



Influenza - One Health in action

Stephan Ludwig

11.02.2014

Influenza - Zoonose mit pandemischen Potential



H1N1v



H7N7



H5N1



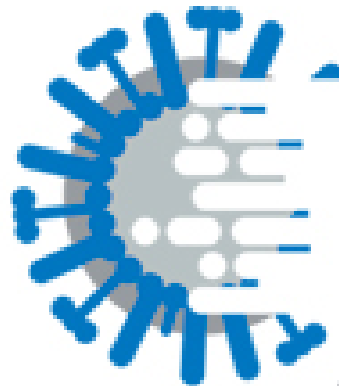
H7N9

H6N1

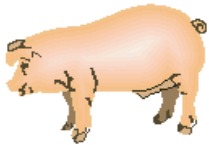


H10N8





FluResearchNet.



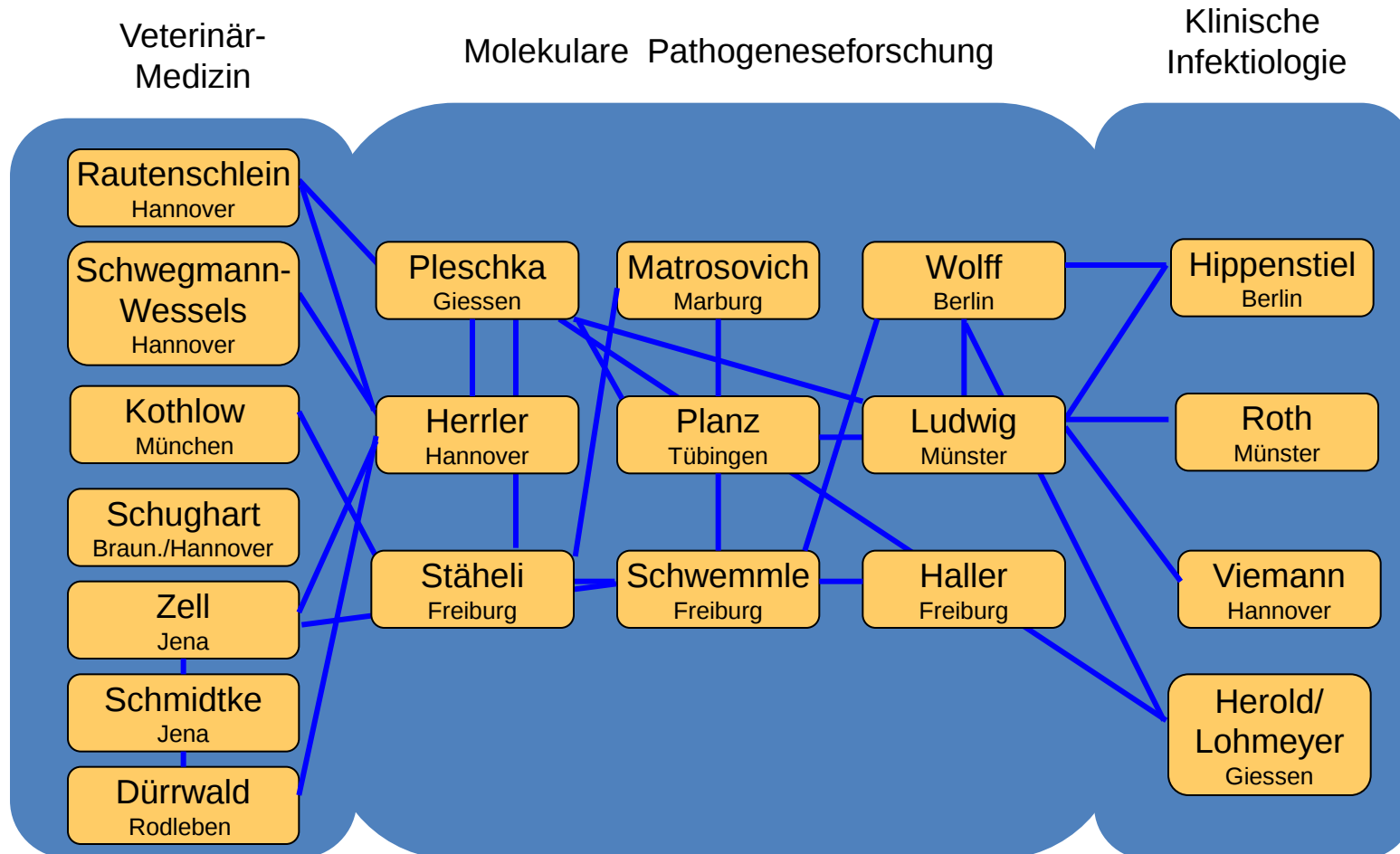
Molekulare Determinanten der Pathogenität und Transmission von Influenza A Viren

Koordinator: Stephan Ludwig – WWU Münster

Interdisziplinärer Ansatz:

