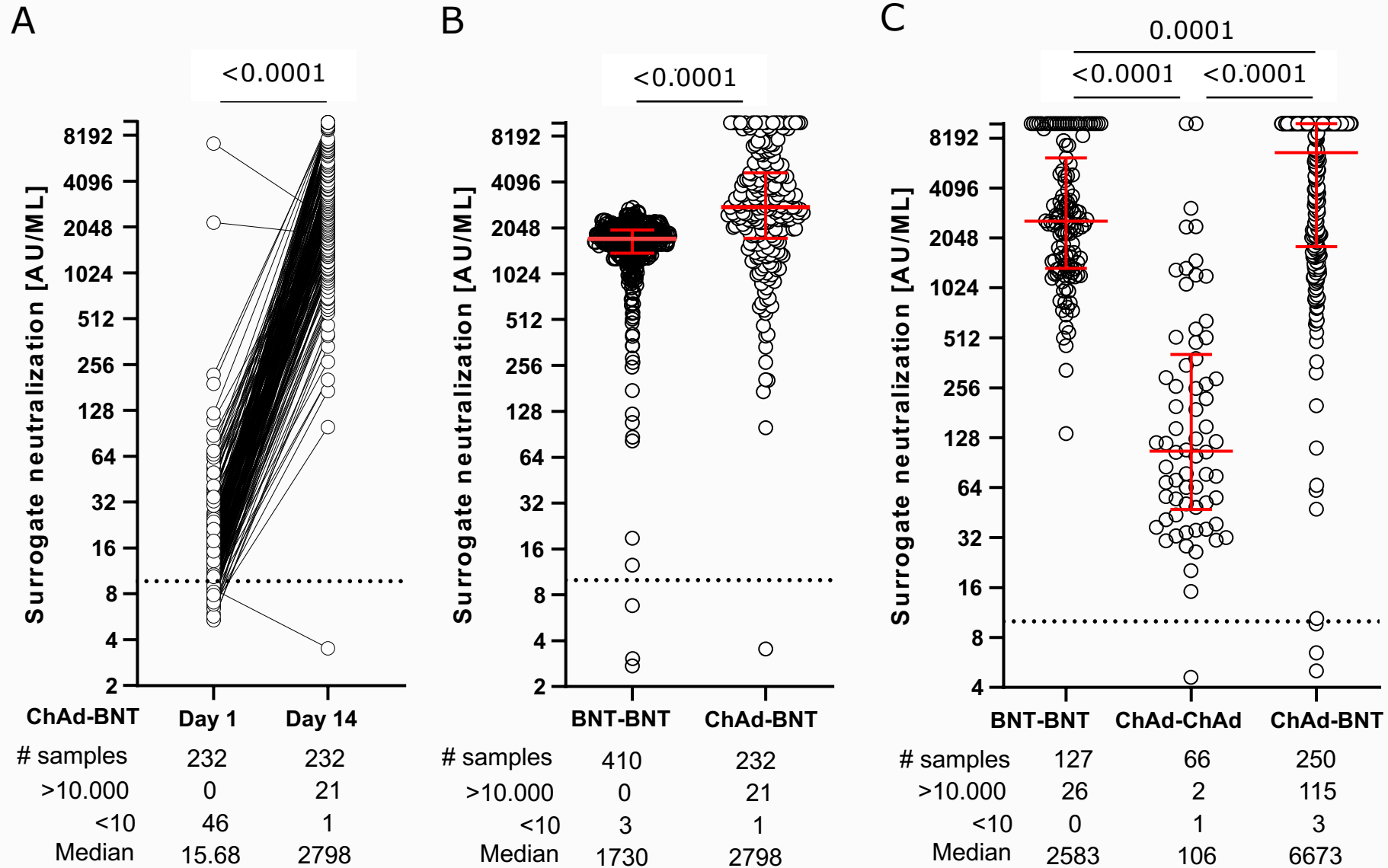
ChAd-BNT	Day 1	Day 14
# samples	232	232
>10.000	0	21
<10	46	1
Median	15.68	2798

