2026 HGF – OCPC – Programme

for the involvement of postdocs in bilateral collaboration projects

Title of the project:

Exploring the factors determining the successful therapeutic vaccination against chronic hepatitis B

Helmholtz Centre and institute:

Institute of Virology, Helmholtz Munich

Project leader:

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Description of the project (max. 1 page)**:**

More than 250 million people worldwide have a chronic infection with the hepatitis B virus (HBV). The infection causes a chronic inflammatory liver disease (hepatitis B) and put those affected at risk to develop liver cirrhosis and liver cancer. According to recent data, 1.1 million humans die from the consequences of a chronic hepatitis B per year. Therefore, the World Health Organization (WHO) committed to eliminating viral hepatitis as a public health threat by 2030.

Current antiviral treatments with nucleos(t)ide analogues effectively suppress hepatitis B virus (HBV) replication. However, the treatment does not affect the virus persistence form, HBVcccDNA, and has to be applied long-term. Only around 0.5% of chronic hepatitis B patients per year reach a cure which is associated with a virus-specific antibody and CD4+ and CD8+ T-cell response. To achieve an HBV cure in a larger group of patients, restoration of virus-specific immunity seems to be essential.

It is well-documented that adaptive immunity against the virus is essential for efficient HBV control. Consequently, therapeutic vaccination that can induce strong anti-HBV immunity represents a promising strategy treat patients with chronic hepatitis B and cure HBV. However, to date, therapeutic hepatitis B vaccines have demonstrated only limited success in clinical trials, implying that these strategies need further improvement.

Previously, our laboratory has developed the heterologous prime-boost vaccine *TherVacB*, employing a protein-prime with particulate hepatitis B S (HBsAg) and core antigens (HBcAg) and a vector-boost with recombinant modified vaccinia virus Ankara (MVA) expressing various HBV antigens. In preclinical animal models of persistent HBV infection, *TherVacB* was able to induce strong HBV-specific immune responses and led to long-term immune control and finally elimination of HBV. These encouraging results of *TherVacB* obtained in preclinical models have already initiated its translation into phase 1 clinical trials.

The focus of this project will be to improve our understanding of the factors determining efficacy of therapeutic vaccination. Our prior experiments indicate an important role of CD4 T cells during the priming phases of *TherVacB* to achieve therapeutic effects. Using preclinical mouse models as well as well as healthy volunteer and patient-derived lymphocytes, we therefore plan to perform extensive transcriptome and cytokine profiling analyses of CD4 T cells induced by *TherVacB* to investigate molecular mechanisms and key cellular components that effectively activate CD4 T cells and determine the success of therapeutic vaccination. Understanding of the underlying mechanisms contributing to the vaccine success from this project will help to rationally improve and optimize the performance of *TherVacB* in chronic hepatitis B patients.

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**

We established a collaboration with Prof. Yuchen XIA, PhD, Director Institute of Medical Virology, Wuhan University, School of Basic Medical Sciences, and Profs. Jia Liu and Xin Zheng, Director Department of Infectious Diseases, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, on the control of hepatitis B virus by cytokines and immune cells. During Yuchen XIA's time at Helmholtz Munich and thereafter at the NIH, USA, a number of common studies have been published.

Selected Literature:

1. **Kosinska AD**, Kächele M, Kerth HA, Mück-Häusl M, Ates Öz E, Gültan M, Hansen-Palmus L, Sacherl J, Ko C, Festag J, Lehmann MH, Mogler C, Steiger K, Knolle PA, Bauer T, Volz AK, **Protzer U**. MVA-HBVac-A novel vaccine vector that allows pan-genotypic targeting of hepatitis B virus by therapeutic vaccination. *Mol Ther Nucleic Acids*. 2025 Jul 23;36(3):102641. doi: 10.1016/j.omtn.2025.102641. PMID: 40799509.
2. Bosch M, Kallin N, Donakonda S, Zhan DJ, Wintersteller H, …. **Kosinska AD,** …, **Protzer U**, Böttcher JP, Zehn D, Lauer G, Wohlleber D, Hofmann M, Luangsay S, Knolle PA. A liver immune rheostat regulates HBV-specific immunity during chronic hepatitis B. *Nature* 2024 024 Jul;631(8022):867-875. doi: 10.1038/s41586-024-07630-7.

