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I. Medizinische Klinik und Poliklinik

iDfellows Selection Committee

Hepatitis E Virus as a Sentinel for Immune Dysfunction in Multiple Myeloma: Mechanisms, Models, and Clinical Implications

Hamburg, 05.10.2025

Dear Members of the iDfellows Selection Committee,

Today, we will submit an ID Fellows project proposal that uniquely positions hepatitis E virus infections as a sentinel indicator disease for understanding immune dysfunction in multiple myeloma and other hematologic malignancies. As co-principal investigators with complementary expertise, we believe this project represents an ideal opportunity for training a young oncologist interested in infectious diseases and translational medicine.

This project is exceptionally well-suited for training a young oncologist in infectious diseases and translational medicine. The project directly addresses the intersection of modern cancer therapeutics and infectious complications, providing ideal exposure to both disciplines. The fellow will gain expertise in understanding how novel immunotherapies create unexpected vulnerabilities to viral infections while learning cutting-edge laboratory techniques with direct clinical applications.

The fellow will benefit from outstanding access to resources through multiple established networks. Through DZIF, the fellow gains access to national expertise and large HEV cohorts across Germany. The project includes partnerships with world-class experts at the University of Basel for TCR/BCR repertoire analysis (with the opportunity for the prospective IDfellow to conduct research in Basel), University of Freiburg for MHC class II HEV-specific tetramer expertise, and Seattle for MHC Class II tetramer expertise. On campus, collaborations with multiple myeloma cohorts, clinical virology, HEV model systems, and humanized mouse models provide a comprehensive research infrastructure.

This project is strategically positioned at the interface of the DFG CRC 1700 and the CRC 1648. This positioning provides the fellow with access to two major research networks and collaborative opportunities that would otherwise be unavailable.

The concept of using HEV as a sentinel indicator disease represents a paradigm shift from descriptive infection studies to a mechanistic understanding of therapeutic immunosuppression. This innovative approach has potential for risk stratification, treatment optimization, biomarker development, and broader applications to other opportunistic infections in immunocompromised hosts.

We strongly support funding this proposal and are committed to providing the comprehensive mentorship and resources necessary for the fellow's success.

Best regards,

Julian Schulze zur Wiesch

(also on behalf of Sven Pischke)

Hepatitis E Virus as a Sentinel for Immune Dysfunction in Multiple Myeloma: Mechanisms, Models, and Clinical Implications

Project leaders:

Prof. Dr. med. J. Schulze zur Wiesch, PD Dr. med. Sven Pischke
I. Medizinische Klinik und Poliklinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Key Collaborators:

- Katja Weisel, UKE: Multiple myeloma cohorts
- Masha Binder lab (Christoph Schultheiß), University of Basel: B-cell and T-cell receptor repertoire analysis
- Tobias Boettler, University of Freiburg: MHC HEV Tetramers
- William Kwok, Seattle: MHC Class II tetramers
- Maura Dandri, UKE: Humanized mouse models
- Marc Lütgehetmann, UKE: Clinical virology
- Toni Meister, UKE: HEV models

Background and preliminary data

Hepatitis E virus (HEV) genotype three infections can become chronic in immunosuppressed patients and lead to life-threatening cirrhosis within 5 years. HEV as an Indicator Disease and Model for Immune Deficiencies in Lymphoma-Patients: HEV infections have become a key indicator of immune dysfunction in patients with lymphomas and other blood cancers, serving as a useful model to understand the extent and complexity of immunosuppression caused by modern cancer treatments. The somewhat unexpected level of immunosuppression induced by CD38-targeted monoclonal antibodies and other novel agents reveals previously unrecognized vulnerabilities in antiviral immunity. The utility of HEV as an indicator disease lies in its ability to reveal the functional consequences of therapeutic immunosuppression in real-time. Unlike opportunistic infections that occur late in the disease course, HEV chronicity develops predictably in immunocompromised hosts, providing measurable endpoints for assessing immune dysfunction. The specific pattern of immune failure—characterized by exhausted CD8+ T-cell responses, impaired viral clearance, and poor treatment responses—mirrors broader cellular immunity deficiencies predisposing patients to other viral reactivations.
Recent mechanistic insights have shown that HEV-specific CD8+ T cells in chronically infected immunocompromised patients exhibit exhaustion phenotypes, characterized by decreased functionality and heightened expression of inhibitory receptors. However, functional reinvigoration can occur when the antigen is cleared through treatment, indicating potential for therapeutic interventions that target T-cell exhaustion pathways. For hematological-oncological patients, the timing and length of ribavirin therapy are crucial, as these patients need prompt immunosuppressive treatments (such as rituximab, CAR-T therapy, or stem cell transplantation) to prevent malignant disease progression. Additionally, HEV infections have been associated with lymphoproliferative disorders, including a case of CD30+ T cell lymphoma that remitted after successful HEV treatment.

