Nationale
Forschungsplattform
für Zoonosen

International Workshop

Common Cold – SARS – Pandemic Influenza
Novel strategies to fight respiratory viral diseases

12-13 October 2009 | Berlin, Germany

Program Organizers

Stephan Ludwig, Westfälische-Wilhelms-University, Münster
Oliver Planz, Friedrich-Loeffler-Institut, Tübingen
for the National Research Platform for Zoonoses

Confirmed Speakers

John Oxford (London, U.K.)
David Fedson (Sergy Haut, France)
Johann Neyts (Leuven, Belgium)
Stephan Pleschka (Giessen, Germany)
Stefan Pöhlmann (Hannover, Germany)
Albrecht von Brunn (Munich, Germany)
Silvie Briand (WHO, Switzerland)
Cornelius Schmaltz (EC, Brussels, Belgium)
Wolfgang Garten (Marburg, Germany)

Venue

Kaiserin-Friedrich-Stiftung
Robert-Koch-Platz 7, D-10115 Berlin-Mitte

Registration and Abstract Submission: www.zoonosen.net.
No registration fee will be charged.

Funded by
Federal Ministry
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and Research

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GENERAL INFORMATION

Nationale Forschungsplattform für Zoonosen

It is our great pleasure to welcome you to the international workshop on **Common cold – SARS – Pandemic influenza: Novel strategies to fight respiratory viral diseases** in Berlin. We have endeavoured to put together an informative program that covers the different facets of most recent developments in strategies to fight respiratory viral diseases.

Several outbreaks of SARS, pandemic influenza, and other respiratory viral diseases during the last 10 years show the economic and social impact of such respiratory viral diseases. Such events indicate the need of increased collaboration of scientists, European agencies and pharmaceutical companies. Networking may contribute to improve research on prevention, control, and therapy of respiratory viral diseases.

The workshop participants combine unique academic and pharmaceutical expertises. Exchanging different experiences will broaden knowledge base concerning most recent developments in strategies to fight respiratory viral diseases. Furthermore the workshop addresses the need for novel therapeutic options against respiratory viral diseases. This could encompass the development of drugs against viral targets as well as drugs interfering with host-response pathways that play a role in the development of respiratory viral diseases.
At the end of the day, research should aim to bridge the gap between basic and clinical research.

Funded and initiated by the Ministry of Education and Research (BMBF), the National Platform for Zoonoses brings together researchers and research activities to develop sustainable and flexible solutions to strengthen research, prevention, and therapy of zoonotic infectious diseases. With our workshop we will stimulate international and interdisciplinary collaborations.

We are delighted to welcome you in Berlin, the capital of Germany. Please enjoy your stay and get-together with your collegues.

Prof. Dr. S. Ludwig

Prof. Dr. Oliver Planz

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Common Cold - SARS - Pandemic Influenza

International Workshop on novel strategies to fight respiratory viral diseases

The National Research Platform for Zoonoses has the pleasure to announce the International Workshop on "Common Cold - SARS - Pandemic Influenza: Novel strategies to fight respiratory viral diseases", to be held in Berlin, October 12-13, 2009 and would like to cordially invite you to join us.

On behalf of the National Research Platform for Zoonoses, the program organizers have worked out an outstanding scientific program covering the most recent developments in strategies to fight respiratory viral diseases. We invite you to use this opportunity to present original work and exchange your experiences in the field. The top ranking abstracts will be presented orally. No registration fee will be charged.

We would be delighted to welcome you in Berlin, the capital of Germany.

National Research Platform for Zoonoses

Initiated and funded by the Federal Ministry of Education and Research in Germany, the National Research Platform for Zoonoses started in spring 2009. This network brings together the researchers and the research activities in the field of zoonoses. It develops sustainable and flexible solutions to strengthen research, prevention, and therapy of zoonotic infectious diseases.

Further information: www.zoonosen.net

Organisation

Date
October, 12-13, 2009

Venue
Kaiserin-Friedrich-Stiftung, Berlin
Robert-Koch-Platz 7, D-10115 Berlin-Mitte
Website: www.kaiserin-friedrich-stiftung.de

Organizer
National Research Platform for Zoonoses
Neustädtische Kirchstraße 6
D-10117 Berlin, Germany

Scientific committee
Stephan Ludwig, Westfälische Wilhelms-Universität, Muenster
Oliver Planz, Friedrich-Loeffler-Institut, Tuebingen

Contact
National Research
Platform for Zoonoses
Dr. Gerlinde Benninger
Phone: +49 (0)2 51 – 83 530 11
E-Mail: benninge@ukmuenster.de
www.zoonosen.net

Registration
Registration is now open at www.zoonosen.net.
No registration fee will be charged.

Nationale Forschungsplattform für Zoonosen

International

Workshop

Novel strategies to fight respiratory viral diseases

Common Cold
SARS
Pandemic Influenza
12 -13 October 2009
Berlin, Germany

Final Program

Funded by
Federal Ministry of Education and Research

Final program

Version: 01.10.2009

Nationale Forschungsplattform für Zoonosen

Monday, October 12, 2009

11:00 am **Registration**

12:45 am **Opening**

Preface

1:00 pm **From 1918 to 2009: Use of human quarantine for studies of influenza**
John Oxford, Retroscreen, UK

Pandemic threat – current situation
Sylvie Briand, WHO, Switzerland

Novel Targets & Approaches – Influenza

2:00 pm **Treating the host response to pandemic influenza: Why it is needed and how it might work**
David Fedson, Sergy Haut, France

Fighting cancer, fighting flu: New aspects in the war against an old foe
Stephan Pleschka, Giessen, Germany

2:50 pm Break

3:30 pm **Novel NF-kappa B inhibitors for the treatment of viral diseases**
Stefan Strobl, 4SC AG, Germany

The NF-kappa B inhibitor SC 75 741 blocks influenza virus propagation *in vitro* and *in vivo*
Christina Ehrhardt, Muenster, Germany

Inhibitors of cellular hemagglutinin-activating proteases as a strategy to fight influenza
Wolfgang Garten, Marburg, Germany
Karolin Dröbner, Tuebingen, Germany

A peptide approach to address drugability of protein-protein-interaction of the PA/PB1 interaction of influenza
Martin Schwemmle, Freiburg, Germany

ca 4:50 pm **Antiviral activity of antimicrobial peptides studied on influenza virus**
Olaf Pinkenburg, Marburg, Germany

H5N1 and swine-origin H1N1 Influenza A viruses are susceptible for interferon type I treatment *in vitro* and *in vivo*
Emanuel Haasbach, Tuebingen, Germany

5:30 pm Break

Novel Techniques for Target Drug Screening and Evaluation

6:00 pm **Individualized controlled breathing improves efficiency and reduces variability of pulmonary drug delivery**
Gerhard Scheuch, Activaero GmbH, Germany

Genome-wide RNAi screen reveals human targets essential for influenza virus replication
Alexander Karlas, Berlin, Germany

Genetic susceptibility to influenza infection in mammals
Paulina Blazejewska, Braunschweig, Germany

7:30 pm **Get-together**

Tuesday, October 13, 2009

Special Lecture

9:00 am **EU-funding for research on influenza and other emerging infectious diseases**
Cornelius Schmaltz, EC, Belgium

Natural Products

9:30 am **Target-based discovery of natural inhibitors to combat common cold and flu**
Michaela Schmidtke, Jena, Germany

CYSTUS052 - exerts potent anti-influenza virus activity in *vitro* and *in vivo* in the mouse model by blocking viral attachment to host cells
Oliver Planz, Tuebingen, Germany

ca 10:10 am **Effectiveness of CYSTUS052 in the prophylaxis and treatment of upper and lower respiratory ract infections**
Holger Kiesewetter, Berlin, Germany

10:30 am Break

Novel targets & approaches - Influenza (II)

11:00 am **The interaction between M1 protein of influenza virus and host cell factors**
Wenjun (Frank) Liu, Center for Molecular Virology, Chinese Academy of Sciences, Beijing, China

High affinity and broadly neutralizing human recombinant antibodies against influenza A H5N1 viruses
Mifang Liang, Chinese Center for Disease Control and Prevention, Beijing, China