B

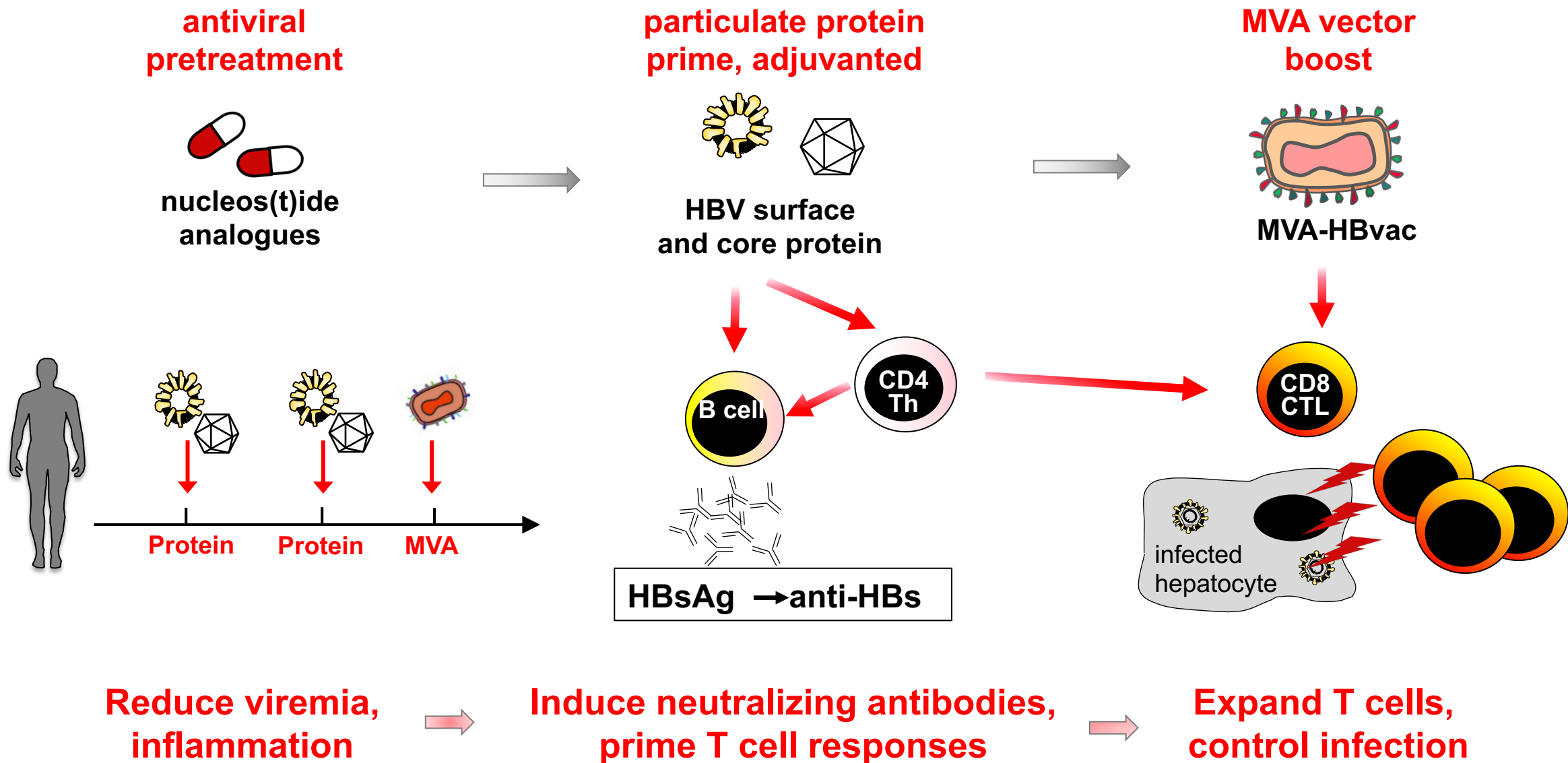


	BNT-BNT	ChAd-BNT
# samples	410	232
>10.000	0	21
<10	3	1
Median	1730	2798

# Heterologous Prime-Boost in COVID-19 Vaccination: ChAd - mRNA



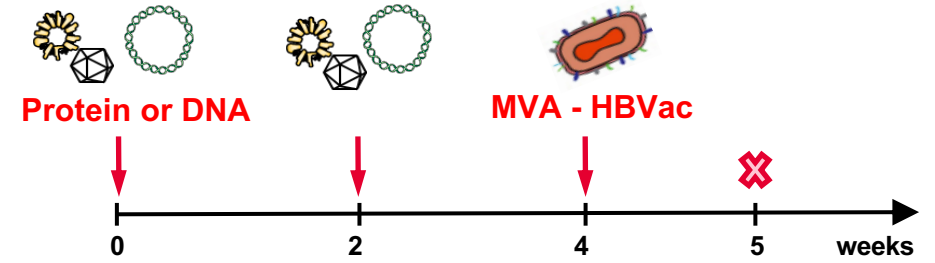
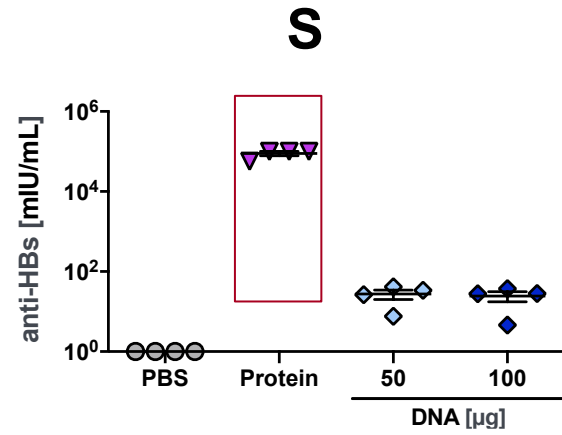
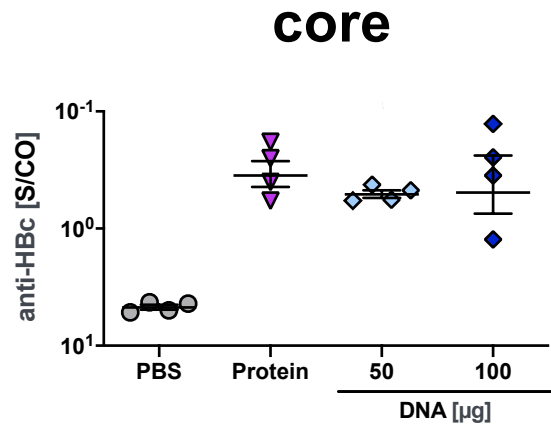
# *TherVac B* – strategy: heterologous prime - boost



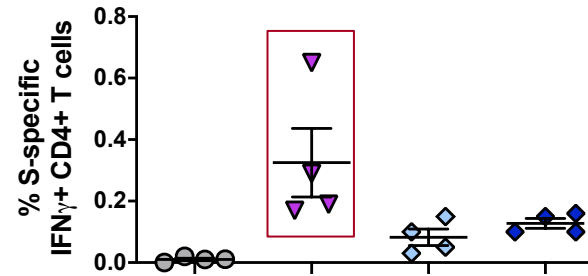
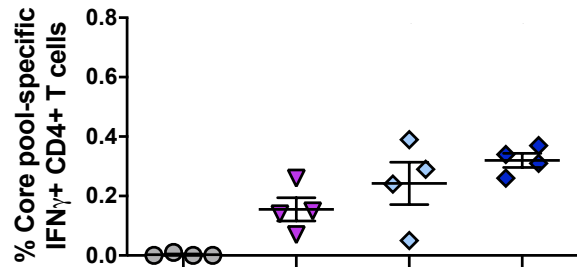


# DNA vs adjuvanted protein for prime

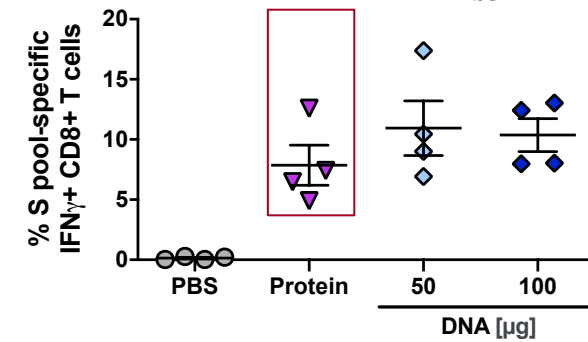
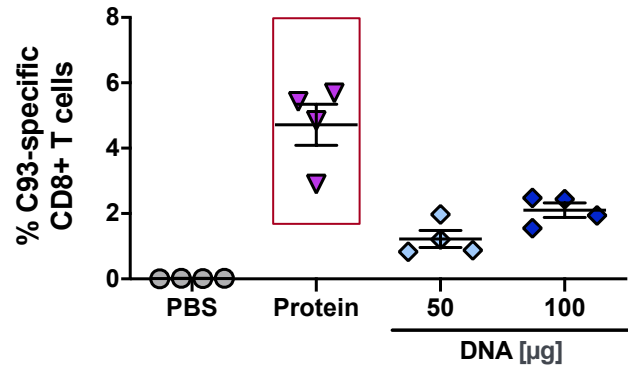
antibody



CD4<sup>+</sup>

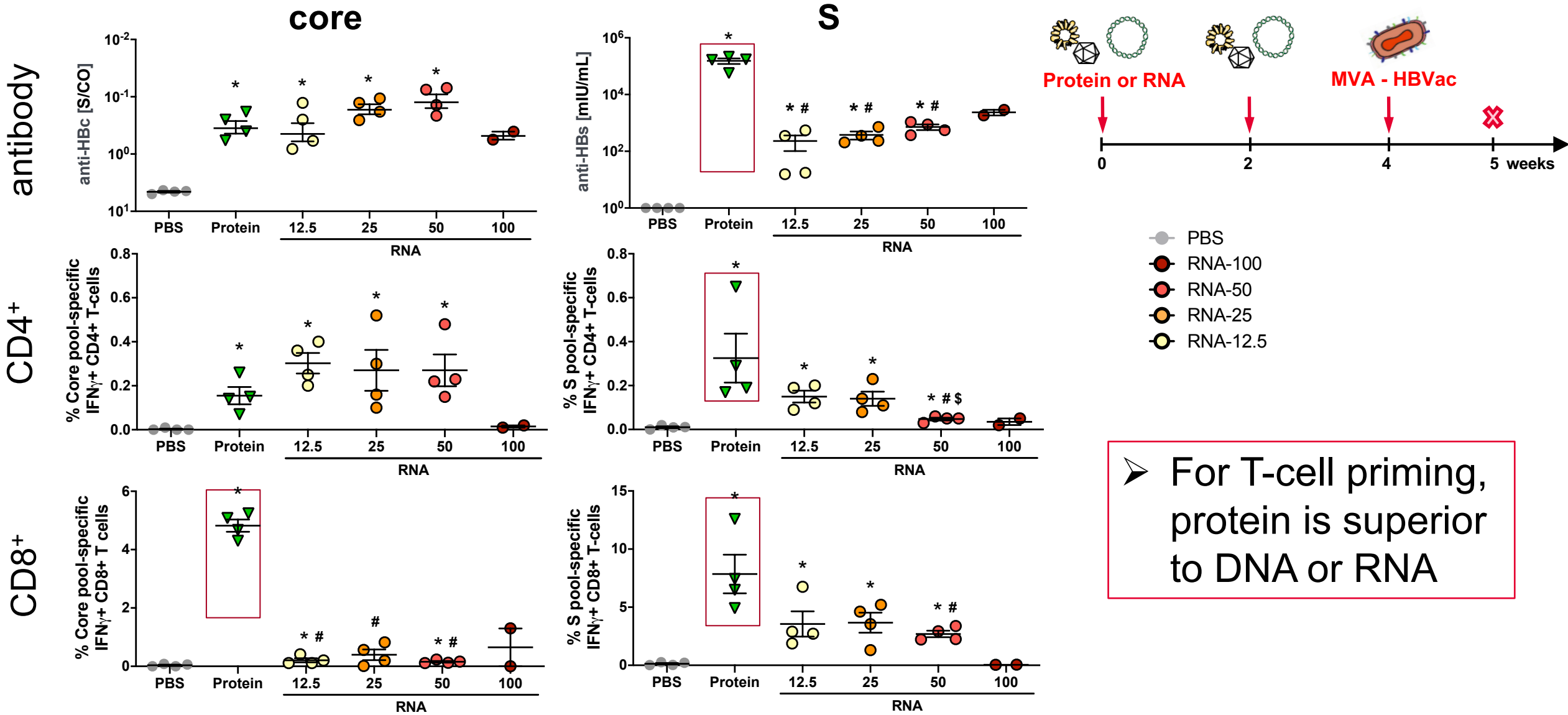


CD8<sup>+</sup>



➤ c-di-AMP adjuvanted protein induces anti-HBs and primes CD8<sup>+</sup> T cells

