Basic Science Award interview – Erik Thiele Orberg

Time and date of presentation: 1650H, Monday 24 April in session G2-04, part of the Presidential Symposium in Amphitheatre Bleu

Erik is the winner of the 2023 EBMT Basic Science Award for his team's study: 'BACTERIOPHAGE-MODULATED PRODUCTION OF INTESTINAL INTERFERON I-INDUCING METABOLITES IS ASSOCIATED WITH PROTECTION IN ALLOGENEIC STEM CELL TRANSPLANTATION PATIENTS.'

Q: For those delegates who do not know you Erik, please tell us a little about yourself.

A: I am 37-year-old clinician scientist and junior research group leader at the Department of Hematology and Oncology at the University Hospital of the Technical University of Munich (TUM).

I hold a medical degree from the Medical University of Vienna, Austria and a doctorate of philosophy in immunology from the Johns Hopkins University School of Medicine, Baltimore, USA. I received my board-certification in internal medicine, hematology and oncology in 2022.

My work in hematology and immunology began during medical school in Vienna, where I worked on T cell vaccines against systemic and mucosal pathogens. After graduation, I moved to Baltimore to pursue a PhD thesis at the intersection of cancer immunology, mucosal immunity, and the microbiome. I returned to Europe, to the TUM, to pursue my dream of combining translational research with patient care. I completed my residency in internal medicine and fellowship at the Department for Hematology and Oncology. During this time, I pursued a research career as clinician scientist, first as Postdoc in the group of Prof. Hendrik Poeck, and recently as junior group leader in our Department. Our recent work has focused on microbiome and microbiota-derived metabolites in stem-cell therapies for hematological malignancies.

I would like to emphasise the collaborative nature of this study across Munich and Regensburg, and am honoured to accept the EBMT Basic Science Award on behalf of my co-authors, Dr. Elisabeth Meedt, Dr. Andreas Hiergeist, Dr. Jinling Xue as well as Prof. Li Deng, Prof. Ernst Holler and Prof. Hendrik Poeck.

Q: Why did you decide to do this study?

A: Allogeneic stem cell transplantation (allo-SCT) remains the most common cellular immunotherapy for curation of hematologic malignancies, but outcomes are limited by severe morbidity and mortality associated with graft-vs.-host disease (GvHD). At the time, clear evidence was emerging that the human intestinal microbiome was a predictor of clinical outcome in patients undergoing allo-SCT. However, it was not well understood why increased bacterial diversity was associated with longer overall survival in these patients. Meanwhile, studies describing microbiota-derived metabolites which could exert immuno-modulatory and tissue-homeostatic functions in mice and humans had just been published. We hypothesized that microbiota-

derived metabolites may be a critical link between microbiota and their human hosts, and explain why reduced diversity, by a depletion of beneficial metabolites, may be associated with increased incidence of GvHD and transplant-related mortality (TRM).

Q: What were the main findings?

A: We report the 2-year follow-up of a prospective, longitudinal, two-center cohort of patients undergoing allo-SCT for hematological malignancies. In 78 patients, we profiled the intestinal bacteriome, fungome, virome and intestinal microbiota-derived metabolites from the start of the pre-transplantation conditioning regimen until day 28 after allo-SCT. By Multi-omics Factor Analysis (MOFA), we identified a functional microbiome signature associated with the production of intestinal immuno-modulatory metabolites (IMMs). We established the IMM Risk Index (IMM-RI) by compounding five MOFA-identified IIMs: Low-risk IMM-RI was associated with greater overall survival (OS), reduced incidence of gastrointestinal graft-versus-host disease (GI-GvHD) and reduced relapse rate.

Mechanistically, IMM-RI low-risk patients had a higher abundance of microbial pathways involved in the biosynthesis of short-chain fatty acids (SCFA), specifically butyric acid via butyryl–coenzyme A (CoA):acetate CoA-transferase (BCoAT). We identified two unique bacteriophages that encoded BCoAT as an auxiliary metabolic gene (AMG), were more abundant in IMM-RI low-risk patients and were strongly correlated with intestinal butyric acid levels. By sequence alignment we show that the bacteriophage-encoded BCoAT was closely related to the *Oscillospiraceae* family of bacteria, suggesting phage-mediated horizontal gene transfer among bacterial strains and among individual patients.

4. What are the implications for the findings, and will you be following up the study?

We believe that our study highlights the role of bacterial consortia together with bacteriophages in protecting against adverse outcomes in allo-SCT patients. We defined specific IMMs that limit GvHD but may also modulate graft-vs-leukemia, and therefore may be important for other T cell-mediated therapies that are influenced by the gut microbiome such as CAR-T cells or immune checkpoint inhibitors. Our data provides intriguing evidence of bacteriophage AMGs in humans, via which they could support metabolite production and potentially benefit patients undergoing allo-SCT.

From a clinical-translational standpoint, administration of IMMs – by (i) selecting fecal microbiota transplantation (FMT) donors based on metabolite profiling, or administration of (ii) defined bacteria/bacteriophage consortia or (iii) metabolite combination drugs – could be explored in clinical trials in allo-SCT patients with biomarker-proven microbiome injury, such as a high-risk IMM-RI, to treat or prevent GvHD and relapse.

Our collaborators at the University Hospital Regensburg (UKR) recently received approval for manufacture of FMT products, and we intend to screen for microbiota-derived metabolites in FMT donors and patients, and to correlate microbiome signatures and metabolite states with overall response and safety.

5. What other projects are you involved in?

Together with Sascha Göttert (UKR), a doctoral student in the lab of Prof. Hendrik Poeck, we are exploring the mechanism of specific microbiota-derived metabolites in preclinical and advanced human organoid models.

With Prof. Bassermann (TUM), we are interested in characterizing the role of microbiome and microbiota-derived metabolites in the transition of precursor conditions to multiple myeloma, as well as the efficacy of anti-myeloma therapy.

In clinical practice, I am committed to upholding the highest standards in regards to patient safety and in the quality of healthcare we provide to our patients by instituting regular morbidity and mortality conferences at our Department.

6. Tell us what you like to do outside of work.

Outside of work, I am passionate about sports and compete in running marathons and cycling races. During graduate school, I realized that sports are an essential tool to balance the everyday demands and challenges of a rigorous academic and clinical career. Since then, I prioritize this hobby along with social interactions with close friends and family, which I believe allows me to work with more focus and sustained motivation towards my research goals.