Novel Targets & Approaches – SARS and Rhinoviruses

12:00 am **Proteases as therapeutic targets in influenza and SARS**
Stefan Poehlmann, Hannover, Germany

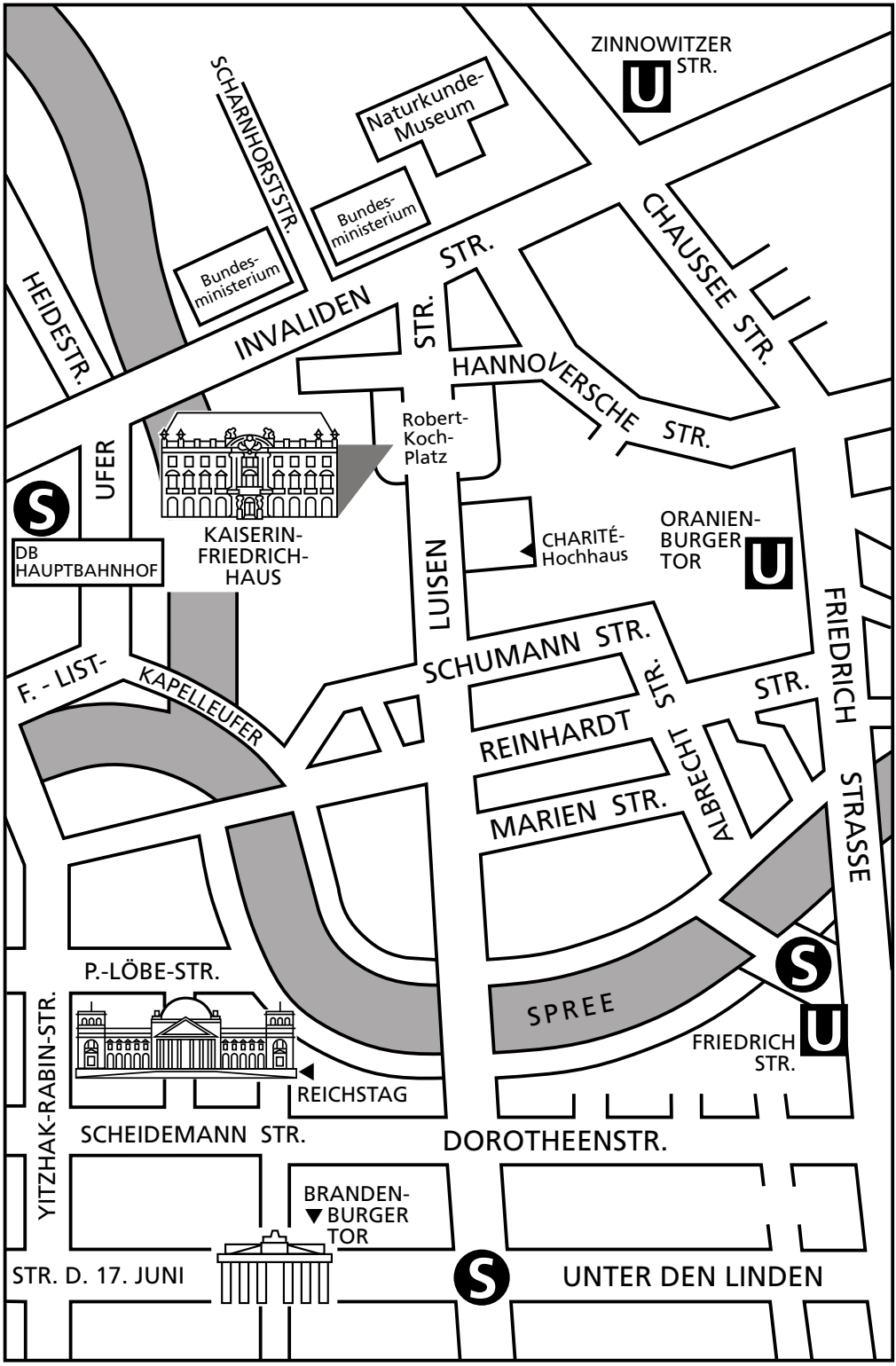
Applying systems biology to severe acute Rrespiratory syndrome coronavirus and its human host
Albrecht von Brunn, Munich, Germany

Interferon priming enables cells to partially overturn the SARS-Coronavirus-induced block in innate immune activation
Thomas Kuri, Freiburg, Germany

1:00 pm Break

2:00 pm **Toward the development of therapy for rhinovirus infections to prevent exacerbations of COPD and asthma**
Johan Neyts, KU Leuven, Belgium

4:00 pm Closure of the Workshop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ABSTRACTS

Treating the Host Response to Pandemic Influenza: Why it is Needed and How it Might Work

David S. Fedson, MD
Sergy Haut, France; dfedson@wanadoo.fr

Despite the best efforts of influenza scientists, companies and health officials to prepare for the current H1N1 influenza pandemic, most of the world's people will not have access to affordable supplies of vaccines and antiviral agents. Instead, they will have to rely on 19th Century public health "technologies" to see them through. In the 21st Century, science ought to be able to provide something better.

Influenza scientists study the molecular characteristics of influenza viruses and their signaling effects in cell culture and animal models of infection. While these studies have been enormously informative, they have been unable to explain the system-wide effects of influenza virus infection on the host, the increased mortality of younger adults in the 1918 influenza pandemic and the much lower mortality rates in children who were more commonly infected with the 1918 virus. Experiments by non-influenza scientists have defined common cell signaling pathways for acute lung injury caused by different agents, including inactivated H5N1 influenza virus. These pathways include several molecular targets that are up-regulated in acute lung injury and multi-organ failure and down-regulated by anti-inflammatory and immunomodulatory agents, including statins, fibrates and glitazones. Among their effects, these agents help reverse the mitochondrial dysfunction that accompanies multi-organ failure, something often seen in fatal Influenza. Laboratory studies show that fibrates and glitazones reduce mortality in experimental influenza. Observational studies suggest that statins are beneficial in treating patients with pneumonia (there are no such studies for fibrates and glitazones). Sharply focused research is urgently needed to determine whether these and other agents that modify the host response might be useful in managing H5N1 influenza and the next pandemic.

References

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2. Fedson DS. Meeting the challenge of influenza pandemic preparedness in developing countries. *Emerg Infect Dis* 2009; 15: 365-71.
3. Fedson DS. Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work*. Influenza Other Respir Virus* 2009; 3: 129-42.

Fighting Cancer, Fighting Flu: New Aspects in the War Against an Old Foe

Stephan Pleschka, Institute of Medical Virology, Justus-Liebig-University Giessen

The Raf/MEK/ERK signalling cascade is the prototype of the mitogen-activated protein kinases (MAPK) and is involved in cell proliferation, differentiation and survival. Active Raf and its upstream activator Ras, are highly oncogenic and a mutated form of the Ras is frequently found in naturally occurring lung tumors. Compounds that block MAPK signalling have long been evaluated for anti-cancer treatment. Several drugs have proven to show little side effects in mice. Specifically Ras- and MEK inhibitors are under clinical investigation. Moreover, influenza virus (IV) infection leads to activation of the MAPK cascade. HA membrane accumulation in lipid-rafts triggers MAPK activation via PKCalpha and induces nuclear RNP export. This represents an auto-regulative mechanism that coordinates RNP export when all viral components are ready for virus budding. Inhibition by specific MEK inhibitors results in nuclear RNP retention. Consequently, production of IV is inhibited.
IV infection can cause severe pneumonia and death. Therapeutic actions are limited to vaccines and a few anti-viral drugs. These target viral functions thereby selecting resistant variants. Aside from promoting RNP transport IV activated MAPK-cascade results in expression of pro-inflammatory host factors. Apart from tissue damage caused by IVs lytic replication, an imbalanced overproduction of anti-viral cytokines can cause severe lung damage as observed in human H5-type IV infections. MAPK-inhibition leads to decreased virus titres and simultaneously modulates cytokine expression *in vitro* and *in vivo*. This could provide new rationales of future therapeutic strategies to treat IV pneumonia.
Consequences of RNA virus-induced MAPK signalling were unclear for a long time. Research on this virus/host-interaction will broaden our understanding of its relevance in viral replication. Importantly, this control centre of cellular responses is differently employed to support the replication of several other important human pathogenic RNA viruses, including Ebola, hepatitis C and SARS corona viruses.