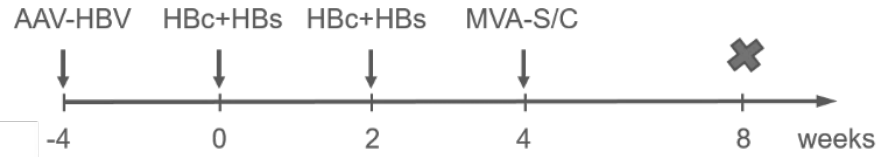
# RNA prime vs protein prime



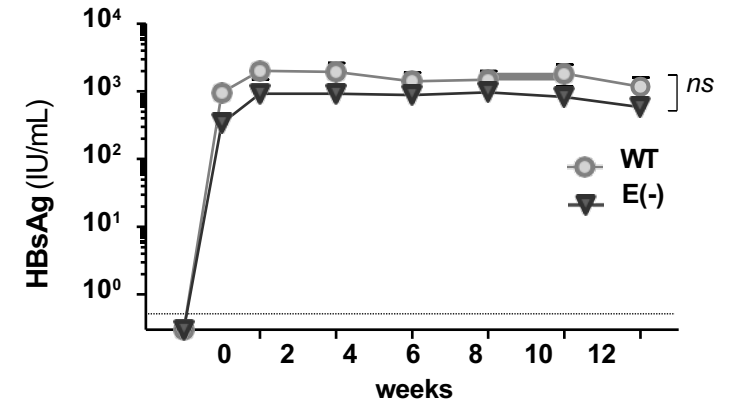
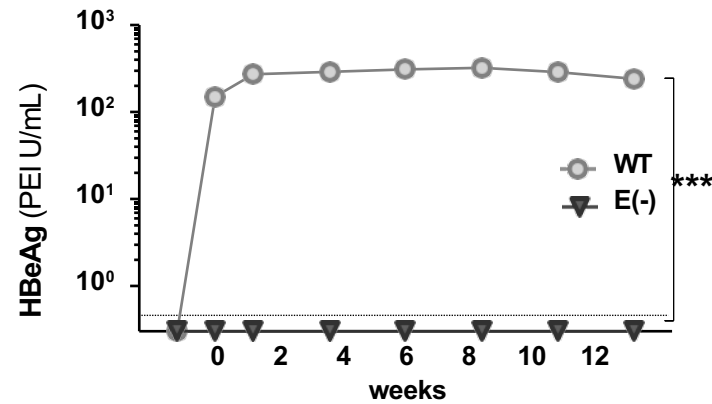
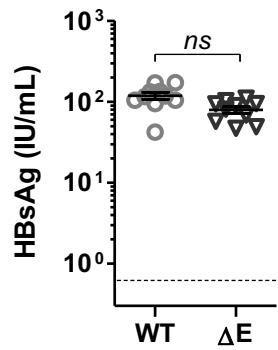
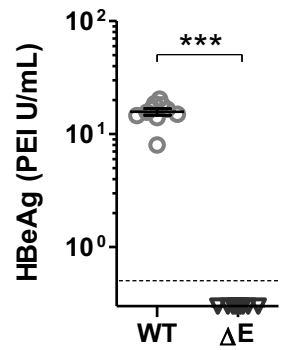
# TherVacB in HBe-negative HBV infection



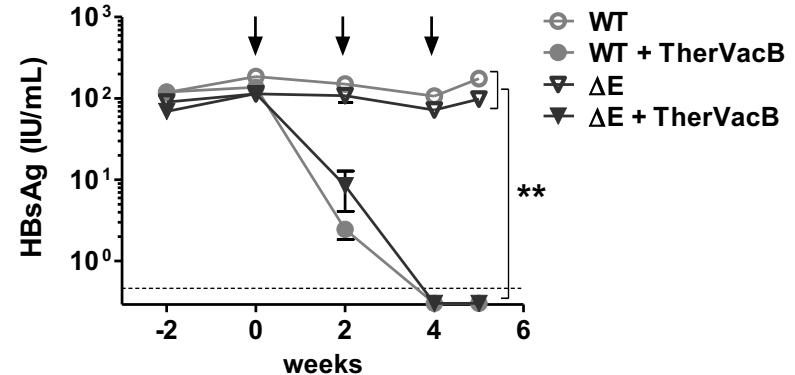
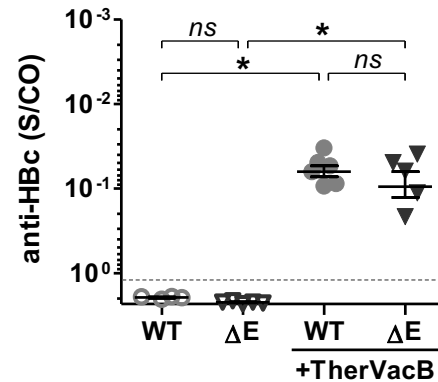
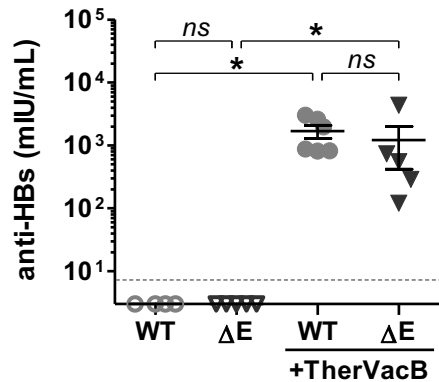
C57BL/6J



