Workshop: Global Challenges & Opportunities for Vaccines

1. Program

Details

- **30th November 2023 – 1st December, 2023**
- **Presence**: Bildungshaus St. Martin, Klosterhof 8, 82347 Bernried am Starnberger See bei München [by prior invite only]
  https://goo.gl/maps/MnMDMnuZTXJaCsMW9 [by prior invite only]
- **Remote:** registration required (see below)
- Organized by **Clarissa Prazeres da Costa** (member GLOHRA Steering Committee), Center for Global Health (CGH) and Institute of Medical Microbiology, Immunology & Hygiene (MIH) and **Stefanie Klug**, Chair of Epidemiology at the Technical University of Munich (UKT) jointly with **Meral Esen** (member GLOHRA Steering Committee), Institute of Tropical Medicine (ITM), University Clinic Tübingen (UKT)

Agenda

- All scientific talks and expert discussions will be livestreamed with a possibility for online participants to engage in Q&A via the chat function only (see agenda below)

Registration

- Remote participation will be available for speaker talks for both days via Zoom (preregistration required)
- **Registration link: https://tum-conf.zoom-x.de/meeting/register/u5Eqf-CrqjMtEtKAnR1rJXZGaDDwbd9j_MMD**
- A final agenda with abstracts of all talks will be sent closer to the meeting
- By registering for the meeting, you consent to be recorded

2. Scientific program

30th November 2023

Time	Topic	Speaker
10 30 – 10 40	Welcome address	Clarissa Prazeres da Costa; Stefanie Klug; Meral Esen

10 40 – 10 50	Opening remarks by GLOHRA	Maeve Cook-Deegan
10 50 – 11 00	Introduction to project *HelmSys*	Clarissa Prazeres da Costa
11 00 - 11 30	First results from the (GLOHRA-supported) project *HelmSys*	Marrium Habib (supported by team *HelmSys*)
11 30 – 12 00	Filarial infections compromise influenza vaccination efficacy: Lessons from the mouse	Minka Breloer
12 00 – 12 30	Population differences in vaccine responses (POPVAC): results of three linked, randomized controlled trials	Alison Elliott
	Lunch break	
13 30 – 14 00	Schistosomiasis limits optimal vaccine-induced responses in previously vaccinated hosts by driving plasma B cell death in the bone marrow	Justin Nono
14 00 – 14 30	Therapeutic vaccination to cure HBV	Ulrike Protzer
14 30 – 15 00	Tools to prevent *Shigella*-induced childhood diarrhea – a global health priority	Esther Ndungo
	End of Day 1 (online participation)	

Talks will be ca. 20 minutes with ca. 10 minutes for Q&A; online audience can engage with speakers via the chat function only

1st December 2023

Time	Topic	Speaker
08 30 – 09 00	Experiences from investigator-initiated clinical phase I trials of vaccines against emerging infections	Anahita Fathi
09 00 – 09 30	Using tissue-specific dendritic cells as potential therapeutic targets to refine vaccine responses locally	Johannes Mayer
09 30 – 10 00	Geographical variation in immune profiles and vaccine hyporesponsiveness	Maria Yazdanbakhsh
10 00 – 10 30	Inhibition of vaccine responses by helminths – lessons from a mouse model	Roland Lang
10 30 – 11 00	**Coffee break**	
11 00 – 11 30	The role of vaccines and combined interventions in malaria control	Benjamin Mordmüller

11 30 – 12 00	How does the STIKO arrive at its recommendations?	Christian Bogdan
12 00 – 12 30	State of vaccine confidence from the perspective of European healthcare providers	Greet Hendrickx
End of Day 2 (online participation)		

Talks will be ca. 20 minutes with ca. 10 minutes for Q&A; online audience can engage with speakers via the chat function only

3. Abstracts

First results from the (GLOHRA-supported) project HelmSys

Marrium Habib,[1,2] Alex Siebner,[3] Vanesa Osmani,[4] Judith Flügge,[3] Meral Esen,[3] Stefanie J. Klug,[4] Clarissa Prazeres da Costa[1,2]