Novel NF-κB Inhibitors for the Treatment of Viral Diseases

Leban J.[1], Vitt D.[1], Ludwig S.[2], Planz O.[3], Strobl S.[1]

[1]4SC AG, Am Klopferspitz 19a, 82152 Martinsried
[2]Universität Münster, IMV, Von-Esmarch-Str. 56, 48149 Münster
[3]FLI, Paul-Ehrlich-Str. 28, 72076 Tübingen

4SC AG discovered a new class of small molecules which are inhibiting the NF-kB signalling pathway independently of the stimulus. These compounds are potent inhibitors of influenza virus proliferation. In depth analysis of the mode of action shows that the substances interfere with activation of caspase 8 resulting in block of apoptosis thus trapping viral ribonucleoprotein particles in the nucleus. Multipassaging experiments show that there is no tendency to induce viral resistance. While secretion of pro-inflammatory cytokines (e.g. TNFa, IL-6) is blocked, there is no effect on INFb response. In this way a harmful overreaction of the immune system (cytokine storm) can be prevented, while the innate immune response is not abrogated. Prophylactic and curative mouse models with various viral strains demonstrated efficacy in *in vivo* mouse models.
Excellent biological, pharmacological and toxicological data, favourable chemical accessibility and a profound IP position are prerequisites for further preclinical and clinical development of these substances. This novel class of small molecules represent a unique treatment option against all influenza sub-types and might be used for the treatment of annual and pandemic influenza.

The NF-κB-inhibitor SC75741 efficiently blocks influenza virus propagation *in vitro* and *in vivo* without the tendency to induce resistant virus variants

Christina Ehrhardt[1], Karolin Droebner[2], Andrea Rückle[1], Eike Hrincius[1], Stephan Ludwig[1] and Oliver Planz[2]

[1]Institute of Molecular Virology (IMV) at the Centre for Molecular Biology of Inflammation (ZMBE), University of Münster, Von-Esmarch-Str. 56, D-48149 Münster, Germany, [2]FLI, Tübingen, Germany

Influenza is still one of the major plagues worldwide. The appearance of highly pathogenic avian H5N1 viruses in humans and the emergence of resistant H5N1 variants against neuraminidase inhibitors highlight the need for new and amply available antiviral drugs. We and others have demonstrated that influenza virus misuses the cellular IKK/NF-κB signalling pathway for efficient replication suggesting that this module may be a suitable target for antiviral intervention. Here we show that the novel NF-κB inhibitor SC75741 efficiently blocks replication of influenza A and B viruses, including avian and human A/H5N1 isolates, *in vitro* and in a mouse infection model in concentration that do not affect cell viability or metabolism. The underlying molecular mechanism of SC75741 action involves impaired expression of proapoptotic factors, subsequent inhibition of caspase activation as well as block of caspase-mediated nuclear export of viral ribonucleoproteins. Besides this direct antiviral effect the drug also suppresses virus-induced overproduction of cytokines and chemokines, suggesting that it might prevent the so-called cytokine burst that is discussed as an important pathogenicity determinant of infections with highly pathogenic influenza viruses, such as the A/H5N1 strains. Most importantly the drug did not show any tendency to induce resistant virus variants. Thus, a SC75741-based drug may serve as a broadly active non-toxic anti-influenza agent.

Inhibitors for cellular hemagglutinin-activating proteases as a strategy to fight influenza

Wolfgang Garten[1], Eva Böttcher-Friebertshäuser[1], Catharina Freuer[1], Yinghui Lu[1], Frank Sielaff[2], Torsten Steinmetzer[2]

Cleavage of the influenza virus hemagglutinin (HA) by host cell proteases is essential for the infectivity and spread of the virus. Therefore, relevant proteases present promising drug targets for an influenza treatment.
HA of mammalian and low pathogenic avian influenza viruses contains a monobasic cleavage site which can be activated by the serine proteases HAT (Human airway trypsin-like protease) and TMPRSS2 (Transmembrane protease, serine 2) from human airway epithelium and thus these proteases support viral multicycle replication in vitro (Böttcher et al., 2006). HAs of high pathogenic avian influenza viruses (H5 and H7) contain multibasic cleavage sites which are activated by furin and closely related proprotein convertases.
We investigate the efficacy of known and newly synthesized peptidomimetics as protease inhibitors to prevent cleavage of HA by TMPRSS2 and HAT as well as by furin and furin-related endoproteases. As a result, multicycle virus replication in cell cultures is markedly suppressed by several protease inhibitors.

A Peptide Approach to Address Drugability of Protein-Protein-Interaction of the PA/PB1 Interaction of Influenza Viruses

Martin Schwemmle[1], Daniel Mayer[1], Kerstin Wunderlich[1], Charlene Ranadheera[2,3], Anne-Sophie Holler[1], Benjamin Mänz[1], Arnold Martin[1], Geoffrey Chase[1], Ronald Frank[4] and Ulrich Kessler[2]

[1]Dept. of Virology, University of Freiburg, Hermann-Herder-Strasse 11, 79104 Freiburg, Germany
[2]PiKe Pharma GmbH, Technoparkstrasse 1, 8005 Zurich, Switzerland
[3]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology (ETH) Zurich, Wolfgang-Pauli-Str. 10, 8093 Zurich, Switzerland
[4]Department of Chemical Biology, Helmholtz Centre for Infection Research, Inhoffenstraße 7, 38124 Braunschweig, Germany

Viral polymerase subunit interaction domains of influenza viruses represent an attractive target for development of new antivirals, since correct assembly of the three viral polymerase subunits PB1, PB2 and PA is required for viral RNA synthesis and infectivity. While structural data for the entire trimeric complex are missing, the crystal structure of a truncated FluA PA in complex with the N-terminus of PB1 was recently reported. The crucial PA interaction domain of PB1 consists of a 3_{10}-helix formed by amino acids (aa) 5-11. This domain is highly conserved and subtype-specific among both influenza A (FluA) and B (FluB) viruses. Using a novel in-vitro binding assay we can show that the PA-binding domains of FluA and FluB are not mutually exchangeable. Screening of a defined peptide library identified a PA-binding peptide that efficiently recognized FluA and FluB PA. Furthermore, this "dual-binding" peptide blocked the polymerase activity and viral spread of both virus types. The identification of this peptide and its ability to inhibit growth of FluA and FluB validates our strategy to aim at the polymerase subunit interaction as a novel target for the development of antiviral drugs. A screening of small molecule libraries has identified compounds specifically blocking the PA-PB1 interaction and inhibiting growth of several FluA and FluB strains, providing an optimistic outlook for the discovery of new broad-spectrum anti-influenza drugs.

Antiviral activity of antimicrobial Peptides studied on Influenza virus.

Olaf Pinkenburg[1], Volker Czudai[2], Gülsah Gabriel[3], Hans-Dieter Klenk[2] und Robert Bals[1].

[1]Klinik für Innere Medizin - Schwerpunkt Pneumologie Philipps-Universität Marburg, Germany
[2]Institut für Virologie, Philipps-Universität Marburg, Germany
[3]Heinrich-Pette-Institut für Experimentelle Virologie, Universität Hamburg, Germany

- Introduction: Cathelicidines are a class of antimicrobial peptides (AMP).They are endogenous antibiotics and part of the innate immunity. Most of these AMPs have also immunomodulating activities and are involved in procedures like wound healing angiogenesis and tumor growth. LL-37 is the only human AMP of its class, the pro-form is the human cathelicidin antimicrobial peptide (hCAP18), and the murine pendant is CRAMP (cathelicidin related antimicrobial peptide). Both can be induced by bacteria or microbial compounds (LPS), but the human LL-37 can also be induced by vitamin D3 (1, 25 OH)

- Methods: Incubation of virus (A/PR8) with LL-37 (or CRAMP) and sLL37 (control peptide) followed by infection of cells (MDCK), Plaque-assay, single-cell-infection. Infection of mice WT/CRAMP$^{-/-}$ (C57B6 or SVJ129) with LD_{50} (SC35), weight control (24h).