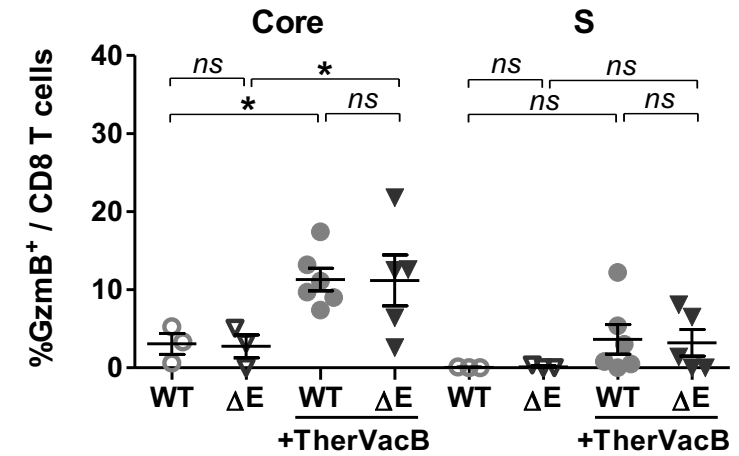
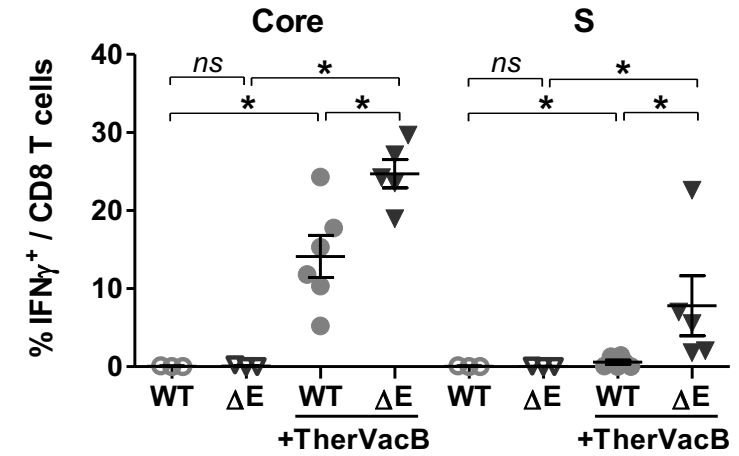
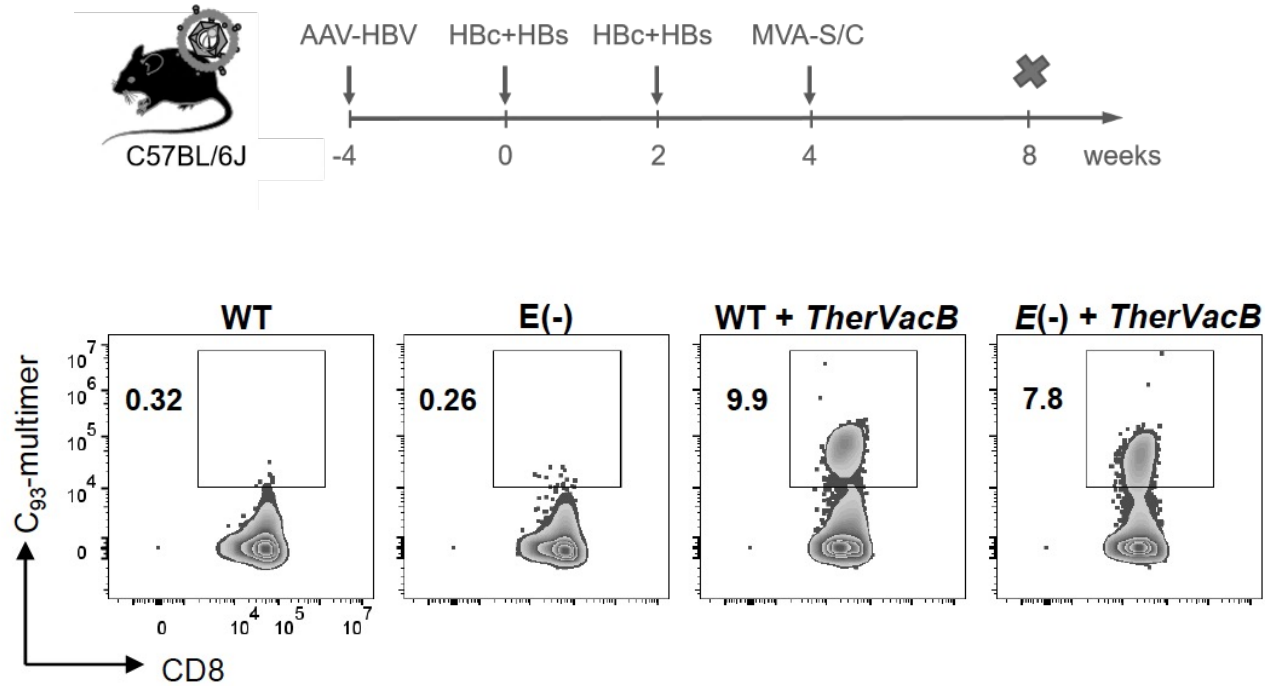
## AAV-HBVe-