3. Su J, Taji ZH, **Kosinska AD**, Oz EA, Xie Z, Bielytskyi P, Shein M, Hagen P, Esmaeili S, Steiger K, **Protzer U***, Schütz AK*. Introducing adjuvant-loaded particulate hepatitis B core antigen as an alternative therapeutic hepatitis B vaccine component. *JHEP Reports* 2023, Dec 30;6(4):100997, doi: https://doi.org/10.1016/j.jhepr.2023.100997.
4. Su J, Brunner L, Ates Oz E, Sacherl J, Frank G, Kerth HA, Thiele F, Wiegand M, Mogler C, Cesar Aguilar J, Knolle P, Collin N, **Kosinska A**, **Protzer U**. Activation of CD4 T cells during prime immunization determines the success of a therapeutic hepatitis B vaccine in HBV-carrier mouse models. *Journal of Hepatology* **2023**, 78: 717-730. doi: 10.1016/j.jhep.2022.12.013. PMID: 36634821.
5. Sacherl J, **Kosinska AD**, Kemter K, Kächele M, Laumen SC, Kerth HA, Öz EA, Wolff LS, Su J, Essbauer S, Sutter G, Scholz M, Singethan K, Altrichter J, **Protzer U**. Efficient stabilization of therapeutic hepatitis B vaccine components by amino-acid formulation maintains its potential to break immune tolerance. *JHEP Reports*, 2022 Oct 13;5(2):100603. doi: 10.1016/j.jhepr.**2022**.100603. PMID: 36714793; PMCID: PMC9880034.
6. Michler T, **Kosinska A**D, Festag J, Bunse T, Su J, Ringelhan M, Imhof H, Grimm D, Steiger K, Mogler C, Heikenwalder M, Michel ML, Guzman CA, Milstein S, Sepp-Lorenzio L, Knolle P, **Protzer U**. Knockdown of Virus Antigen Expression Increases Therapeutic Vaccine Efficacy in High-titer HBV Carrier Mice. *Gastroenterology* **2020**,158: 1762-1775. PMID: 32001321
7. Teng Y, Xu Z, Zhao K, Zhong Y, Wang J, Zhao L, Zheng Z, Hou W, Zhu C, Chen X, **Protzer U**, Li Y, **Xia Y**. Novel function of SART1 in HNF4α transcriptional regulation contributes to its antiviral role during HBV infection. *Journal of Hepatology* **2021,** 75(5): 1072-1082. doi: 10.1016/j.jhep.2021.06.038. Epub ahead of print. PMID: 34242702.
8. Bockmann JH, Stadler D, **Xia Y**, Ko C, Wettengel JM, Schulze zur Wiesch J, Dandri M and **Protzer U**. Comparative analysis of the antiviral effects mediated by type I and III interferons in hepatitis B virus infected hepatocytes. *Journal of Infectious Diseases* **2019**, 220(4):567-577, PMID 30923817
9. **Xia Y**, Schlapschy M, Morath V, Roeder N, Vogt EI, Stadler D, Cheng X, Dittmer U, Sutter K, Heikenwalder M, Skerra A, **Protzer U**. PASylated IFNα Efficiently Suppresses HBV and Induces anti-HBs Seroconversion in HBV-transgenic Mice. *Antiviral Research* **2019**,161:134-143.
10. Li Y*, **Xia Y***, Han M, Chen G, Zhang D, Thasler W, **Protzer U***, Ning Q*. IFN-α-mediated Base Excision Repair Pathway Correlates with Antiviral Response Against Hepatitis B Virus Infection. *Scientific Reports* **2017***,* Oct 5;7(1):12715..
11. **Xia Y**, Carpentier A, Cheng X, Block PD, Zhao Y, Zhang Z, **Protzer U**, Liang TJ. Human stem cell-derived hepatocytes as a model for hepatitis B virus infection, spreading and virus-host interactions. *J Hepatology* **2017,** 66:494-503.
12. **Xia Y***, Stadler D*, Lucifora J, Reisinger F, …, Thimme R, Thasler WE, Heikenwalder M and **Protzer U**. Interferon-γ and Tumor Necrosis Factor-α Produced by T cells Reduce the HBV Persistence Form, cccDNA, Without Cytolysis. *Gastroenterology* **2016**, 150:194-202.
13. Lucifora J*, **Xia Y***, Reisinger F, Zhang K, Stadler D, Cheng X, ..., Münk C, Heim MH, Browning JL, Dejardin E, Dandri M, Schindler M, Heikenwalder M* and **Protzer U***. Specific and non-hepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science* **2014**, 343: 1121-1128.

Required qualification of the post-doc:

- PhD in Virology or Virus Immunology
- A track record in vaccination research and / or virus-host-interaction is expected
- Experience with animal experiments, handling of primary immune cells, multicolour flow cytometry and ideally single-cell analysis via NGS is expected
- Additional skills in molecular biology and bioinformatics are of advantage
- Language requirement: fluent communication and good writing skills in English
- Experience in writing scientific publications in English