- Results: LL-37 and CRAMP cause a time and concentration dependent antiviral activity *in vitro*. Hemagglutination can be reduced to 25 % with the AMP. The viral activity (infection) can be reduced by 2 log. *In vivo* we found a weight loss of the KO-mice which is significant higher compared to the WT-mice. Regarding the virus clearance on day 9 (pi) a significant difference can be observed.

- Discussion: We suppose a direct antiviral activity of the AMP because the effect can't be reversed by dialysis or sedimentation it also indicates a strong binding or an irreversible process of this inhibition. It must be a direct inactivation of virus because preincubation of cells (MDCK) has no effect on infectivity. The reduced HA-titer shows an effect on the HA-protein. The surface protein HA can be masked by the LL-37 peptide.

H5N1 and swine-origin H1N1 influenza A viruses are susceptible for interferon type I treatment *in vitro* and *in vivo*

Emanuel Haasbach[1)], Karoline Droebner[1)], Annette B. Vogel[1)] and Oliver Planz[1,#)]

[1)] Friedrich-Loeffler-Institut, Institute of Immunology, Paul-Ehrlich Str. 28, 72076 Tübingen, Germany

Highly pathogenic avian influenza (HPAI) H5N1 virus infection leads to high lethality in mammals as a result of extensive alveolar immune inflammatory infiltrates causing tissue damage that compromises lung function. Additionally, H1N1 viruses are a major topic of human health care especially after the current pandemic caused by the new emerging swine-origin influenza virus (S-OIV). The innate immune response to influenza A viruses initially involves the production of type I and type II interferons (IFN). Innate cytokine responses, such as interferon alpha and beta (IFN-α/β) play a crucial role in determining the rate of virus replication in the initial stage of the infection and in shaping the initial inflammatory and downstream adaptive immune responses. The fact that there is an urgent need for new antivirals against influenza virus and that type I IFN is already in clinical use raise the question whether IFN type I treatment would be suitable against influenza virus infection.

In our study we examined the effect of IFN alpha on the replication of HPAI H5N1 and S-OI virus *in vitro* and *in vivo* after IFN-α treatment. Therefore, we treated mice intranasaly (i.n.) with low dose IFN-α (1000 units) during virus infection. A single pretreatment reduces progeny virus titer in the lung up to 1.4 log units. The antiviral effect against H5N1 was increased up to 2 log units after multiple pretreatment. Survival analyses showed that IFN-α treatment protected mice against a lethal H5N1 influenza virus infection. Furthermore, we determined reduction of S-OIV titers *in vitro* and *in vivo*. The amount of IFN-α used caused no toxicological findings in the spleen or liver.

Our data gave rise to the assumption that oral IFN type I treatment leads to the induction of antiviral cytokines that might be involved in the reduction of H5N1 and S-OIV titer in the lung.

Individualized Controlled Breathing Improves Efficiency and Reduces Variability of Pulmonary Drug Delivery

A. Fischer, B. Müllinger, G. Scheuch

Activaero GmbH, Wohraer Str. 37, 35285 Gemünden, Germany

Inhaled medications have been around for decades, particularly in the treatment of respiratory disease like asthma and chronic obstructive pulmonary disease (COPD)[1]. The rationale for delivering drugs directly to the lungs is the availability of a higher dose at the site of the disease and reduced side effects by lower systemic exposure. Therefore the lung is also the ideal target organ for vaccination and anti-viral therapy, since the lung is highly immune-active. [2]
The efficiency of inhaled drug delivery (measured by percent lung deposition) is influenced by different factors e.g. particle size, inspiration volume and speed. Whilst most of the commercially available inhalation devices produce a particle size in the favorable range, the breathing pattern of the patients are often disregarded and cannot be controlled by the conventional technologies. This results in a low amount of drug-load depositing in the lungs after inhalation.

Taking into account the given efficiency of conventional devices, the limitations of today's inhalation therapy become obvious:

- only drugs with a relatively wide therapeutic range can be applied,
- only relatively cheap drugs have a chance for commercial success,
- due to the dose variability, clinical efficacy of an investigated drug may be shaded by different breathing patterns of the subjects.

Recent studies have shown that control over the aerodynamic environment during the particles' flight through the respiratory tract represents the major impact factor to improve lung deposition and to reduce the inter-subject variability at the same time[3,4].

The AKITA® inhalation system (Activaero GmbH, Gemünden) enables a controlled particle deposition to different lung regions by controlling the patient's breathing pattern during the inspiration. It induces the optimum inhalation speed and volume, thus ensuring evenly and reproducible inspirations. After a patient has triggered a breath, the device takes control of inhalation and provides the patient with status information on a display. This breathing control is achieved by using a patient- and drug-specific smart card, which predetermines the inhalation flow rate and inhaled volume based specifically on the patient's respiratory condition.

This technology is validated in multiple clinical trials in e.g. Asthma, Cystic Fibrosis and a1-AT deficiency and can also be used in the pre-clinical setting (animal models).[5]

In Conclusion, the AKITA technology for controlled breathing provides a more efficient and reliable dosing to the lungs which leads reduced drug cost and to better insight of the investigated drug.

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Genome-wide RNAi screen reveals human targets essential for influenza virus replication

Alexander Karlas[1], Nikolaus Machuy[1], Yujin Shin[1], Klaus-Peter Pleissner[1], Anita Artarini[1], Dagmar Heuer[1], Daniel Becker[1], Hany Khahil[1], Simone Hess[1], André Mäurer[1], Thorsten Wolff[2], Elke Müller[1], Thomas Rudel[1], Thomas F. Meyer[1]

Affiliation:
1: Max-Planck-Institute for Infection Biology, Berlin, Germany;
2: Robert Koch-Institute, Berlin, Germany

Influenza viruses are a significant cause of human mortality, responsible for recurring epidemics leading to 250.000 to 500.000 deaths per year, worldwide. The current suite of available vaccines unfortunately provides protection against only a limited range of strains and may not be effective against emerging influenza viruses, such as the avian H5N1 or the currently prevalent swine H1N1 strain. At the moment, antiviral drugs constitute the best defence against pandemic strains, but already first resistant virus isolates have been identified.
Targeting human factors, temporarily dispensable for the host but crucial for virus replication, is supposed to prevent the development of viral resistance and provides coverage against newly emerging virus variants.
To search for these cellular factors, we performed a genome-wide RNAi based screen using about 62000 siRNAs. From a total of 24, 000 genes (annotated and predicted), 287 passed our robust selection criteria and were designated as primary hits. Among these high confidence candidates we found genes known to play a pivotal role in influenza replication, e.g. the nuclear export factors NXF1 and XPO, as well as ATP6V0D1, which was identified as hit in a recent Drosophila-based RNAi screen for factors affecting influenza replication. Importantly, the majority of factors tested were essential for replication of both the highly pathogenic avian H5N1 and the current pandemic (H1N1) 2009 'swine flu' influenza strains, indicating a broad dependency of variant influenza viruses. Thus, these results highlight the applicability of our genome-wide RNAi approach not only for the dissection of virus-host interactions but for the identification of potential broad-spectrum antiviral targets.

Genetic susceptibility to influenza infection in mammals

Paulina Blazejewska[1], Nuno Viegas[1], Klaus Schughart[1,2].

[1]Department of Experimental Mouse Genetics, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany.
[2] University of Veterinary Medicine, Hannover, Germany.

Several extrinstic and intrinstic factors contribute to the course and severity of influenza A virus infections, e.g. the virulence of the pathogen, the dose of the virus as well as health status, age and the nutritional status of the host. One crucial factor on the host side to mount an efficient defense against intruding pathogens is genetic predispositions. Using mouse model system, we tested different inbred mouse strains. Our results revealed strong differences of the host in susceptibility and resistance to influenza A virus subtypes H1N1 and H7N7 between mouse strains. In particular, virus load in infected mice and replication in mouse embryonic fibroblasts are very different, already at early time points after infection.
We are currently investigating different host factors that may be involved in the progress of virus entry, replication and propagation.
This work is funded by intra-mural grants from Helmholtz-Association (Program 'Infection and Immunity'), a research grant 'FluResearchNet' (No. 01KI07137) from the German Ministry of Education and Research and a fellowship from the Georg-Christoph-Lichtenberg Foundation to PB.