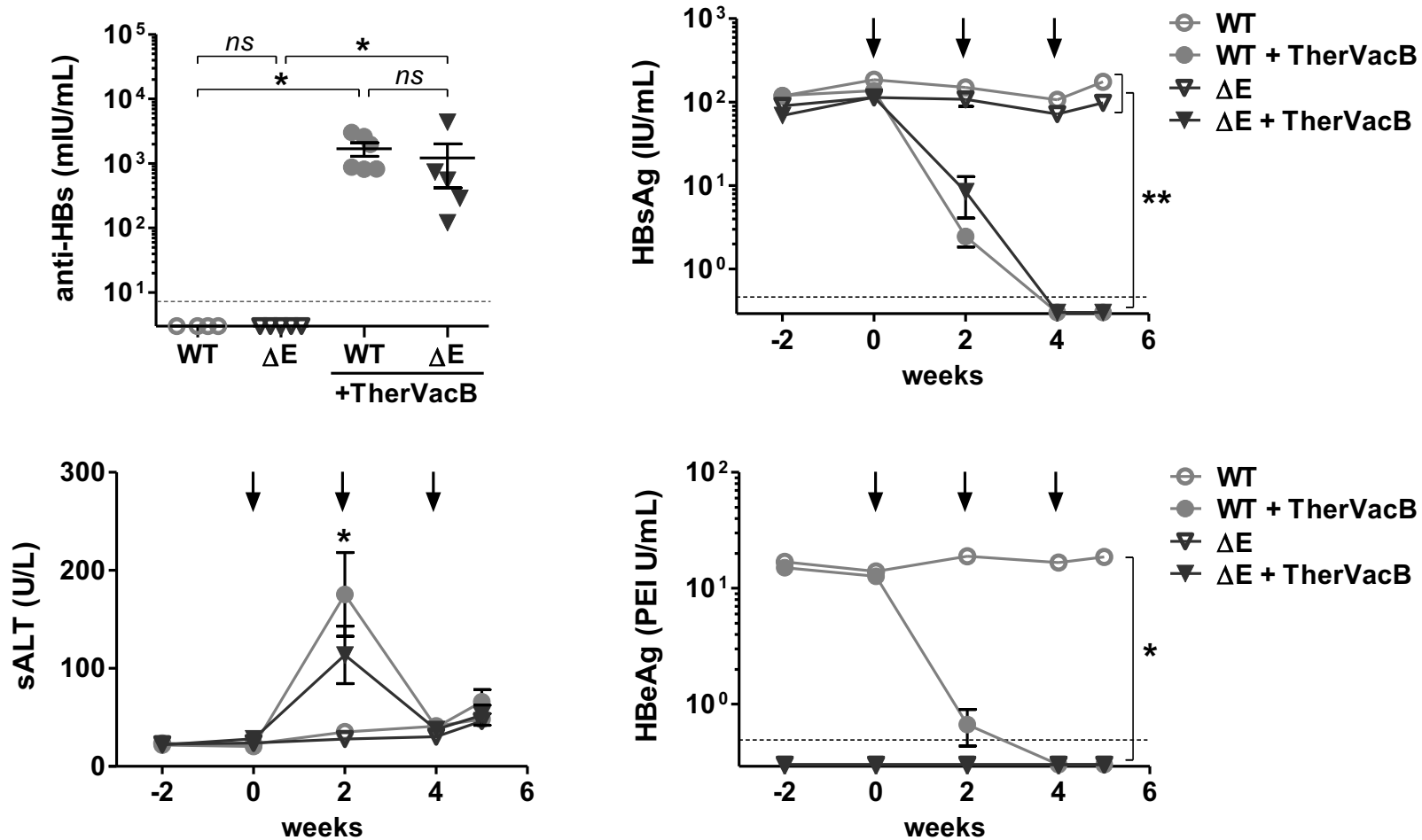
## TherVacB



# *TherVacB* in HBe-negative HBV infection

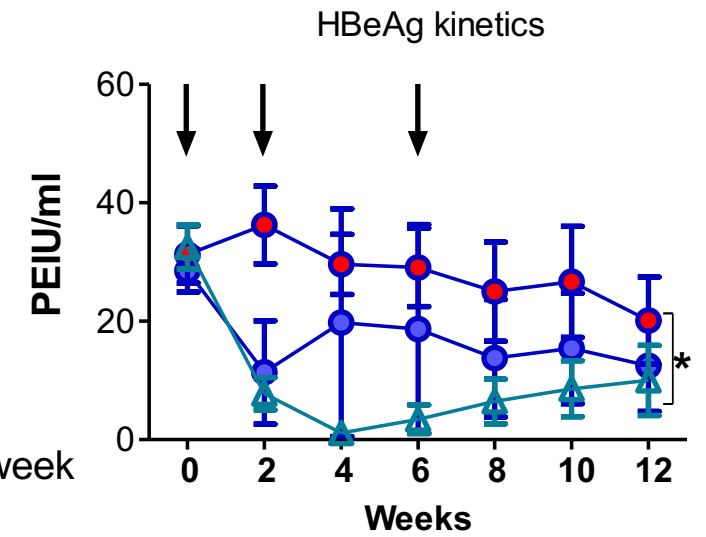
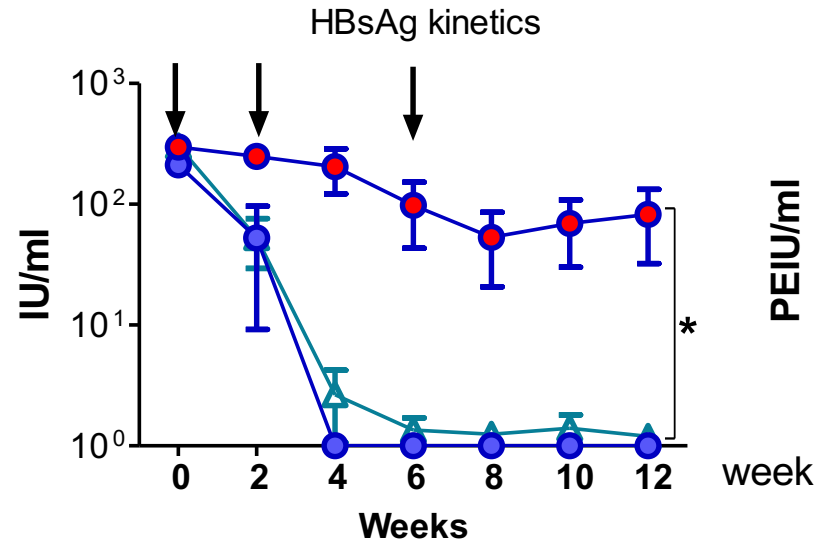
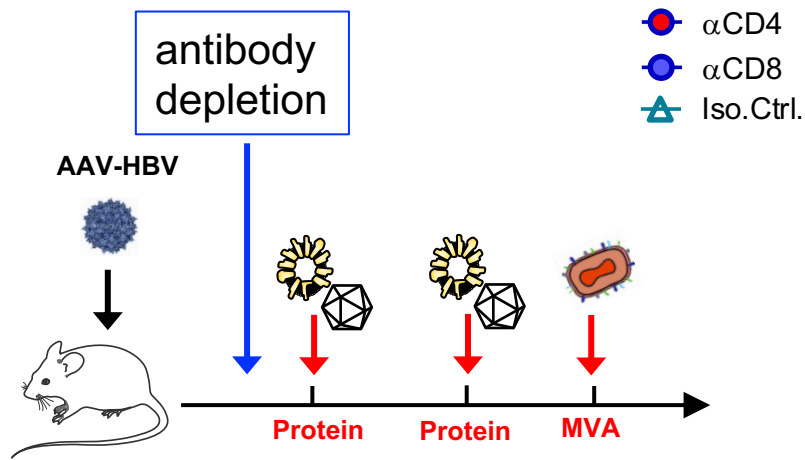


# *TherVacB* in HBe-negative HBV infection

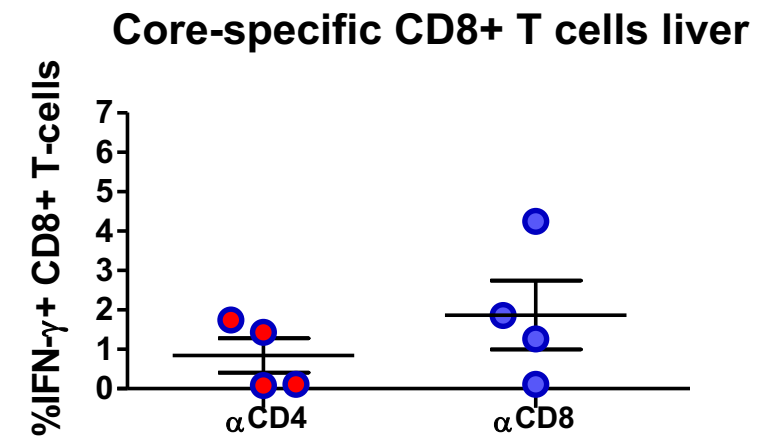
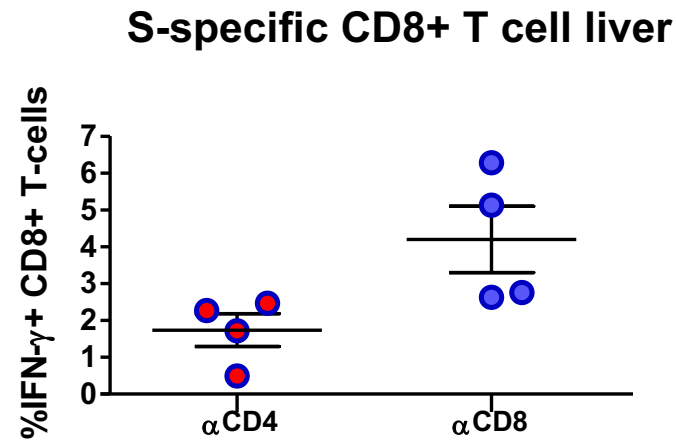
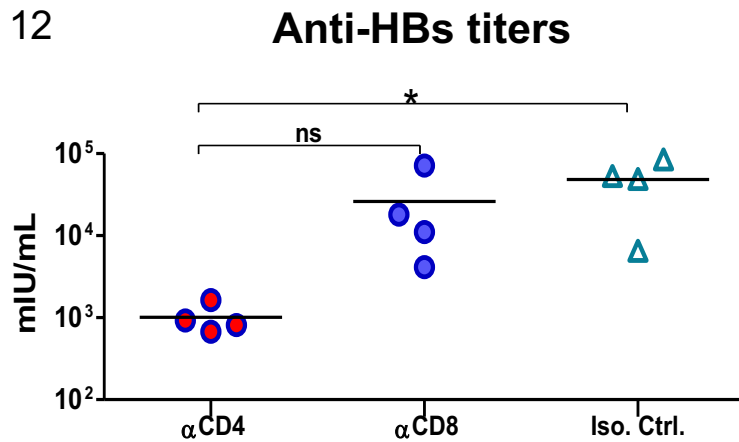


