

Project title: Influenza at the Animal-Human Interface

Project number: P51/2017

Executive Summary

Within the Leibniz Professorinnen Programme, we could identify key pathomechanisms contributing to disease severity. The proposal was focused on understanding the pathogenicity of influenza viruses as a blueprint for pandemic pathogens. During epidemics (ZIKV and H7N9) and the 2020 SARS-CoV-2 pandemic, we were able to rapidly implement the findings obtained with influenza viruses to those of epidemic and pandemic concern.

1. Achievement of objectives and milestones

Key milestones were achieved within this programme.

- (1) We could identify pathomechanisms contributing to increased influenza disease severity in high-risk groups. We could show - in a murine model - that influenza during pregnancy causes long-term immune modulation in their offspring. This was associated with an increased susceptibility of the offspring towards other respiratory viral and bacterial infections (Jacobsen et al., *Nature Communications* 2021).
- (2) We could transfer our models established to study influenza during pregnancy (Engels et al., *Cell Host and Microbes* 2017) to other pathogens of epidemic concern, such as ZIKV that caused an epidemic in South America in 2017, eventually leading to microcephaly in babies born to infected mothers. In the murine pregnancy model, we could show that maternal ZIKV infection affects neurodevelopment in the unborn offspring. Moreover, even offspring born to ZIKV infected dams who were clinically unapparent showed neurocognitive impairments (Stanelle-Bertram et al., *Nature Microbiology* 2018).
- (3) For the H7N9 influenza outbreak that emerged in 2013 in Southeast Asia, we could show that infection was associated with low testosterone in male patients, further increasing the risk for a lethal outcome (Bai et al., *Nature Communications* 2022).
- (4) During the SARS-CoV-2 pandemic, we were able to rapidly transfer our knowledge gained on influenza pathomechanisms. We could show that severe SARS-CoV-2 infection in males is also associated with low testosterone levels as observed for H7N9 influenza. However, in parallel, in COVID-19 patients, low testosterone levels were accompanied by elevated estradiol levels in male patients due to an increased CYP19A1 activity (Stanelle-Bertram et al., *Cell Reports Medicine* 2023).
- (5) We were among the first worldwide to detect SARS-CoV-2 in the adipose tissue of patients who died of COVID-19. SARS-CoV-2 was able to replicate in human adipose tissue even beyond the lung (Zickler et al., *Cell Metabolism* 2021).

2. Activities and obstacles

The SARS-CoV-2 pandemic in 2020 hit in the middle of this project. Therefore, we immediately transferred our knowledge gained in understanding the pathomechanisms of influenza viruses to SARS-CoV-2. We were very successful in identifying first descriptions, such as the endocrine hits caused by SARS-CoV-2 (Zickler et al., *Cell Metabolism* 2021; Schroeder et al., *Emerging Microbes & Infection* 2022; Stanelle-Bertram et al., *Cell Reports Medicine* 2023). The ability of SARS-CoV-2 to infect the adipose tissue and replicate beyond the lung leads to the hypothesis that adipose tissue might act as yet undetected reservoir for virus replication that

could lead to long-term health impairments. The findings obtained within this project gave rise to a new research field that we call **infection endocrinology**.

3. Results and successes

The key findings obtained within the funding period are highlighted under 1.. All publications and acquired additional third party funding is listed in the excel file.

Most importantly, the findings obtained within this Proposal gave rise to the development of a respiratory pathogen focused programme for pandemic preparedness: the Leibniz Lab Pandemic Preparedness: One Health, One Future.

4. Equal opportunities, career development and internationalisation

We are dedicated to the overarching goal of promoting gender equality in science and increasing the number of women in academia. We have therefore developed an active policy of supporting equal opportunities for early career researchers by enabling them the attendance e.g. of conferences and supporting them throughout their employment.

5. Structures and collaboration

This is a PI-based project and collaborations were established according to the scientific questions raised during the SARS-CoV-2 pandemic. All collaborators were listed as co-authors.

6. Quality assurance

All staff attends regular meetings on good laboratory practice. Obtained research data are documented in electronic lab books. The research included animal experiments. Animal project licences were obtained from the local authorities in accordance with all regulations on animal welfare (2R principle).

7. Additional resources

This programme was additionally co-funded by the PIs institutional budget as well as her budget obtained through LOM (performance oriented budget).

8. Outlook

The findings obtained within this project gave rise to a new research field that we call **infection endocrinology**. Future studies will be directed to understand how acute respiratory infections reprogramme metabolic pathways eventually leading to long-term health impairments.