EU-funding for research on influenza and other emerging infectious diseases

Cornelius Schmaltz, DG Research, European Commission

Through successive Framework Programmes (FP) for Research, the European Commission has lent significant support to research in the field of influenza and – to a lesser extent – other respiratory viral diseases. Since 2001, around 50 influenza research projects ranging from fundamental virology to the development of diagnostics, vaccines and novel therapeutics, all the way to the assessment of public health protection measures have been funded in FP5, FP6 and FP7 as well as in the EU (Public) Health Programmes[6]. Though a large number of success stories, such as the development of the first human H7N1 vaccine, the initial identification of widespread oseltamivir-resistance in seasonal H1N1 during the 2007/2008 season, or the determination of basic epidemiological parameters of the current H1N1 pandemic, can be credited to these projects, a systematic evaluation of their outcome is currently still lacking. Support for other respiratory viral diseases has been sparser, with the exception of 7 research projects on SARS (EU funding > 13 million EUR)[7]. The legal basis of the FP7 Health theme[8] introduced in 2006 for the first time a specific area dedicated to "Potentially new and re-emerging epidemics", which explicitly includes influenza and should allow for strategic planning of research needs in this area. Following significant investments into a broad variety of influenza research in the first FP7 call for proposals (2006/2007), a currently open call topic on novel therapeutics against influenza should complement the project portfolio in this area. Planning for future call topics will have to consider research needs in fundamental virology as well as more applied research to provide tools in the fight against these diseases.

[6] A full list with details of all supported projects is available at http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/projects_en.html.
[7] See footnote 1
[8] Council Decision Specific Programme "Cooperation", Official Journal of the European Union L400/124, 30.12.2006

Target-based discovery of natural inhibitors to combat common cold and flu

Michaela Schmidtke[1], Peter Wutzler[1], and Judith M. Rollinger [2]

[1] Institute of Virology and Antiviral Therapy, Jena University Hospital, Hans-Knoell-Straße 2, D-07745 Jena, Germany

[2] Institute of Pharmacy / Pharmacognosy and Center for Molecular Biosciences Innsbruck, University of Innsbruck, Innrain 52c, A-6020 Innsbruck, Austria

Despite the grand successes in the treatment of flu in the past ten years, the search for new antivirals against respiratory viruses remains an area of active investigations. For human rhinoviruses inducing the common cold effective treatment regimes are not available. Moreover, the emergence and worldwide spread of ion channel blocker- and oseltamivir-resistant influenza A viruses ask for the discovery of new drugs providing additional treatment strategies.

Recently, we successfully applied *in silico* techniques to discover new anti-rhinoviral and anti-influenza virus natural compounds using well defined molecular targets e.g. the neuraminidase (NA) and the hydrophobic pocket in the viral capsid, respectively, and to create reliable pharmacophore models.

Computational approaches include molecular modeling, molecular simulation studies, docking and pharmacophore-based virtual screening of multiconformational 3D databases consisting of structures from synthesis or nature (available in-house). These methods allow for prioritizing compounds for isolation from natural materials (e.g. herbal remedies, nutritionals) and for experimental investigations. Rapid, highly standardised, and inexpensive cytopathic effect inhibition assays are available to study the anti-influenza virus and anti-rhinoviral activity of newly discovered agents. Active compounds can be scheduled for additional testing using other assays e.g. virus yield or plaque reduction assays, for studies on the spectrum of activity including about 50 human rhinovirus serotypes as well as human and swine influenza viruses isolated in Germany, and for preliminary studies on the mechanism of action. Moreover, well characterized mouse models can be applied to confirm the activity of potential antiviral drugs *in vivo*.

CYSTUS052 exerts potent anti-influenza virus activity *in vitro* and *in vivo* in the mouse model by blocking viral attachment to the host cells

Oliver Planz

Friedrich-Loeffler-Institut, Institute of Immunology, Paul-Ehrlich Str. 28, 72076 Tübingen, Germany

Influenza still represents a major threat to humans and several animal species. Beside vaccination, only two classes of drugs are available for antiviral treatment against this pathogen. The appearance of the H1N1 pandemic and the highly pathogenic avian influenza viruses of the H5N1 subtype being able to infect humans reveal the urgent need for new and efficient countermeasures against this disease. Even though several antiviral compounds have been developed against influenza virus, their long-term efficacy is often limited, because of their toxicity or the emergence of drug-resistant virus mutants. Moreover, it is also widely discussed that neuraminidase inhibitors the most common anti-influenza agents, are less effective against new H5N1 isolates and seasonal H1N1 strains. In this regard, we were able to show that a polyphenol rich plant extract from a special variety of Cistus incanus named CYSTUS052 exhibits antiviral activity against influenza viruses *in vitro* and in a mouse model. On a molecular basis theprotective effect of CYSTUS052 appears to be mainly due to binding of the polymeric polyphenol components of the extract to the virus surface, thereby inhibiting binding of the hemagglutinin to cellular receptors. In addition, we investigated the antiviral potential of CYSTUS052 in comparison to oseltamivir against the swine origin influenza virus (SOIV) H1N1 and various H5N1 influenza viruses. We tested the antiviral efficacy of a single treatment with CYSTUS052 or oseltamivir, against SOIV, six H5N1 viruses, isolated 2006 and 2007 from avian species in Germany and against the human H5N1 isolate Thailand/1(KAN-1)/2004. Using an *in vitro* infectivity inhibition assay we found that during the first 24 hours after infection a single treatment of CYSTUS052 is up to 100 fold more effective against these H5N1 viruses compared to oseltamivir. Therefore, we conclude that CYSTUS052 given prior to infection might be an effective antiviral with prophylactic potential against influenza viruses including the current pandemic strain and A/H5N1.

Effectiveness of CYSTUS052 in the prophylaxis and treatment of upper and lower respiratory tract infections

Prof. Dr. Dr. Holger Kiesewetter

Charité - Universitätsmedizin Berlin

In the present work, we aimed to investigate the clinical effect of a special Cistus extract (CYSTUS052®) in comparison to placebo on 160 patients with infections of the upper respiratory tract. These infections are the most common illnesses in the world resulting in substantial morbidity, mortality, and financial loss. Several antiviral compounds have been developed but their long term efficacy is often limited because of their toxicity or the emergence of drug-resistant virus mutants. Therefore the development of alternative anti-viral agents is necessary. One example for medicinal herbs that have been perpetuated along several generations based simply on a folk tradition is Cistus incanus. Principal active constituents of the genus Cistus incanus are polyphenolic compounds. Polyphenols exhibit a wide range of antibacterial, antifungal and anti-inflammatory effects.
The present randomized, placebo controlled clinical study was designed to compare the symptom scores in patients with common cold treated either with CYSTUS052 or with placebo. The patients were treated with CYSTUS052® given in lozenges or with placebo. The patients scored the subjective severity of target symptoms using a predefined scale. The score of subjective symptoms decreased significantly over the course of treatment with Cistus, whereas treatment with placebo resulted in a less distinct decrease of symptoms. Among the inflammatory markers investigated, the C-reactive protein was mostly affected by Cistus and decreased significantly in the treatment group.
CYSTUS052 therefore proved to be an effective adjuvant for the treatment of respiratory infections.

The interaction between M1 protein of influenza virus and host cell factors

Wenjun (Frank) Liu, DVM, PhD

Center for Molecular Virology, Department of pathogenic Microbiology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China

Influenza A virus matrix protein (M1) is the most abundant protein in the viral particle, consisting of highly conserved 252-amino acids. M1 is a multifunctional protein in the influenza virus replication. Several host cell factors have been identified possibly to be required for regulation of influenza virus replication through interacting with M1. The knowledge obtained from these virus-host cell interactions are continuing provide critical insights into the molecular mechanisms of the biology and pathology of the virus. In our study the yeast two-hybrid system was performed using M1 as the bait to search for possible counterpart host proteins. Several candidate proteins have been identified including cyclophilin A (CypA), specifically interacting with M1. We have demonstrated that CypA was able to directly bind to the M1 protein. The functional analysis indicated that CypA regulated the influenza virus replication.