➤ TherVacB is able to “cure” HBV in AAV-HBV infected, HBV-carrier mice

# Anti-CD4 and -CD8 depletion during prime vaccination

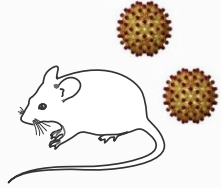


week 12



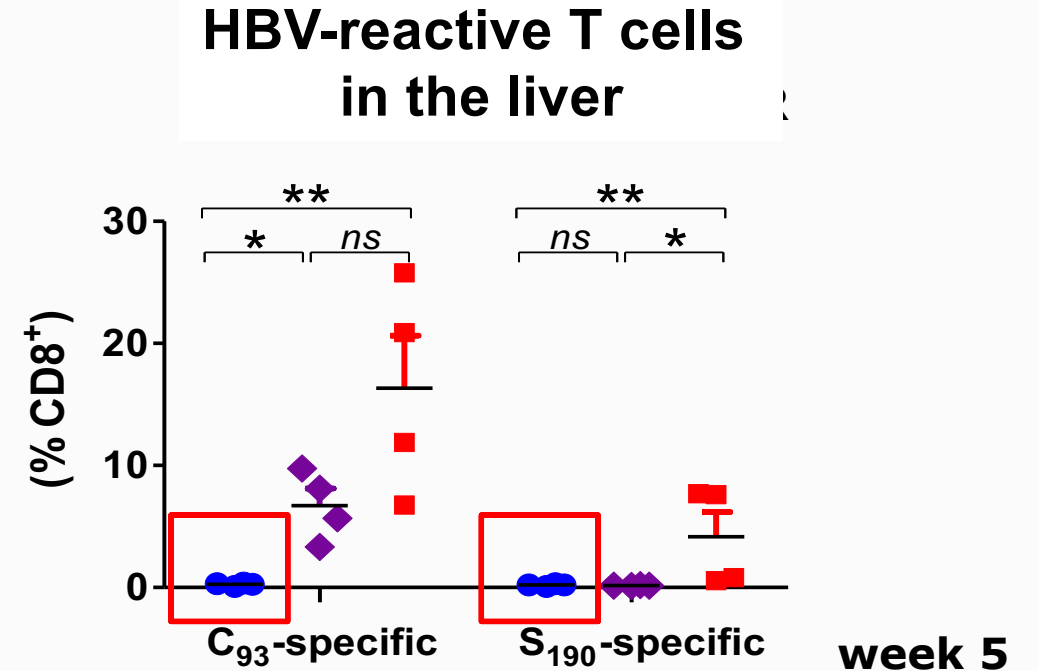
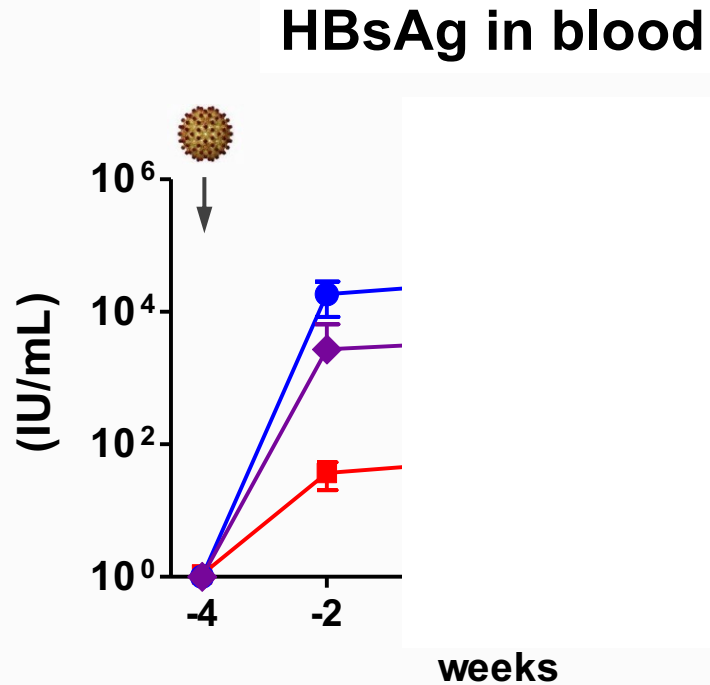
➤ Activation of CD4+ T cells during prime is essential for success of ***TherVacB***

# HBV titers influence T-cell response to *THERVACB*



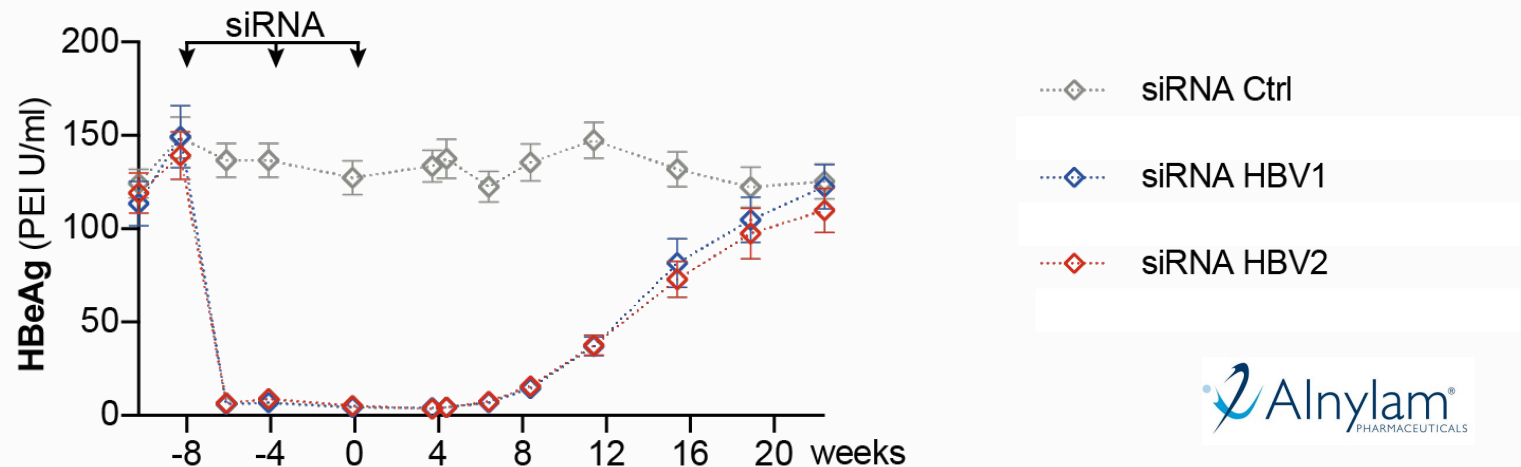
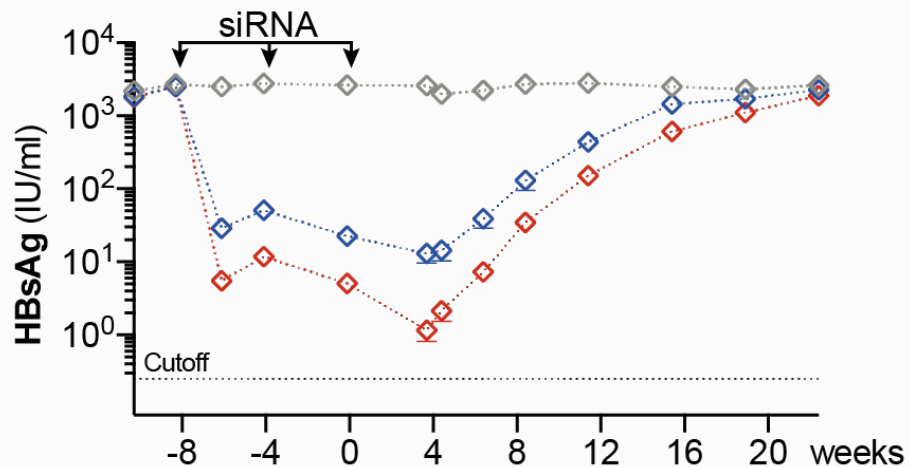
AAV-HBV (v.g.):

- $1 \times 10^{11}$
- ◆  $1 \times 10^{10}$
- $3 \times 10^9$



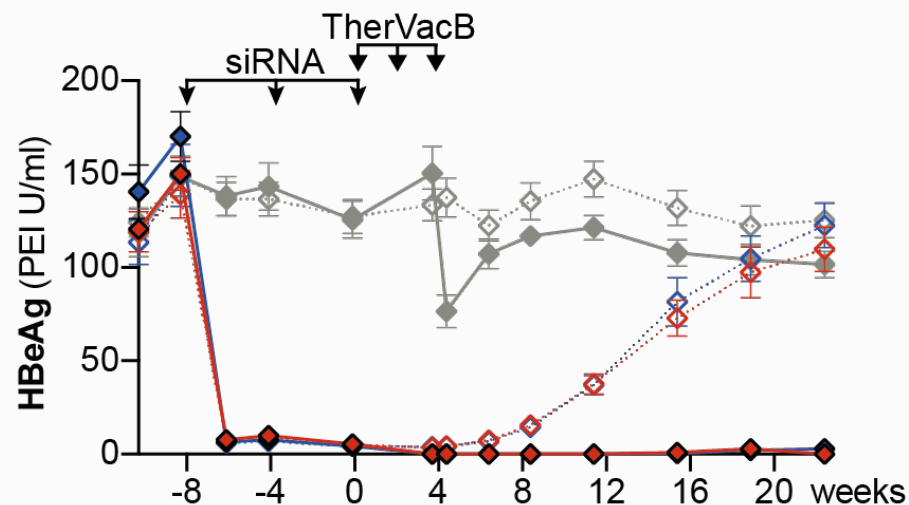
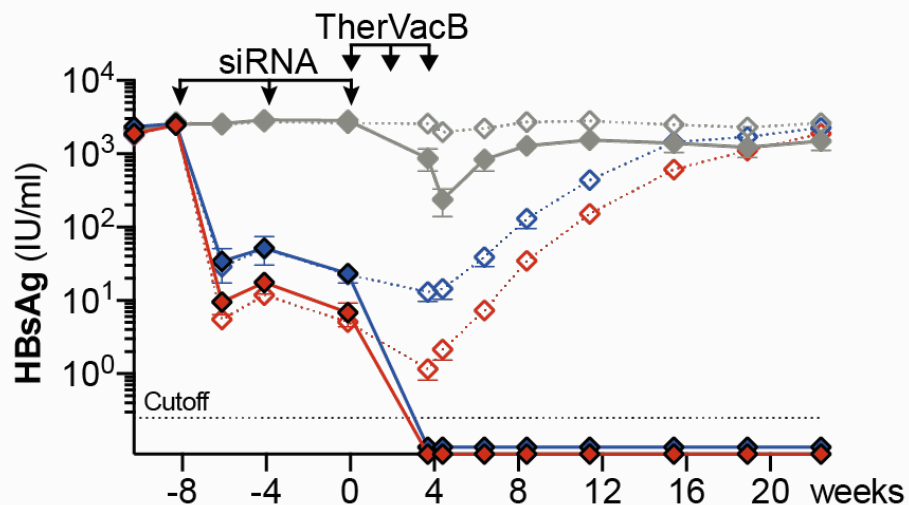
➤ High HBV antigen levels impair the efficacy of therapeutic vaccination