Virologie, Innate Immunity, Zellbiologie, Epidemiologie
Grundlagenforschung - Veterinärmedizin - Humanmedizin

Bündelung der nationalen Kompetenzen und Ressourcen

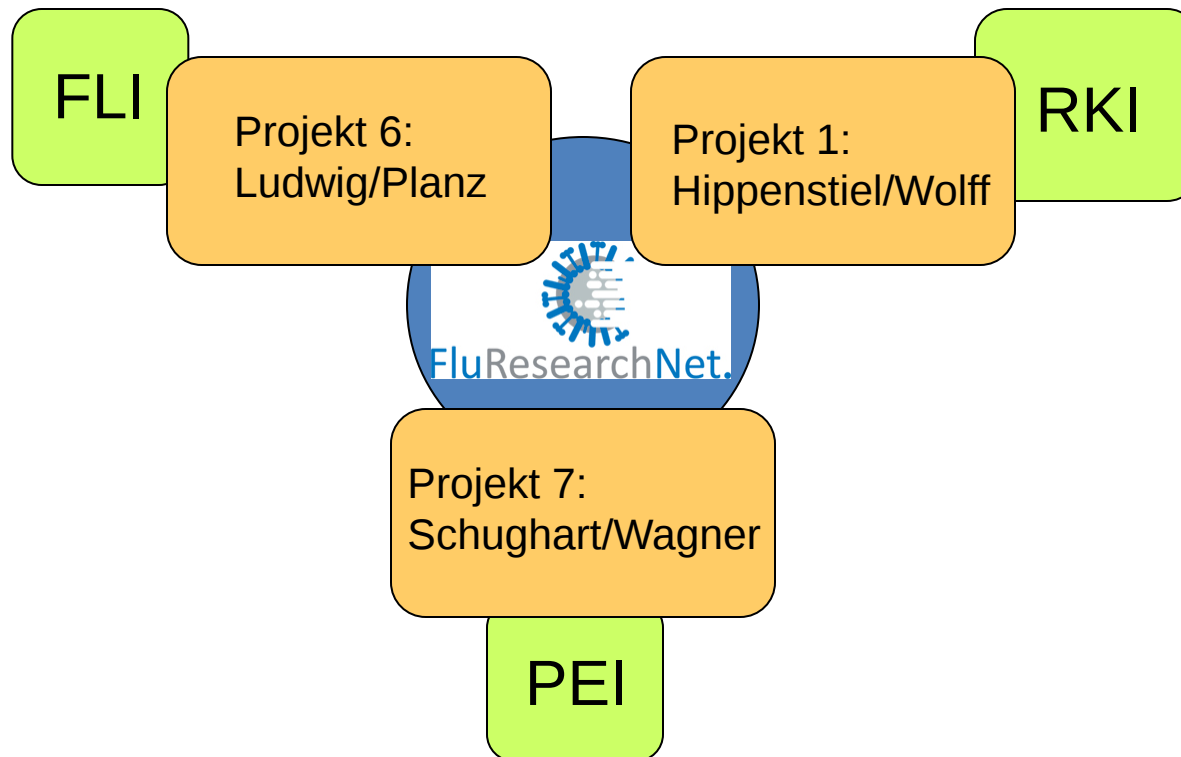


Einbeziehung/Zusammenarbeit mit den
Nationalen Referenzzentren und Bundesinstituten..