High Affinity and Broadly Neutralizing Human Recombinant Antibodies against Influenza A H5N1 Viruses

Prof. Dr. Mifang Liang

State Key Laboratory for Infectious Disease Control and Prevention, Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, 100 Ying Xin Jie, Xuan Wu District, Beijing 100052, China.

The development of new therapeutic targets and strategies to control HPAI H5N1 virus infection in humans is urgently needed. Broadly cross-neutralizing recombinant human antibodies obtained from the survivors of H5N1 avian influenza provide an important role in immunotherapy for human H5N1 virus infection and definition of the critical epitopes for vaccine development. We have characterized two recombinant baculovirus-expressed human antibodies (rhAbs), AVFluIgG01 and AVFluIgG03, generated by screening a Fab antibody phage library derived from a patient recovered from infection with a highly pathogenic avian influenza A H5N1 clade 2.3 virus. AVFluIgG01 cross-neutralized the most of clade 0, clade 1, and clade 2 viruses tested, in contrast, AVFluIgG03 only neutralized clade 2 viruses. Passive immunization of mice with either AVFluIgG01 or AVFluIgG03 antibody resulted in protection from a lethal H5N1 clade 2.3 virus infection. Furthermore, through epitope mapping, we identify two distinct epitopes on H5 HA molecule recognized by these rhAbs and demonstrate their potential to protect against a lethal H5N1 virus infection in a mouse model. Importantly, localization of the epitopes recognized by these two neutralizing and protective antibodies has provided, for the first time, insight into the human antibody responses to H5N1 viruses which contribute to the H5 immunity in the recovered patient. These results highlight the potential of a rhAbs treatment strategy for human H5N1 virus infection and provide new insight for the development of effective H5N1 pandemic vaccines.

Proteases as therapeutic targets in influenza and SARS

Stephanie Bertram[1], Ilona Glowacka[1], Paulina Blazejewska[2], Petra Herzog[3], Susanne Pfefferle[3], Imke Steffen[1], Elizabeth Soilleux[4], Klaus Schughart[2], Christian Drosten[5] and Stefan Pöhlmann[1]

[1]Institute for Virology, Hannover Medical School, Hannover, Germany;
[2]Department of Experimental Mouse Genetics, Helmholtz-Center for Infection Research, Braunschweig, and University of Veterinary Medicine Hannover, Germany; [3]Bernhard-Nocht-Institute, Hamburg, Germany;
[4]John Radcliffe Hospital, Oxford, England,
[5]Institute of Virology, University of Bonn Medical Centre, Bonn, Germany

The influenza virus hemagglutinin (HA) mediates viral entry into target cells. HA is synthesized as an inactive precursor protein, which is activated by host cell proteases. Proteolytic activation is essential for HA function and the proteases involved are attractive targets for intervention. Recent studies suggest that the type II transmembrane serine proteases TMPRSS2, HAT and TMPRSS4 activate the HA-proteins of human influenza viruses. Here, we analyzed the contribution of TMPRSS2 and TMPRSS4 to influenza virus spread in cell lines and we determined if these proteases also cleave the spike (S)-protein of the SARS-coronavirus (SARS-CoV).
We found that ectopic expression of TMPRSS2 and TMPRSS4 allowed influenza virus spread in the absence of trypsin. Endogenous TMPRSS2 was detected in Caco-2 cells, which supported trypsin-independent influenza virus replication, in agreement with published results. Knock-down of TMPRSS2 expression by siRNA reduced influenza virus spread in Caco-2 cells, indicating that endogenous TMPRSS2 activates influenza virus in this cell line. Finally, immunohistochemistry revealed coexpression of TMPRSS2 and 2,6-linked sialic acid in human lung tissue, suggesting that TMPRSS2 may promote influenza virus spread in the infected host.
Ectopic expression of TMPRSS2 but not TMPRSS4 induced cleavage of SARS-S at several sites and resulted in the release of SARS-S-fragments into the cellular supernatants. The respective supernatants diminished neutralization of wt SARS-S-driven entry into target cells, suggesting that the cleavage products might act as decoys for neutralizing antibodies. Immunostaining of SARS-CoV-infected cells revealed that a fraction of the SARS-S-proteins are transported to the cell surface and TMPRSS2 was found to be coexpressed with the SARS-CoV receptor ACE2 on type II pneumocytes, the major SARS-CoV target cells. TMPRSS2 could therefore induce production of soluble SARS-S in infected patients, which might reduce viral control by the humoral immune response.

Applying systems biology to Severe Acute Respiratory Syndrome Coronaviurs and its human host

J. Schöpf (1), M. Kögl (2), S. Pfefferle (3), T. Kuri (4), M. Müller (3), F. Ebel (1), C. Friedel (5), R. Zimmer (5), F. Weber (4), J. Haas (1), C. Drosten (3), A. von Brunn (1)*

(1) Max-von-Pettenkofer Institut, LMU München
(2) DKFZ, Heidelberg
(3) IfV Rheinische Friedrich-Wilhelms-Univ. Bonn, BNI Hamburg
(4) IMMH, Albert-Ludwigs-Universität Freiburg
(5) Inst. Für Informatik, LMU München

Coronaviruses are important human and animal pathogens with SARS-CoV as the most aggressive one in humans. To understand pathogenesis it is necessary to elucidate viral and cellular key molecules and signalling pathways. Using high throughput technologies we have performed undirected whole genome interaction screens of viral and cellular proteins to identify molecular targets for antiviral intervention.
We have cloned the viral orfeome by PCR amplifying and subcloning 28 ORFs and 14 subfragments without transmembrane regions into GATEWAY- compatible plasmids allowing the quick transfer into pro- and eukaryotic expression vectors. Interaction screens were performed by automated Y2H system, PCR amplification, sequencing and blast analyses. A number of interactions were validated by a modified Lumiersystem in eukaryotic cells. Between 33-46% of the interactions were verified.
For one of the SARS-CoV proteins we could show its interaction with different classes of proteins, which influence the calcineurin/NFAT pathway. Latter is important for the regulation of a number of cytokines and thus might be involved in the development of their disordered expression in SARS-CoV- infected patients.
In an NFAT reporter assay we show the upregulation of NFAT promoter sequences in HEK293 and Jurkat cells. As a consequence Interleukin promoters are also influenced by the protein. Promotor upregulation as well as virus replication can be blocked by an inhibitor of the cellular interaction partner of the viral protein. We thus have identified a possible cellular target for antiviral intervention.

* corresponding author
vonbrunn@mvp.uni-muenchen.de

Interferon priming enables cells to partially overturn the SARS-Coronavirus-induced block in innate immune activation

Thomas Kuri and Friedemann Weber
Abt. Virologie, IMMH, Hermann-Herder-Str. 11, 79104 Freiburg

SARS-coronavirus (SARS-CoV) is known to efficiently suppress the induction of antiviral type I interferons (IFN-alpha/beta) in non-lymphatic cells through inhibition of the transcription factor IRF-3. Plasmacytoid dendritic cells, by contrast, respond to infection with production of high levels of IFNs. Here, we show that pretreatment of non-lymphatic cells with small amounts of IFN-alpha (IFN priming) partially overturns the block in IFN induction imposed by SARS-CoV. In perticular, microarray and RT-PCR analyses revealed that IFN priming combined with SARS-CoV infection substantially induced genes for IFN induction, IFN signaling, antiviral effector proteins, ubiquitinylation and ISGylation, antigen presentation, and other cytokines and chemokines, whereas each individual treatment had no major effect.
Curiously, however, despite this typical IFN response, neither IRF-3 nor
IRF-7 was transported to the nucleus as a sign of activation. Taken together, our results suggest that (i) IFN, as it is produced by plasmacytoid dendritic cells, could enable tissue cells to launch a host response to SARS-CoV, (ii) IRF-3 and IRF-7 can possibly be active at sub-detectable levels, and (iii) SARS-CoV does not activate IRF-7.