# HBV Cure by TherVacB if antigen levels are high



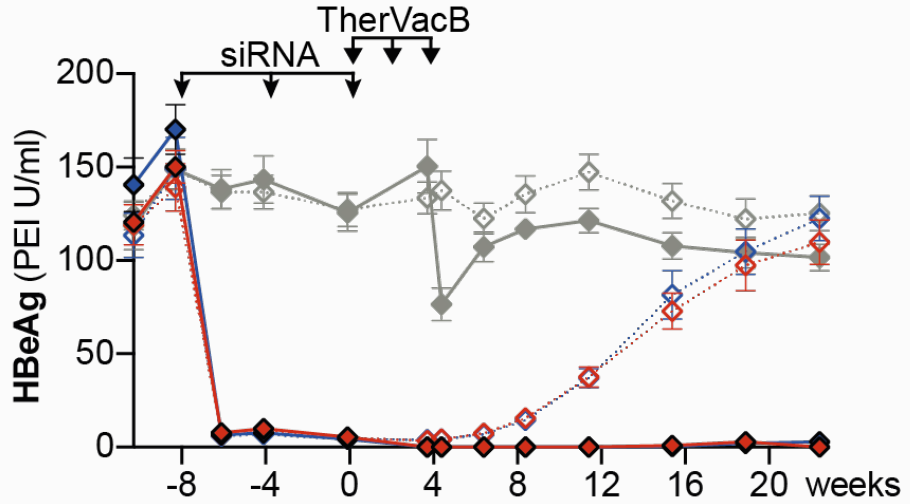
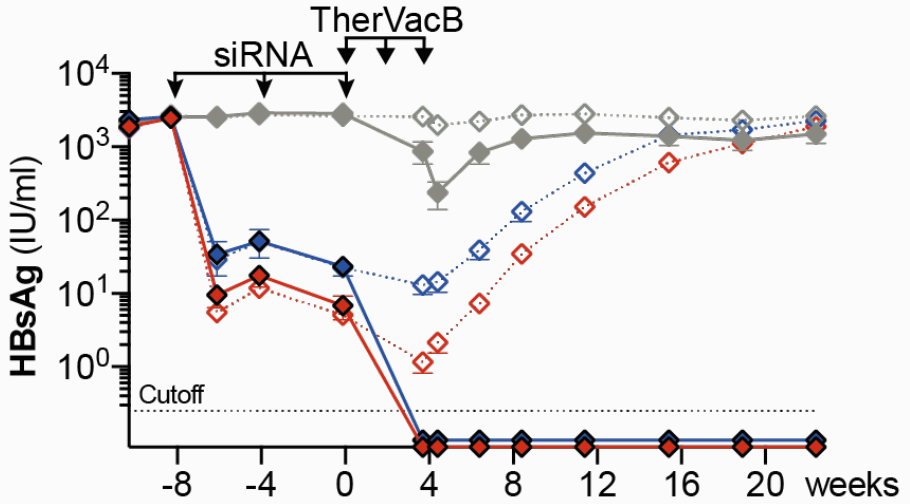


# HBV Cure by TherVacB if antigen levels are high

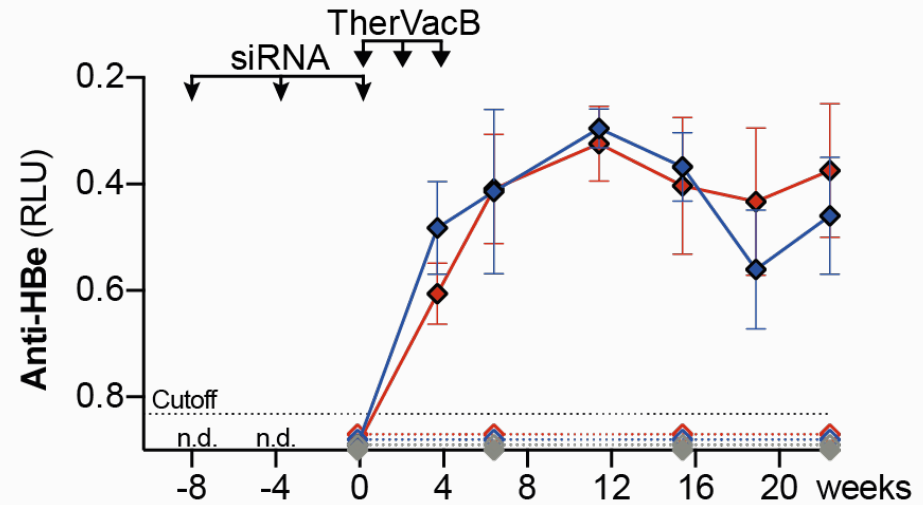
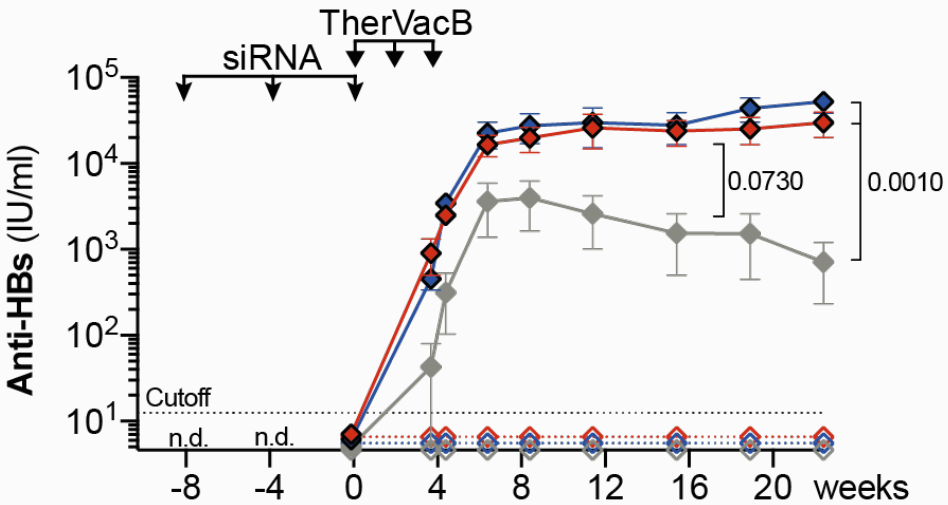


- siRNA Ctrl
- siRNA Ctrl → TherVacB
- siRNA HBV1
- siRNA HBV1 → TherVacB
- siRNA HBV2
- siRNA HBV2 → TherVacB