Hypotheses

1. MM patients receiving novel immunotherapeutic agents demonstrate distinct patterns of HEV-specific immune dysfunction compared to transplant recipients, characterized by altered T-cell exhaustion profiles, compromised B-cell responses, and impaired NK cell function.
   HEV infection serves as an indicator disease revealing the full spectrum of immune deficiencies induced by these therapies.
2. The chronicity of HEV infection correlates with specific immunological signatures detectable through comprehensive analysis of virus-specific T-cell populations, TCR/BCR repertoire architecture, and tetramer-based responses.
   These signatures can serve as biomarkers for broader immune dysfunction in patients with lymphoma.
3. HEV infections may contribute to lymphomagenesis through virus-induced B-cell dysregulation and chronic immune activation.
   HEV represents both a consequence of and a potential contributor to lymphoma pathogenesis.

Aims and Work Program

Aim #1: Comprehensive immunological characterization of HEV-specific responses

Advanced T-Cell Analysis Using Overlapping Peptide Libraries:

- Comprehensive mapping of HEV ORF2 and ORF3-specific T-cell responses using overlapping peptide pools, focusing on immunodominant epitope regions (amino acids 73-156, 289-372, 361-444, 505-588 of ORF2).

HLA Class I and Class II Tetramer-Based Analysis:

- Development and utilization of HEV-specific HLA class I tetramers (collaboration with Tobias Boettler) and class II tetramers (collaboration with William Kwok) for direct ex vivo detection of virus-specific T cells.
- Investigation of rare class II-restricted CD8+ T-cell populations representing alternative antiviral mechanisms.
- Assessment of Memory development and T-cell exhaustion (TOX, Eomesodermin, PD-1, TIGIT, CD39, CD73) as well transcriptional patterns in virus-specific CD8+ T cells, including TOX+Eomesodermin+ terminally exhausted vs. progenitor memory phenotypes using multicolor flow cytometry (Aurora) as well as RNAseq with live sorted cells.
- Analysis of TCR clonality and functional capacity of tetramer-positive and bulk populations.

TCR and BCR Repertoire Analysis:

- Comprehensive T-cell receptor (TCR) repertoire analysis using high-throughput sequencing (collaboration with Masha Binder lab, Christoph Schultheiß) to assess TCR diversity, clonality, and repertoire architecture in HEV-infected MM patients and controls.
- B-cell receptor (BCR) repertoire analysis to evaluate diversity, somatic hypermutation, and clonal evolution in response to HEV and immunosuppressive therapy.
- Investigation of IGHV gene usage patterns, with attention to potential lymphoma-associated transcriptomic changes in virus-specific B cells.
- Integration of TCR and BCR repertoire data to understand coordinated adaptive immune responses and repertoire signatures predictive of HEV chronicity.

B-Cell Tetramer Analysis:

- Implementation of B-cell tetramer technology to directly identify HEV-specific B cells and assess functional capacity.

Aim #2: Analysis of innate and unconventional immune responses

NK Cell and Unconventional T-Cell Assessment:

- Comprehensive phenotyping of NK cell subsets with functional analysis of cytotoxicity and cytokine production.
- Analysis of invariant NKT cells, MAIT cells, and γδ T cells, profoundly affected by novel MM therapies.
- Investigation of NK cell-mediated regulation of T-cell responses as rheostats modulating antiviral function.