1 Institute for Medical Microbiology, Immunology & Hygiene, School of Medicine & Health, Technical University of Munich (TUM), Munich, Germany

2 Center for Global Health (CGH), Technical University of Munich (TUM), Munich, Germany

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Filarial infections compromise influenza vaccination efficacy: lessons from the mouse

Minka Breloer[1,2] and Wiebke Hartmann[1]

1 Section for Molecular Biology and Immunology, Helminth-Immunology Group, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

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Helminth parasites infect more than a quarter of the human population and inflict significant changes to the immunological status of their hosts. Several human studies report impaired responses to vaccinations in helminth-infected individuals. Analysing the impact of helminth infections on the efficacy of influenza vaccinations in the mouse system helps to elucidate the underlying immunological processes. Concurrent infection with the parasitic nematode *Litomosoides sigmodontis* reduced the quantity and quality of antibody responses to vaccination against seasonal influenza in BALB/c and C57BL/6 mice. This led to impaired vaccination-induced protection against challenge infections with the human pathogenic 2009 pandemic H1N1 influenza A virus in helminth-infected mice. Impaired responses were also observed if vaccinations were performed after immune-driven or drug-induced clearance of a previous helminth infection. Mechanistically, the suppression was associated with a systemic and sustained expansion of IL-10-producing CD4+CD49b+LAG-3+ type 1 regulatory T cells and partially abrogated by in vivo blockade of the IL-10 receptor. In summary, these findings raise the concern that individuals in helminth-endemic areas may not always benefit from vaccinations, even in the absence of an acute and diagnosable helminth infection.

Schistosomiasis limits optimal vaccine-induced responses in previously vaccinated hosts by driving plasma B cell death in the bone marrow

Fungai Musaigwa[1,2,3] Severin Donald Kamdem[1,2,3,4] Thabo Mpotje[1,2,3] De'Broski R. Herbert[5] Frank Brombacher[1,2,3,6] and **Justin Komguep Nono**[1,2,7]

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7 The Unit of ImmunoBiology and Helminth Infections, Laboratory of Molecular Biology and Biotechnology, Institute of Medical Research and Medicinal Plant Studies, Ministry of Scientific Research and Innovation, 13033, Yaoundé, Cameroon

Schistosomiasis is a debilitating parasitic disease that is most common in Sub-Saharan Africa. The disease has previously been shown to influence systemic immunity towards unrelated antigens such as vaccines. However, mechanisms behind the parasite's impact on vaccine mounted long-term immunity are not fully understood. We investigated the impact of chronic Schistosoma mansoni infection on the efficacy of vaccine-induced immunity in school-aged Cameroonian children and laboratory mice. Our findings highlighted impaired maintenance of long-term anti-polio vaccine-specific serological immunity in both vaccinated children and mice. Using a mouse model of anti-viral vaccination, additional mechanistic evaluations demonstrated that chronic schistosomiasis caused vaccine-elicited immunity impairment through reduced survival of plasmablasts and antibody-producing plasma B cells in the bone marrow. Treatment with praziquantel partially reversed the impact of chronic schistosomiasis on serological immunity of both vaccinated children and mice, and plasma B cell populations in the bone marrow of mice. Our results, therefore, demonstrate the morbid impact and a potential mechanism thereof, of chronic schistosomiasis on immunological responses induced by anti-viral vaccination. Further, this study presents praziquantel treatment as a potential strategic tool to improve vaccination effectiveness through ameliorated sustainability post-vaccination in at-risk population groups in schistosomiasis endemic regions. These findings are timely for the informed rollout of much needed antiviral COVID-19 vaccines and possibly anti-malarial vaccines in Schistosomiasis-infested countries.