Toward the development of therapy for rhinovirus infections to prevent exacerbations of COPD and asthma

Johan Neyts
Rega Institute for Medical Research, KULeuven, B-3000 Belgium

Today, there is a gain of interest in the development of anti-picornavirus drugs. The main reason is that recent data provide clear evidence that rhinoviruses are implicated in exacerbations of asthma and chronic obstructive pulmonary disease (COPD). Since (i) a growing number of people in the Western world are suffering from asthma and (ii) COPD is predicted by the World Health Organization to be the third leading cause of death worldwide by 2030, the development of an anti-rhinovirus drug has become a serious challenge. In high-risk patients, a broad-spectrum anti-rhinovirus drug might be used prophylactically to prevent rhinovirus-induced COPD exacerbations or therapeutically, to shorten the severity and duration of symptoms. Unlike the days when rhinoviruses were thought to cause nothing more than a common cold, it is conceivable that in the context of asthma and COPD, anti-rhinovirus drug may have a greater chance of approval. The capsid binders pleconaril (Schering-Plough) and BTA-798 (Biota) are currently being developed for the treatment of rhinovirus-induced exacerbations of asthma and COPD in high-risk patients. Several other picornavirus proteins [including the 3C protease, the RNA dependent RNA polymerase, the 3A protein and the 2C protein (a putative helicase/NTPase)] have been shown to be excellent targets for inhibition of picornavirus replication. Ideally, drugs that are being developed for the treatment of rhinovirus infections should exert broad-spectrum anti-picornavirus activity, so that they can be also been used for the treatment of serious and often life-threatening enterovirus infections and even to help in end stages of the polio eradication. We will review recent developments in the search for therapies against human rhinoviruses and related enteroviruses.

PARTICIPANTS

A

Nina Alex
Paul- Ehrlich-Institut
Tel: +49 (0) 6103-772362
E-Mail: aleni@pei.de

Munir Al-zeer
Max Planck institute for infection biology
E-Mail: al-zeer@mpiib-berlin.mpg.de

B

Paulina Blazejewska
Helmholtz Centre for Infection Research
E-Mail: pbl07@helmholtz-hzi.de

Prof. BO Zhang
Wuhan Institute of Virology
Chinese Academy of Sciences
E-Mail: zhangbo@wh.iov.cn

Sylvie Briand
Global Influenza Programme (GIP)
Health Security and Environment (HSE)
World Health Organization
20, Avenue Appia, CH-1211 Geneva 27
T el.: +41 (22) 791 23 72
Mobile: +41 (0) 79 47 55 465
Fax: +41 (22) 791 48 78
E-Mail: briands@who.int

Dr. Albrecht von Brunn
Max-von-Pettenkofer Institut
Ludwig-Maximilians University Munich
Pettenkoferstraße 9a, 80336 Munich
Tel.: +49 (0) 89-51605220
Fax: +49 (0) 89-51605292
E-Mail: vonbrunn@mvp.uni-muenchen.de

C

CAO Shengbo, PhD
Huazhong Agricultural University
E-Mail: sbcao@mail.hzau.edu.cn

Prof. Dr. CHEN Qijun
Institute of Pathogen Biology
Chinese Academy of Medical Sciences
Institute of Zoonosis, The Ministry of Education,
Jilin University, China
E-Mail: cqi@ilu.edu.cn

CUI Shangjin, PhD
Harbin Veterinary Research Institute,
Chinese Academy of Agricultural Sciences
E-Mail: cuishangjin@yahoo.cn

D

Dr. Kurt E.J. Dittmar
Helmholtz Centre for Infection Research
Braunschweig
Tel.: +49 (0) 531-61815010
E-Mail: ked@gbf.de

Prof. Dr. Christian Drosten
Institute of Virology
University of Bonn Medical Centre
Sigmund Freud Straße 25, 53105 Bonn
Tel.: +49 (0) 228-28711055
Fax: +49 (0) 228-28714433
E-Mail: drosten@virologybonn.de

Dr. Ralf Dürrwald
IDT Biologika GmbH
Tel.: +49 (0) 34901-8855432
E-Mail: ralf.duerrwald@idt-biologika.de

Sabine Eva Dudek, Ms. Sc.
ViroLogik GmbH, Erlangen
Institute of Molecular Virology, Muenster, Germany
Tel.: +49 (0) 251-8357795
E-Mail: s.dudek@virologik.com

E

Dr. Christina Ehrhardt
Institute of Molecular Virology
University of Muenster, Germany
Von-Esmarch-Straße 56, 48149 Muenster
Tel.: +49 (0) 251-8353010
E-Mail: ehrhardc@uni-muenster.de

F

Prof. David Fedson, MD
57, chemin du Lavoir, 01630 Sergy Haut, France
E-Mail: dfedson@wanadoo.fr

Judith Friesenhagen
Institute of Immunology
University Hospital Muenster, Germany
E-Mail: jf1510@aol.com

G

Prof. Dr. Wolfgang Garten
University of Marburg, Germany
E-Mail: garten@staff.uni-marburg.de

H

Emanuel Haasbach
Institute of Immunology
Friedrich-Loeffler-Institute
Tel.: +49 (0) 7071-967254
E-Mail: emanuel.haasbach@fli.bund.de

Peter Hagedorn
Robert Koch-Institut
Tel.: +49 (0) 30-187542116
E-Mail: hagedornp@rki.de

Prof. Dr. Otto Haller
Dept. Virology
University of Freiburg, Germany
Hermann-Herder-Straße 11, 79008 Freiburg
Tel: +49 (0) 761-2036533
Fax: +49 (0)761-2036562
E-Mail: haller.office@uniklinik-freiburg.de

I

J

K

Dr. Alexander Karlas
Max Planck Institute for Infection Biology
Tel.: +49 (0) 30-28460421
E-Mail: karlas@mpiib-berlin.mpg.de

Ulrich Kessler, PhD
RTH Zurich, Switzerland
E-Mail: ulrich.kessler@pikepharma.com

Hany Khalil
Max-Planck Institute for Infection Biology
Tel.: +49 (0) 152-06296801
E-Mail: hkhalil@mpiib-berlin.mpg.de

Prof. Dr. Dr. Holger Kiesewetter
Medical faculty of the Humboldt University
Institute of Transfusion Medicine
Charité Berlin, Germany
Campus Charité Mitte
Luisenstr. 65, 10117 Berlin
Tel.: +49 (0) 30-450525101
Fax: +49 (0) 30-450525942
E-Mail: holger.kiesewetter@charite.de

Dr. Ursula Kopp
Project Management in the DLR
Heinrich-Konen-Straße 1, 53227 Bonn
Visitors address: Suedstraße 125, 53175 Bonn
Tel.: +49 (0) 228-3821230
Fax: +49 (0) 228-3821257
E-Mail: ursula.Kopp@dlr.de

Dr. Andi Krumbholz
Institute of Virology and Antiviral Therapy
University Hospital Jena, Germany
E-Mail: andi.krumbholz@med.uni-jena.de

Dr. Thomas Kuri
Institute for Medical Microbiology and Hygiene
Department of Virology University of Freiburg, Germany
Tel.: +49 (0) 761-2036578
Fax: +49 (0) 761-2036634
E-Mail: thomas.kuri@uniklinik-freiburg.de

L

LI Ming, PhD
Beijing Institutes of Life Science
E-Mail: lim@mail.biols.ac.cn

Prof. LIANG Mifang
Department of Viral Hemorrhagic Fever
Institute of Virology, China CDC
E-Mail: mifangl@sina.com

LIU Wenjun
Director
Beijing Zhongguancun Science Park
Laboratory of Molecular Virology and Biological Products
E-Mail: liuwj@im.ac.cn

Prof. Dr. Stephan Ludwig
Institute of Molecular Virology
ZMBE
Von-Esmarch-Straße 56, 48149 Muenster
Tel.: +49 (0) 251-8357791
Fax : +49 (0) 251-8357793
E-Mail: ludwigs@uni-muenster.de

LUO Tingrong, PhD
College of Animal Science and Veterinary Medicine, Guangxi University
E-mail: trluo@tom.com;
tingrongluo@gxu.edu.cn

M

Dr. Gisela Martens
Berufsgenossenschaft der chemischen Industrie
Tel.: +49 (0) 6221-523403
E-Mail: gmartens@bgchemie.de

