2017 Helmholtz – OCPC – Programme

for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project: Host proteases as targets for anti-viral therapy of influenza A infections

Helmholtz Centre and institute: Helmholtz Centre for Infection Research, Department Infection Genetics

Project leader: Prof. Dr. Klaus Schughart

Web-address: https://www.helmholtz-hzi.de/en/research/research_topics/bacterial_and_viral_pathogens/infection_genetics/our_research/

Description of the project:

Host proteases are required for the proteolytic activation of the influenza A virus (IAV) hemagglutinin and thus represent an ideal target for anti-viral therapy. We found that knock-out of the host protease gene Tmprss2 in mice completely blocks IAV replication and protects mice from pathology and lethality against infections with H1N1 virus. However, H3N2 IAV is still able to replicate. We subsequently showed that knock-out of both Tmprss2 and Tmprss4 is needed to strongly reduce replication in mouse lungs and rescue infected mice from otherwise lethal H3N2 IAV infection.

In the proposed project, we will generate re-assortant IAV that carry the HA segment of different IAV subtypes (H2, monobasic H5, moinobasic H7, H9, H10) on the PR8 virus backbone. We will infect Tmprss2, Tmprss4 single and Tmprss2 Tmprss2 double mutant knock-out mice with the different re-assortant viruses. Infected mice will be monitored for body weight loss, survival, viral load and pathology in infected lungs. These studies will reveal the sequence requirements for HA to be cleavage-activated by host proteases and subsequent pathology in infected lungs. In collaboration with structural biologists, we will then model HA-protease interactions based on the above results, design peptide inhibitors and test their activity in cell culture, organ culture and in mice.

Relevant publications:

Kuhn, N., Bergmann, S., Kosterke, N., Lambertz, R.L., Keppner, A., van den Brand, J.M., Pohlmann, S., Weiss, S., Hummler, E., Hatesuer, B., Schughart, K. (2016). The Proteolytic Activation of (H3N2) Influenza A Virus Hemagglutinin Is Facilitated by Different Type II Transmembrane Serine Proteases. J Virol 90, 4298-4307.

Hatesuer, B., Bertram, S., Mehnert, N., Bahgat, M.M., Nelson, P.S., Pohlman, S., and Schughart, K. (2013). Tmprss2 is essential for influenza H1N1 virus pathogenesis in mice. PLoS Pathog 9, e1003774.

Bertram, S.*, Glowacka, I.*, Blazejewska, P.*, Soilleux, E., Allen, P., Danisch, S., Steffen, I., Choi, S.Y., Park, Y., Schneider, H., K. Schughart, and S. Pöhlmann (2010). TMPRSS2 and TMPRSS4 facilitate

trypsin-independent spread of influenza virus in Caco-2 cells. J Virol 84, 10016-10025.

Ruth L.O. Lambertz, Jan Pippel, Joern Krausze, Nora Kühn, Klaus Schughart (2016). Importance of H1 and H3-hemagluttinin amino acid sequences on influenza A virus for cleavage processing by TMPRSS2 protease in vivo. submitted to J Virol.

Description of existing or sought Chinese collaboration partner institute:
TBD

Required qualification of the post-doc:

- PhD in biology or veterinary sciences
- Experience with virus pathogens, ideally with influenza A virus, virological methods
- Additional skills in animal experimentation

PART B

Documents to be provided by the post-doc:

- Detailed description of the interest in joining the project (motivation letter)
- Curriculum vitae, copies of degrees
- List of publications
- 2 letters of recommendation

PART C

Additional requirements to be fulfilled by the post-doc:

- Max. age of 35 years
- PhD degree not older than 5 years
- Very good command of the English language
- Strong ability to work independently and in a team