Population differences in vaccine responses (POPVAC): results of three linked, randomised controlled trials

Ludoviko Zirimenya,[1,2] Gyaviira Nkurunungi,[1,4] Jacent Nassuuna,[1] Agnes Natukunda,[1,4] Emily L Webb,[4] **Alison M Elliott**,[1,2] and the POPVAC trial team

1 Immunomodulation and Vaccines Focus Area, Vaccine Research Theme, Medical Research Council/Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine (MRC/UVRI and LSHTM) Uganda Research Unit, Entebbe, Uganda

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4 International Statistics and Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background. Vaccine responses differ between populations, and are often impaired in rural, low-income settings, but the reasons for this are not fully understood. The immunomodulating effects of chronic, active infections or prior infection exposure may contribute. *Hypothesis*. Helminth and malaria infections suppress, and BCG vaccination improves, responses to unrelated vaccines. *Methods*. We enrolled adolescents in rural high-schistosomiasis (trial A) and rural high-malaria (trial B) settings and from an established urban birth cohort (trial C). We tested the effects of intensive vs standard praziquantel treatment of Schistosoma mansoni (Sm) (trial A), monthly intermittent preventive treatment of malaria with dihydroartemisinin-piperaquine (DP) (trial B), and BCG revaccination (trial C), on a common set of vaccine responses. Participants received BCG on day '0'; yellow fever (YF-17D), oral typhoid (Ty21a), and human papilloma virus (HPV) vaccines at week 4; and HPV and tetanus/diphtheria (Td) booster vaccine at week 28. Outcomes were BCG-specific IFN-□ 8 weeks post-BCG vaccination, YF neutralising antibody titres, Salmonella typhi LPS-, HPV 16- and HPV 18- specific IgG 4 weeks post-vaccination, and Td-specific IgG 24 weeks post-Td vaccination. We analysed (1) effects of the intervention in each trial, (2) differences between vaccine responses in the three settings and (3) role of schistosomiasis and malaria as mediators of differences between settings. *Results*. In trial A, intensive Sm treatment improved the week 8 BCG-specific IFN-γ ELISpot response (among all participants) geometric mean ratio 1.20 (95%CI 1.01-1.43) but reduced the response to HPV (among baseline Sm-positive participants) 0.71 (95%CI 0.54-0.94). In trial B, there was no effect of DP versus placebo on primary vaccine response outcomes but DP reduced waning of the yellow fever response between weeks 8 and 52. In trial C, there was no effect of BCG revaccination on vaccine responses. There were statistically significant differences in vaccine responses between settings for BCG, yellow fever, Ty21a and tetanus, but mediation analyses did not support a major role for schistosome or malaria infection as mediators of these differences. *Conclusion*. Despite substantial differences between settings, we found only modest evidence of a role for schistosome or malaria infection or exposure in these effects. The role of other environmental exposures, and mechanisms by which they act, needs to be explored further in order to identify ways in which vaccine impact can be optimised for all communities.

Tools to prevent Shigella-induced childhood diarrhea – a global health priority

Esther Ndungo[1]

1 Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore (UMB), USA

Shigella species are responsible for a high burden of moderate-to-severe diarrhea globally. Children younger than 5 years of age, particularly toddlers 2-3 years old, are the most affected. Repeated infection impairs physical and cognitive development leading to lifelong disability. The rapid and widespread prevalence of antibiotic resistant Shigella spp. has also become a major public health concern. Currently, there are no approved vaccines against shigellosis. Two candidate vaccine approaches are being pursued by our group: Shigella O-polysaccharide conjugated with Invasion plasmid protein B (IpaB) and conserved type 3 secretion system proteins and virulent antigens. These vaccines can overcome the limitation of clinically advanced vaccine candidates that rely only on immunity targeting the bacterial lipopolysaccharide, which is serotype specific - as there are multiple disease-causing serotypes, a combination of vaccines is needed to prevent disease caused by circulating strains. Our vaccines include

proteins that are highly immunogenic and conserved among strains, therefore affording broad protective immunity. Preclinical data of vaccine efficacy and immune responses and mechanistic analyses of immunity elicited through infection and vaccination will be discussed. On a more fundamental level, our lab is poised to understand the underpinnings of natural immunity acquired by exposure to Shigella in endemic areas, especially in early childhood years, which is being studied in a maternal-infant cohort (up to 2 years of age) from Malawi. We are also investigating antimicrobial features of mucosal immunity that contribute to protective immunity to inform vaccine design. Finally, an in vitro human enteroid/colonoid model is utilized to dissect immune components that can prevent infection and evaluate tools to treat Shigella infection.The presentation will discuss essential aspects of Shigella infection and immunity and progress in the development of tools to prevent and treat childhood dysentery.

