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Universitätsklinik für Anästhesiologie und Schmerztherapie
Direktor und Chefarzt:
Prof. Dr. med. Frank Stüber

PhD Thesis Project in Anaesthesiology

Title	**Inflammatory regulation of microRNAs on both innate and adaptive immunity under physiological and traumatic conditions**
Background	Human leukocyte antigen–DR isotype (HLA-DR) is a major histocompatibility class II (MHC-II) cell surface receptor found on antigen-presenting cells and plays a key role in initiating adaptive immune responses. In severely immunocompromised patients with conditions like sepsis and severe cases of coronavirus disease 2019 (COVID-19), the number of HLA-DR molecules expressed on leukocytes is considered to correlate with infectious complications and patients' probability of survival. Neutrophil Extracellular Trap (NET) formation, NETosis, is a relatively newly identified function of neutrophils. Although NETosis is shown to involve in various innate immune processes including the pathogenesis of sepsis, until today NETs formation during an immunosuppressed state such as in perioperative surgical trauma remains largely unclear. It is conceivable that NETosis may be compromised during an immunodeficiency state.
Aim	We aim to investigate if the above-described perioperative immunosuppression could be reflected in the reduction of monocytic HLA-DR expression and the NETosis rate using *in vitro*, *ex vivo*, and *in vivo* models. Furthermore, we will systematically examine the HLA-DR regulation by microRNAs, pro- or anti-inflammatory cytokines, hormones, and neurotransmitters. The overarching goal of this research project is to facilitate clinical anesthesiology and immunology studies by providing an efficient preclinical screening platform for candidate therapeutics, in compliance with the 3R (Replace, Reduce, Refine) concepts.
Research work, methods	Main research methods will cover cell culture, whole-blood culture, animal model, RNAi (microRNA transfection in human cell line and primary cells), flow cytometry (FCM), real-time qPCR, plasma miRNA analysis, drug administration, cytokine stimulation, immunohistochemistry, RNA *in situ* hybridization, live fluorescence microscopy, and statistical analysis. Additional methods may cover ELISA, western blot, Fluorescence-activated cell sorting (FACS), RNA sequencing, and droplet digital PCR (ddPCR).
Potential Relevance	Until now genome-wide association studies have not yielded early sepsis biomarkers or targets for treatment. We expect to identify novel candidate miRNA regulators of monocytic surface HLA-DR expression. Further, the whole blood assay may provide a broader assessment of additional serum biomarker and/or biosignature profiles. The outcome of this research will not only advance our knowledge of the genetic regulatory network underlying HLA-DR expression alterations during an immunosuppressed state, such as in severe surgical trauma, but will also help reveal early biomarkers and ultimately potential novel treatment options for critically ill patients with severe sepsis and septic shock.
References	1) Houseman & Huang et al., Eur J Immunol. 2022; DOI: 10.1002/eji.202149735 2) Paul et al., Cell. 2011; DOI:10.1016/j.cell.2011.03.023 3) Papayannopoulos et al., Nat Rev Immunol. 2018; DOI: 10.1038/nri.2017.105 4) Schulte et al., Mediators Inflamm. 2013; DOI: 10.1155/2013/165974

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Requirements	A team player who possesses a genuine interest in basic science and translational medical research and in acquiring lab skills and experimental techniques. Good knowledge in molecular and cell biology; knowledge of neurobiology and immunology and/or experience with animal experimentation would be a plus.
Preferred start date	The PhD thesis can be started upon mutual agreement (earliest on January 9th, 2023)
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