Markus Matthaei
RKI Berlin, Germany
E-Mail: matthaeim@rki.de

Prof. Dr. Thomas F. Meyer
Max Planck Institute for Infection Biology
Tel.: +49 (0) 30-28460402
E-Mail: meyer@mpiib-berlin.mpg.de

Konstantin Müller
Institute of Immunology, Luxembourg
E-Mail: Konstantin.Mueller@lns.etat.lu

N

Dr. Tatiana Nedelko
Helmholtz Centre for Infection Research
Tel.: +49 (0) 176-80286057
E-Mail: tne08@helmholtz-hzi.de

Prof. Johan Neyts, PhD
Rega Institute for Medical Research
KULeuven - University of Leuven
Minderbroedersstraat 10, 3000 Leuven
Belgium
Tel.: 0032-16-337353
Fax: 0032-16-337340
E-Mail: johan.neyts@rega.kuleuven.be

O

Prof. John Oxford
Retroscreen Virology Ltd
London Bioscience Innovation Centre
2 Royal College Street
London NW1 0NH
Tel: +44 (0)207 118 0727
Clinical Fax: +44 (0) 203 070 0084
General Fax: +44 (0) 203 070 0086
E-Mail: j.oxford@retroscreen.com

P

Dr. Eva-Katharina Pauli
ViroLogik GmbH
E-Mail: E.Pauli@virologik.com

Dr. Tanja Pies
Bayer Schering Pharma AG
Tel.: +49 (0) 202-365811
E-Mail: tanja.pies@bayerhealthcare.com

Dr. Dr. Olaf Pinkenburg
Internal Med. SP Pneumology
University of Marburg
Tel.: +49 (0) 6421-2865064
E-Mail: op68@gmx.de

Prof. Dr. Oliver Planz
Institute of Immunology
Friedrich-Loeffler-Institute
Federal Research Institute for Animal Health
Paul-Ehrlich-Straße 28, 72076 Tübingen
Tel.: +49 (0) 7071-967254
Fax: +49 (0) 7071-967105
E-Mail: oliver.planz@uni-tuebingen.de

Prof. Dr. Stefan Pleschka, PhD
Institute of Medical Virology
Justus-Liebig-University Giessen
Frankfurter Straße 107, 35392 Giessen
Tel.: +49 (0) 641-9947750
Fax: +49 (0)641- 9941209
E-Mail: stephan.pleschka@mikro.bio.uni-giessen.de

PD Dr. Stefan Pöhlmann
Institute of Virology OE 5230
Hannover Medical School
Carl-Neuberg-Straße 1, 30625 Hannover
Tel.: +49 (0) 511-5326736,
Fax: +49 (0)511-5328736
E-Mail: Poehlmann.Stefan@mh-hannover.de

Q

R

Prof. Dr. Axel Rethwilm
University of Wuerzburg, Institute of Virology
E-Mail: virologie@vim.uni-wuerzburg.de

Prof. Dr. Judith Rollinger
Institute of Pharmacy / Pharmacognosy
Leopold-Franzens-University of Innsbruck
Innrain 52c, Josef-Moeller-Haus
6020-Innsbruck AUSTRIA
Tel.: +43 512-5075308
Fax: +43 512-5072939
E-Mail: judith.rollinger@uibk.ac.at

S

Dr. Gerhard Scheuch
Activaero, Germany
Wohraer Str. 37, 35285 Gemünden
Tel.: +49 (0)6453-6481811
Fax: +49 (0)6453-6481822
E-Mail: gscheuch@activaero.de

Cornelius Schmaltz
Policy Officer - Coordination of FP7 operations
Office: SDME 02/19
European Commission
DG Research - Unit A.6.001
1049 Bruxelles, BELGIUM
Tel. +32-2-29-58984
Fax: +32-2-29-21536
E-Mail:
Cornelius.SCHMALTZ@ec.europa.eu

Dr. Michaela Schmidtke
Institute of Virology and Antiviral Therapy
University Hospital Jena, Germany
Hans-Knöll-Straße 2, 07745 Jena
Tel.: +49 (0) 3841-657222
Fax: +49 (0)3841-657202
E-Mail: michaela.schmidtke@med.uni-jena.de

Prof. Dr. Klaus Schughart
Department of Experimental Mouse Genetics
Helmholtz Center for Infectious Diseases Braunschweig & University of Veterinary Medicine, Hannover
Inhoffenstr. 7, 38124 Braunschweig
Tel.: +49 (0) 531-61811100
Fax: +49 (0) 531-61811099
E-Mail: klaus.schughart@helmholtz-hzi.de

Prof. Dr. Martin Schwemmle
Dept. Virology, University of Freiburg
Hermann-Herder-Str. 11, 79104 Freiburg
Tel.: +49 (0)761-2036526
E-Mail: martin.schwemmle@uniklinik-freiburg.de

Dr. Ilia Semmler
National Research Platform for Zoonoses
c/o Telematikplattform für Medizinische Forschungsnetze e.V. (TMF)
Neustädtische Kirchstraße 6, 10117 Berlin
Tel.: +49 (0)30-31011972
E-Mail: ilia.semmler@tmf-ev.de

Nadine Sept
National Research Platform for Zoonoses
c/o Telematikplattform für Medizinische Forschungsnetze e.V. (TMF)
Neustädtische Kirchstraße 6, 10117 Berlin
Tel.: +49 (0)30-31011971
E-Mail: nadine.sept@tmf-ev.de

Prof. Dr. Peter Stäheli
Dept. Virology, University of Freiburg
Hermann-Herder-Str. 11, 79104 Freiburg
Tel: +49 (0) 761-2036579
Fax: +49 (0) 761-2035350
E-Mail: peter.staeheli@uniklinik-freiburg.de

Dr. Stefan Strobl
4SC AG
Tel.: +49 (0) 89-7007630
E-Mail: andrea.aigner@4sc.com

T

U

V

Daniel Voß
RKI, Berlin, Germany
E-Mail: vossd@rki.de

W

Dr. Ralf Wagner
Department of Virology, Paul-Ehrlich-Institut (PEI)
Paul-Ehrlich-Straße 51–59, 63225 Langen
Tel.: +49 (0)6103-772351
Fax: +49 (0) 6103-771234
E-Mail: wagra@pei.de

Prof. WANG Xiaomei
National Institute for Communicable Disease Control and Prevention, Chinese Center
Harbin Veterinary Research Institute, CAAS
E-mail: xmw@hvri.ac.cn

Dr. Thorsten Wolff
RKI, Berlin, Germany
E-Mail: wolfft@rki.de

Kerstin Wunderlich
University of Freiburg, Germany
E-Mail: kerstin.wunderlich@sgbm.uni-freiburg.de

X

Y

YE Changyun
National Institute for Communicable Disease Control and Prevention
Chinese Center for Disase Control and Prevention
E-mail: yechangyun@icdc.cn

Z

PD Dr. Roland Zell
Department of Virology and Antiviral Therapy (IVAT)
University Hospital Jena
Hans-Knöll-Straße 2, 07745 Jena
Tel.: +49 (0) 3641-9395711,
Fax: +49 (0) 3641-9395732
E-Mail: Roland.Zell@med.uni-jena.de

Contact:

National research platform for Zoonoses
Office BERLIN
c/o Telematikplattform für Medizinische Forschungsnetze e.V. (TMF)
Neustädtische Kirchstraße 6, 10117 Berlin

Office GREIFSWALD-INSEL RIEMS
c/o Friedrich-Loeffler-Institute
Federal Research Institute for Animal Health
Institute for Novel and Emerging Infectious Diseases (INEID)
Südufer 10, 17493 Greifswald-Insel Riems

Office MÜNSTER[9]
c/o Institute of Molecular Virology
Centre for Molecular Biology of Inflammation (ZMBE)
Von-Esmarch-Str. 56
48149 Muenster, Germany

Gerlinde Benninger, PhD
- Scientific manager -
Tel.: +49 (0) 251-8353011
Fax: +49 (0) 251-8357793
E-Mail: benninge@ukmuenster.de

Vanessa Hugo
- Administrative assistant –
Tel.: +49 (0) 251-8353013
Fax: +49 (0) 251-8357793
E-mail:
Vanessa.Hugo@ukmuenster.de

Website: www.zoonosen.net

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