# HBV Cure by TherVacB if antigen levels are high

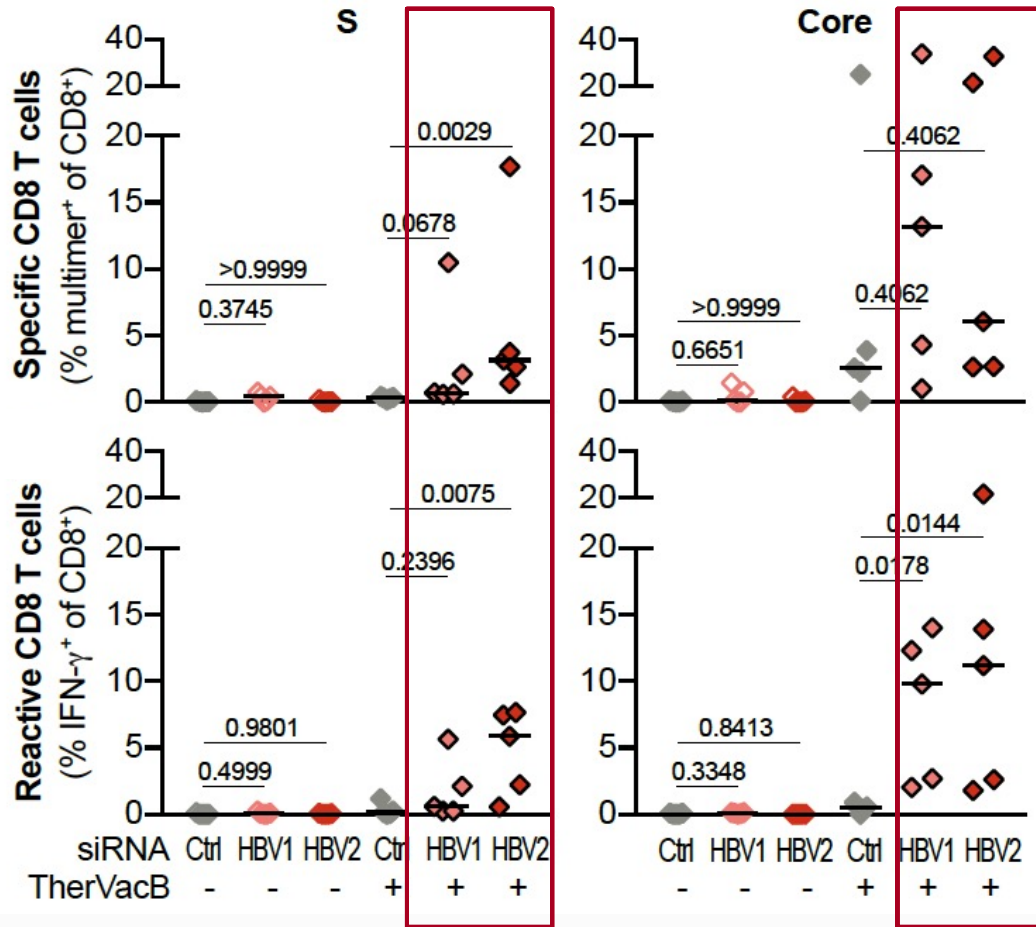


- ◇ siRNA Ctrl
- ◆ siRNA HBV1
- ◇ siRNA HBV2
- ◆ siRNA HBV1 → TherVacB
- ◇ siRNA HBV2 → TherVacB

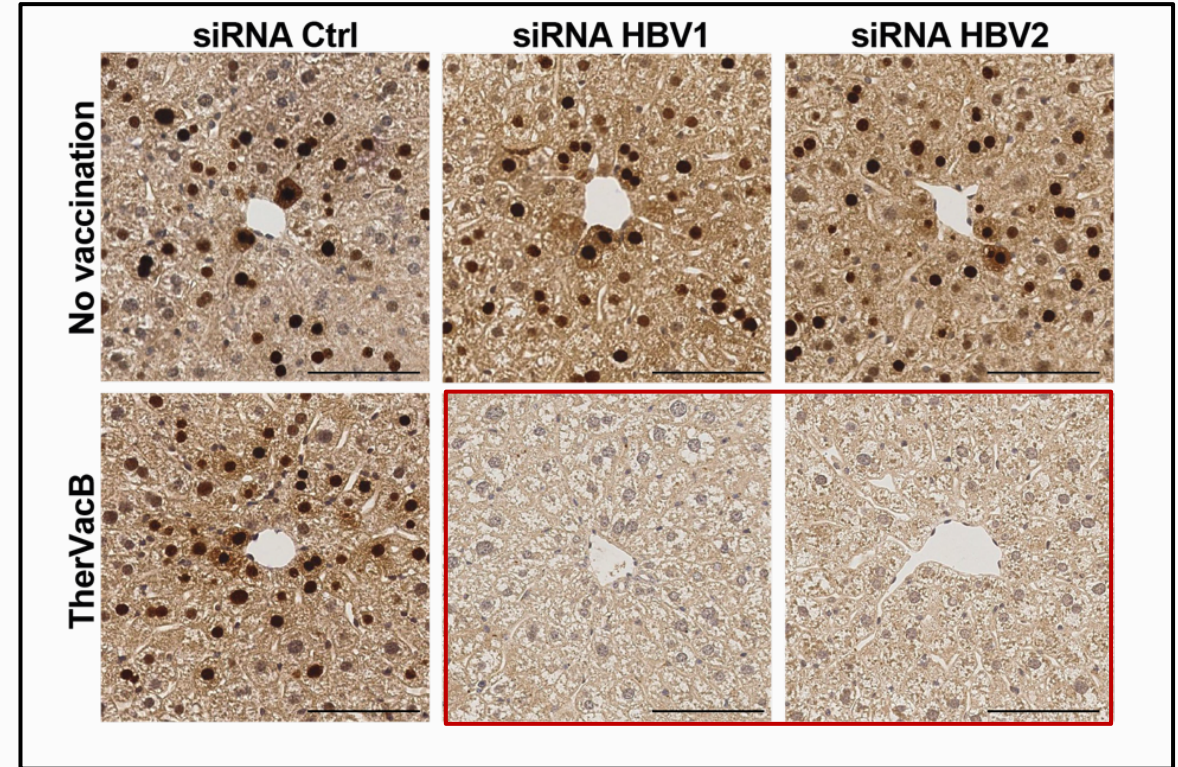


# „Cure“ of HBV 5 months after *TherVacB*

## T-cell response



## Liver immunohistochemistry HBV core staining

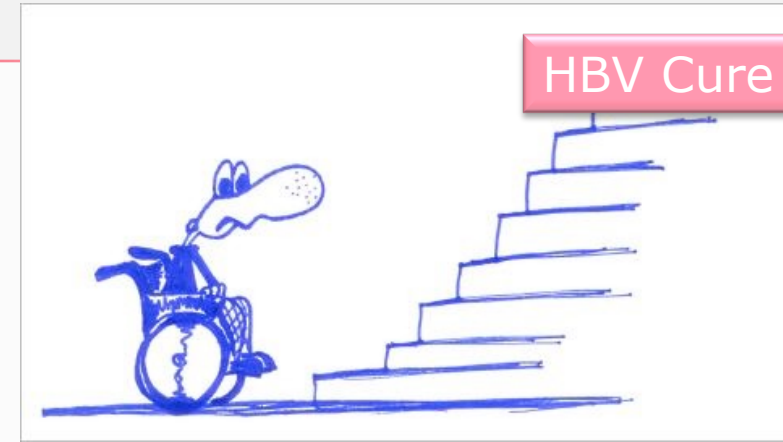


Michler, Kosinska et al. *Gastroenterology* 2020

➤ ***TherVacB*** cures high-titer HBV carriers after siRNA pre-treatment

# Summary

- HBV is able to avoid and to escape immune responses
- **Antivirals** control but **do not** eliminate HBV
- ... **immune activation** will be necessary to clear the virus
- **Therapeutic Vaccination** activating virus-specific T cells seems most promising
- **T cells are scarce** in chronic HBV infection – **new T cells** need to be primed
- **Activation of CD4 T cells** are important to help B cells and CD8 T cells
- Neutralizing antibodies help to limit further virus spread
- **High antigen load** (over longer time) will limit vaccine efficacy
- Therapeutic vaccination **is safe and can cure HBV** in preclinical models – **humans??**





# Outlook: Clinical translation

- Therapeutic vaccination should **activate B-, CD4<sup>+</sup> and CD8<sup>+</sup> T cells**
- Optimal **vaccine design**: heterologous (protein prime / MVA boost)
- Antigen and vector design should **cover HBV genotypes A-E**
- In initial trials, a preselection of low HBsAg patients may be necessary
- To treat high-titer infection, a **combination** with siRNA is promising



# Acknowledgements

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