Therapeutic Vaccines moving forward

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Immune control determines the course of hepatitis B

HBV

strong antibody and effector T cell response
self-limiting infection

therapeutic vaccine

no neutralizing antibodies
T cells are scarce,
chronic infection

immune control

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

**Therapeutic hepatitis B vaccine activating T cells**

- Nucleos(t)ide analogues
- Capsid Assembly inhibitors
- Interferons
- TLR agonists
- siRNA
- Entry blocker
- NAP siRNA
Rational for the heterologous prime-boost *TherVac B* strategy

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

Day 1
Day 14

ChAd-BNT

Surrogate neutralization [AU/ML]

# samples
>10,000
<10
Median

232
46
15.68

232
21
2798

<0.0001

B

Day 1
Day 14

BNT-BNT
ChAd-BNT

Surrogate neutralization [AU/ML]

# samples
>10,000
<10
Median

410
46
1730

232
21
2798

<0.0001

Tenbusch, ..., Protzer Lancet ID, 2021
Heterologous Prime-Boost in COVID-19 Vaccination: ChAd - mRNA

Tenbusch, ..., Protzer Lancet ID, 2021
**TherVac B** – strategy: heterologous prime - boost

- **antiviral pretreatment**
  - nucleos(t)ide analogues

- **particulate protein prime, adjuvanted**
  - HBV surface and core protein

- **MVA vector boost**
  - MVA-HBvac

Reduce viremia, inflammation → Induce neutralizing antibodies, prime T cell responses → Expand T cells, control infection

Buchmann *Vaccine* 2013; Backes *Vaccine* 2016; Kosinska *Sci Rep* 2018; Gehring & Protzer; *Gastroenterology* 2019; Michler, Kosinska *Gastroenterology* 2020
DNA vs adjuvanted protein for prime

- **c-di-AMP adjuvanted protein induces anti-HBs and primes CD8+ T cells**

  - **Core Antibody:**
    - PBS: 10^1
    - Protein: 10^2
    - DNA [µg]:
      - 50: 10^1
      - 100: 10^2

  - **S Antibody:**
    - PBS: 10^0
    - Protein: 10^0
    - DNA [µg]:
      - 50: 10^0
      - 100: 10^0

  - **Core CD4+ T cells:**
    - PBS: 0.2
    - Protein: 0.2
    - DNA [µg]:
      - 50: 0.2
      - 100: 0.2

  - **S CD4+ T cells:**
    - PBS: 0
    - Protein: 0
    - DNA [µg]:
      - 50: 0
      - 100: 0

  - **Core CD8+ T cells:**
    - PBS: 2
    - Protein: 2
    - DNA [µg]:
      - 50: 2
      - 100: 2

  - **S CD8+ T cells:**
    - PBS: 5
    - Protein: 5
    - DNA [µg]:
      - 50: 5
      - 100: 5
RNA prime vs protein prime

For T-cell priming, protein is superior to DNA or RNA
TherVacB in HBe-negative HBV infection

TherVacB in HBe-negative HBV infection

Kosinska A. et al, Vaccines 2021
**TherVacB** in HBe-negative HBV infection

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

Kosinska A. et al, Vaccines 2021
Anti-CD4 and -CD8 depletion during prime vaccination

Anti-HBs titers

S-specific CD8+ T cell liver

Core-specific CD8+ T cells liver

Activation of CD4+ T cells during prime is essential for success of TherVacB
High HBV antigen levels impair the efficacy of therapeutic vaccination.
HBV Cure by TherVacB if antigen levels are high

Michler, Kosinska et al. Gastroenterology 2020
HBV Cure by TherVacB if antigen levels are high

Michler, Kosinska et al. Gastroenterology 2020
HBV Cure by TherVacB if antigen levels are high

Michler, Kosinska et al. Gastroenterology 2020
„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
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??
Therapeutic vaccination should activate B-, CD4+ and CD8+ 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.
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