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Cyclophilin inhibitors restrict Middle East respiratory syndrome coronavirus *via* interferon-λ *in vitro* and in mice

Lucie Sauerhering[1], Alexandra Kupke[1], Lars Meier[1], Erik Dietzel[1], Judith Hoppe[2], Achim D. Gruber[2], Stefan Gattenloehner[3], Biruta Witte[4], Ludger Fink[5], Nina Hofmann[6], Tobias Zimmermann[6], Alexander Goesmann[6], Andrea Nist[7], Thorsten Stiewe[7,8], Stephan Becker[1,10], Susanne Herold[9,10] and Christin Peteranderl[9,10]

Affiliations: [1]Institute of Virology, Philipps University of Marburg, Member of the German Center for Infection Research (DZIF), TTU Emerging Infections, Marburg, Germany. [2]Dept of Veterinary Pathology, Free University Berlin, Berlin, Germany. [3]Dept of Pathology, University Hospital of Giessen, Giessen, Germany. [4]Dept of General and Thoracic Surgery, University Hospital of Giessen, Giessen, Germany. [5]Institut für Pathologie und Zytologie, Wetzlar, Germany. [6]Bioinformatics and System Biology, University of Giessen, Giessen, Germany. [7]Genomics Core Facility, Philipps University of Marburg, Marburg, Germany. [8]Institute of Molecular Oncology, Universities of Giessen and Marburg Lung Center, Member of the German Center for Lung Research (DZL), Marburg, Germany. [9]Dept of Internal Medicine II, University of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Giessen, Germany. [10]Equal contribution.

Correspondence: Christin Peteranderl, Universities of Giessen and Marburg Lung Center, Department of Internal Medicine II, Klinikstr. 36, D-35392 Giessen, Germany. E-mail: Christin.Peteranderl@innere.med.uni-giessen.de

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The cyclophilin inhibitors cyclosporin A and alisporivir activate host innate immunity by induction of interferon-λ *via* activation of IRF1 in human lung epithelial cells and *in vivo*, resulting in a significant inhibition of MERS-CoV https://bit.ly/37gzIBH

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ABSTRACT While severe coronavirus infections, including Middle East respiratory syndrome coronavirus (MERS-CoV), cause lung injury with high mortality rates, protective treatment strategies are not approved for clinical use.

We elucidated the molecular mechanisms by which the cyclophilin inhibitors cyclosporin A (CsA) and alisporivir (ALV) restrict MERS-CoV to validate their suitability as readily available therapy in MERS-CoV infection.

Calu-3 cells and primary human alveolar epithelial cells (hAECs) were infected with MERS-CoV and treated with CsA or ALV or inhibitors targeting cyclophilin inhibitor-regulated molecules including calcineurin, nuclear factor of activated T-cells (NFATs) or mitogen-activated protein kinases. Novel CsA-induced pathways were identified by RNA sequencing and manipulated by gene knockdown or neutralising antibodies. Viral replication was quantified by quantitative real-time PCR and 50% tissue culture infective dose. Data were validated in a murine MERS-CoV infection model.

Both CsA and ALV reduced MERS-CoV titres and viral RNA replication in Calu-3 cells and hAECs, improving epithelial integrity. While neither calcineurin nor NFAT inhibition reduced MERS-CoV propagation, blockade of c-Jun N-terminal kinase diminished infectious viral particle release but not RNA

accumulation. Importantly, CsA induced interferon regulatory factor 1 (IRF1), a pronounced type III interferon (IFNλ) response and expression of antiviral genes. Downregulation of IRF1 or IFNλ increased MERS-CoV propagation in the presence of CsA. Importantly, oral application of CsA reduced MERS-CoV replication *in vivo*, correlating with elevated lung IFNλ levels and improved outcome.

We provide evidence that cyclophilin inhibitors efficiently decrease MERS-CoV replication *in vitro* and *in vivo via* upregulation of inflammatory antiviral cell responses, in particular IFNλ. CsA might therefore represent a promising candidate for treating MERS-CoV infection.