Experiences from investigator-initiated clinical phase I trials of vaccines against emerging infections

Anahita Fathi[1]

1 *Center for Internal Medicine, Medical Clinic and Polyclinic (Gastroenterology with Sections of Infectiology and Tropical Medicine), University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Early clinical trials of vaccines for emerging infectious diseases (EID) are a crucial tool for pandemic preparedness. They allow us to assess the safety and immunogenicity of vaccine candidates well before disease outbreaks occur. Furthermore, they form the cornerstone for swiftly initiating efficacy studies when epidemics strike. The expertise of our group lies in the conduct of clinical phase I investigator-initiated trials (IITs) for EID vaccines. These trials present a set of unique challenges. They often take place in a rapidly evolving (pre-) pandemic environment, require significant and immediate funding, and demand rapid result delivery. Nonetheless, IITs offer various opportunities. Researchers are actively engaged in multiple phases of the trial, including trial design, execution, and safety evaluation, experimental work, data analysis, and collaboration with project partners. This involvement grants them a comprehensive and in-depth understanding of the vaccine candidate. During this presentation. I will share our experiences with coronavirus vaccine trials, specifically those related to SARS-CoV-2 and MERS-CoV.

Using tissue-specific dendritic cells as potential therapeutic targets to refine vaccine responses locally

Johannes Mayer[1]

1 *Johannes U. Mayer, Professor for Dermatological Immunotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Department of Dermatology, Mainz, Germany*

Dendritic cells (DC) play a crucial role in informing the adaptive immune system about pathogens or innocuous and self antigens and direct T cell responses towards effector activation or tolerance. DC represent one of the most sophisticated antigen-presenting cells and have been identified in all tissues of the body in most mammals, including mice and humans. They are crucial for initiating adaptive immune responses against newly encountered pathogens by priming CD4 and CD8 T cells in tissue-draining lymph nodes. DC also play an important role in driving effective and long-lived immune responses against vaccines, as they are activated by vaccine adjuvants or cellular signals. However, DCs are highly specialised and display a significant tissue-specific heterogeneity that has been linked to subset-specific functions. For example, DC in the lung present a different transcriptomic and proteomic signature than DC described in the skin or the intestine, maintained by local immune imprinting networks and influencing

the strength and specificity of the ensuing adaptive immune response. Recent technological advances in the field of single-cell OMICS approaches and focused analyses on antigen-presenting cells have improved our understanding of the tissue-specific heterogeneity and function of DC. New concepts are now emerging to harness this knowledge and target functionally specialized tissue-specific DC subsets to invoke localized and targeted immune responses and the priming of tissue-resident T cell populations in an effort to enhance tissue-specific vaccine efficacy and reduce vaccine hesitancy by limiting off-target effects.

Geographical variation in immune profiles and vaccine hyporesponsiveness

Maria Yazdanbakhsh[1]

1 Leiden University Medical Center, The Netherlands

Prevention of infectious diseases through vaccination is one of the greatest achievements of medicine, yet there is growing realisation that vaccine immunogenicity and efficacy varies greatly across populations in high- versus low/middle- income countries (LMIC) and in urban- versus rural areas within one country. For example, whereas vaccination of volunteers in Europe with attenuated malaria vaccine can result in 100% protection, the efficacy drops to only 29% when tested in Africa, where it is needed most. Other vaccines, such as rotavirus, BCG, yellow fever and Ebola show similar trends in either immunogenicity or efficacy. In parallel, using technologies for in depth characterization of the immune system, shows strong variation in immunological profiles across geographical areas. In particular, the expansion of highly activated immune cell subsets, along with increased regulatory T and B cell frequencies, and skewing towards Th2, characterize the immune profiles of populations residing in rural areas of LMIC; areas where vaccine performance is poor. Identification of immunological pathways involved in vaccine hyporesponsiveness is needed for interventions to reverse it.