Aim #3: Longitudinal analysis and mechanistic studies

Building on our established UKE MM cohort in collaboration with Katja Weisel, we will prospectively collect samples at defined timepoints to:

- Compare immune parameters between MM patients receiving different therapeutic regimens (CD38 antibodies, bispecific antibodies, CAR-T cells)
- Analyze transplanted patients with B-cell depletion as comparative controls
- Correlate immunological findings with clinical outcomes including time to HEV clearance, chronicity rates, and treatment response
- Establish HEV infection patterns as predictive indicators for broader immune dysfunction

Viral and mechanistic analysis:

- Collaborations with Marc Lütgehetmann (clinical virology) and Toni Meister (HEV models)
- Investigation of viral sequence evolution and escape mutations using established sequencing approaches
- Assessment of ribavirin resistance mutations and CD8+ T-cell escape variants
- *(prospective/ in collaboration) Humanized mouse model studies (collaboration with Maura Dandri, UKE) to investigate HEV pathogenesis and immune responses under controlled immunosuppressive conditions*

Aim #4: Survey of anti-HEV IgG seroprevalence

Compare anti-HEV IgG seroprevalence in MM patients (in collaboration with Katja Weisel for MM cohorts) with age- and sex-matched organ transplant recipients to determine whether MM patients have an increased likelihood of prior HEV infection, suggesting HEV as a potential trigger for lymphoma development. This comprehensive analysis, using HEV as both an indicator of disease and a model system for immune dysfunction, will provide valuable insights into risk stratification, treatment optimization, and guide the development of immune monitoring strategies for managing unexpected immunosuppressive effects of modern cancer therapies.

Project-related publications (max. 5)

1. Al-Bazaz M, Pischke S, Alsdorf W, Sonnemann P, Cichutek S, Wiesch J, Schaefers C, Artzenroth J, Leypoldt L, Kamili A, Bokemeyer C, Weisel K, Kosch R, Schulze zur Wiesch J. Hepatitis E virus infections in people with multiple myeloma: an emerging challenge in the era of immunotherapeutic approaches. *Haematologica.* 2025. [Epub ahead of print]
2. Kemming J, Thimme R, Neumann-Fraune M, Omran H, Hofmann-Sieber H, Boege F, Lohse AW, Protzer U, Schulze Zur Wiesch J, Emmerich F, Llewellyn-Lacey S, Goulder P, van de Sand C, Cornberg M, Wedemeyer H, Antar AA, Rice CM, Bjorkstrom NK, Bockmann JH, Horvatits T, Polywka S, Pischke S. Mechanisms of CD8+ T-cell failure in chronic hepatitis E virus infection. *J Hepatol.* 2022;77(4):1069-1081.
3. Schulze zur Wiesch J, Ciuffreda D*, Lewis-Ximenez L, Kasprowicz V, Nolan BE, Streeck H, Aneja J, Reyor LL, Allen TM, Lohse AW, McGovern B, Chung RT, Kwok WW, Kim AY, Lauer GM. Broadly directed virus-specific CD4+ T cell responses are primed during acute hepatitis C infection, but rapidly disappear from human blood with viral persistence. *J Exp Med.* 2012;209(1):61-75. (*shared authorship)
4. Wildner NH, Walker A, Brauneck F, Ditt V, Peine S, Huber S, Haag F, Beisel C, Timm J, Schulze zur Wiesch J. Transcriptional Pattern Analysis of Virus-Specific CD8+ T Cells in Hepatitis C Infection: Increased Expression of TOX and Eomesodermin During and After Persistent Antigen Recognition. *Front Immunol.* 2022;13:886646.
5. Schulze zur Wiesch J, Lauer GM, Day CL, Kim AY, Ouchi K, Duncan JE, Wurcel AG, Timm J, Jones AM, Mothe B, Allen TM, McGovern B, Lewis-Ximenez L, Sidney J, Sette A, Chung RT, Walker BD. Broad repertoire of the CD4+ Th cell response in spontaneously controlled hepatitis C virus infection includes dominant and highly promiscuous epitopes. *J Immunol.* 2005;175(6):3603-13.