Therapeutic vaccination to cure HBV

Ulrike Protzer[1]

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Hepatitis B virus (HBV) is a major public health threat with more than 290 million humans chronically infected worldwide at risk to develop end-stage liver disease and hepatocellular carcinoma. Each year, more than 880,000 people die from the consequences of HBV infection. Available antivirals control HBV replication but do not cure HBV infection. Immune therapies including therapeutic vaccines, antibody and T-cell therapies are most promising to achieve a cure. We proved T-cell therapies to be effective in relevant preclinical models and on this basis designed a therapeutic hepatitis B vaccine that allows activation of CD4 and CD8 T cells. Such a therapeutic vaccine represents a promising treatment approach. However, development of such a vaccine is challenging since simultaneous stimulation of vigorous antibody- as well as T-cell responses is necessary to overcome the HBV-specific immune tolerance and the therapeutic vaccine needs to cover different HBV strains. The heterologous TherVacB prime-boost vaccination scheme proved most suited to achieve this. We found that activating CD4 T cells is essential for the success of a therapeutic vaccine, and that this can best be achieved by using a protein prime. We therefore combined recombinant, particulate HBsAg and HBcoreAg for prime vaccination with an adjuvant that activates a balanced Th1/Th2-type helper T-cell response. To boost effector T-cell responses, we designed a vaccine vector based on modified vaccinia virus Ankara (MVA). To cover all circulating HBV

strains worldwide, we designed and characterized a novel vaccine vector, MVA-HBVac, capable of inducing strong and multi-specific T-cell responses in a mouse model of chronic hepatitis B. The MVA-HBVac transgenic vector contains a polycistronic expression cassette optimized to induce a broad response by covering the HBV epitopes of the five most prevalent genotypes, A-E, covering 95% of global circulating isolates. Application of the MVA-HBVac in HBV-carrier mice showed that the vector led to HBsAg seroconversion, induction of a strong and HBV-specific CD4+ and CD8+ T-cell response and caused sustained reduction or elimination of HBeAg and HBsAg from the serum. Moreover, the TherVacB regimen employing MVA-HBVac could reliably overcome the virus-mediated immune tolerance and induced therapeutic anti-viral effect against persistent HBV infection with several relevant HBV genotypes such as A, B and D as well as HBeAg-negative HBV. Currently, we are translating this approach into the clinics.

The role of vaccines and combined interventions in malaria control

Benjamin Mordmüller[1]

1 *Professor at the Department of Medical Microbiology, Radboud University Medical Center (Radboudumc), Nijmegen, The Netherlands*

In my presentation, I will discuss if there is a role for vaccines in malaria control and introduce the audience to the current malaria vaccine portfolio. Besides active vaccines, monoclonal antibodies to prevent malaria and transmission are currently under development and case scenarios for their use are explored. In case that malaria vaccines and passive immunization strategies improve malaria control, they need to be integrated into ongoing programs. I will give an overview of strategies that are currently under discussion and summarize first results of trials that tested combined interventions.

Vaccination in Germany: How does the STIKO arrive at its recommendations?

Christian Bogdan[1,2]

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The Standing Committee for Vaccination (Ständige Impfkommission, STIKO) is a national consortium of 18 independent experts, who are appointed by the Federal Ministry of Health and develop recommendations for all vaccines that are authorized and applied in Germany. The members of the STIKO work on an honorary basis and must disclose any possible conflict of interest. The activities of the STIKO are coordinated by an office located in the Vaccination Prevention Department of the Robert Koch Institute in Berlin and supported by several scientists, who, for example, carry out systematic reviews of the literature. The overarching goal is to optimally adapt the vaccination recommendations to new research findings and vaccine developments. Since 2011, the standard operating procedure of the STIKO is strictly based on the methods and rules of evidence-based medicine and entails the careful analysis of the basic science articles as well as clinical studies relevant for the assessment of a particular vaccine. Published clinical studies are evaluated following the recommendations by the GRADE working group. In the presentation, I will focus on the parameters that influence the decision making process of the STIKO and provide examples why and how various vaccine recommendations have recently been adjusted.

State of vaccine confidence from the perspective of European healthcare providers

Greet Hendrickx[1]

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