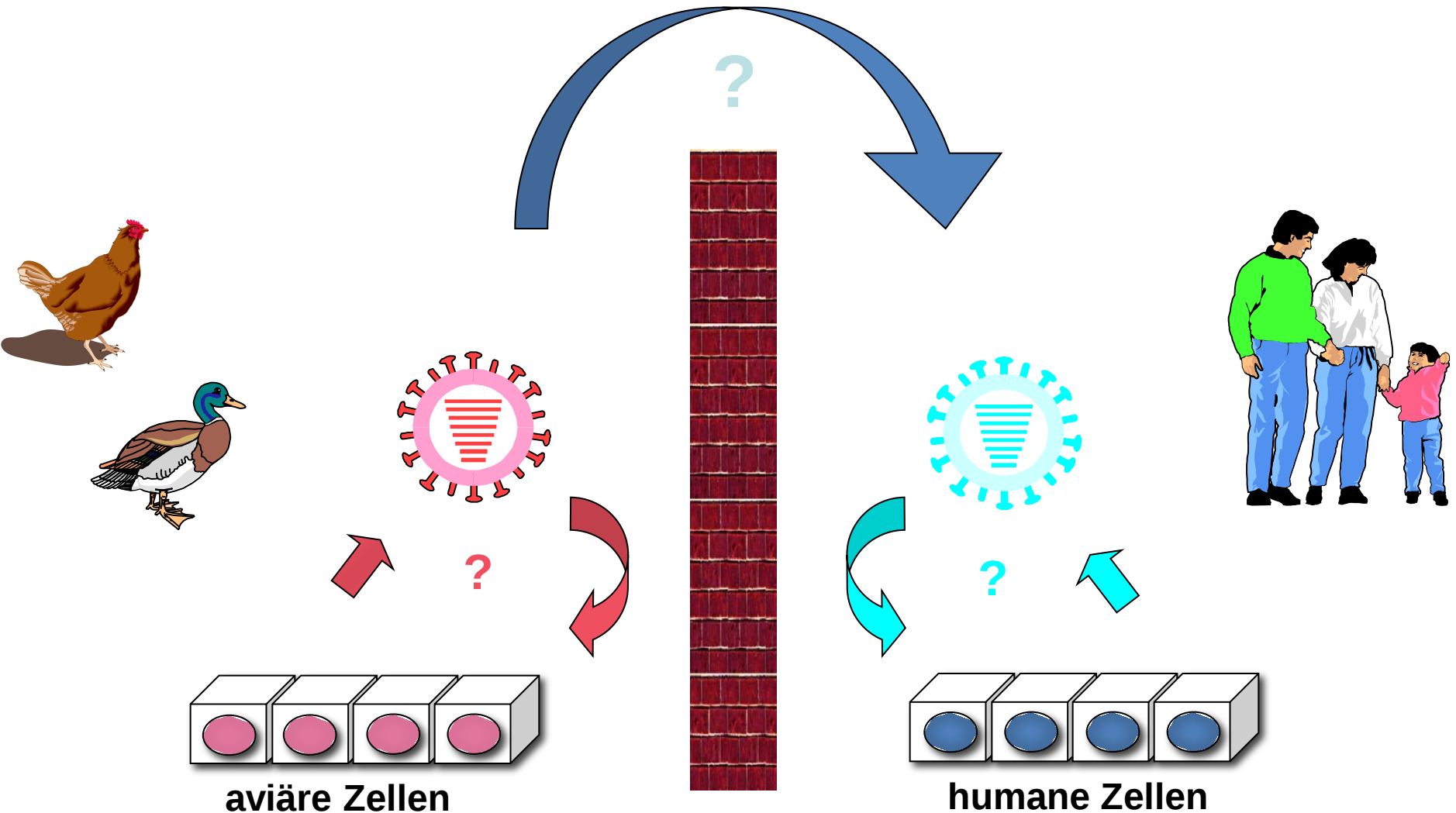
FluResearchNet.

...durch kollaborative Projekte im Netzwerk





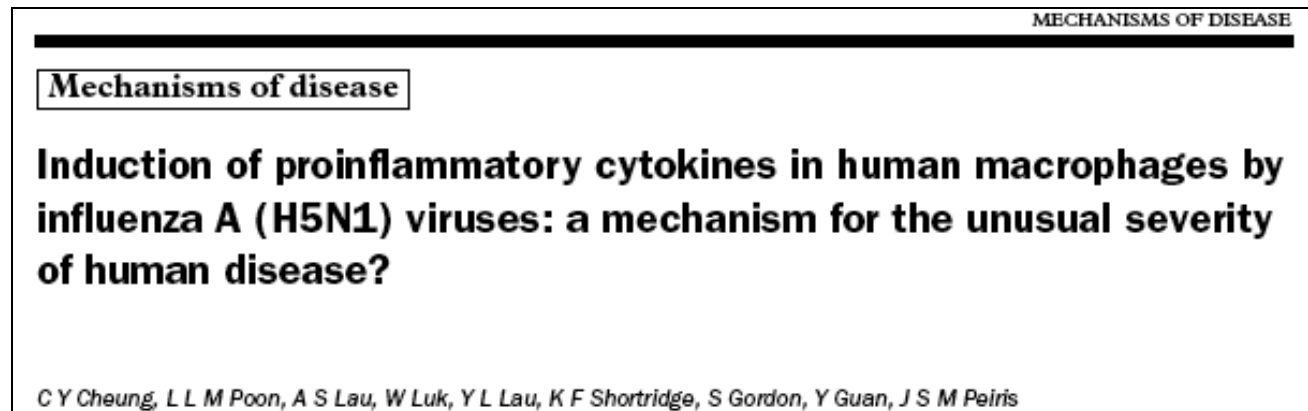
Welche Faktoren bestimmen die Wirtsspezifität und Pathogenität von Influenza Viren, sowie die Fähigkeit zum Überspringen der Speziesbarriere ?



- A) Zelltypspezifische Antworten
(Projektpartner 1, 2 und 3)
- B) Virale Determinanten, zelluläre Interaktionspartner
und genetische Prädisposition
(Projektpartner 4, 5, 6 und 7)
- C) Die Rolle von Interferon und IFN induzierten Genen
(Projektpartner 8, 9, und 12)
- D) Wirtsspezies Schwein: Epidemiologie und Pathogenese
(Projektpartner 10 und 11)

Special molecular feature of
highly pathogenic influenza A viruses:

- hyperinduction of cytokines
„Cytokine burst“



Cell intrinsic mechanisms of cytokine induction ?

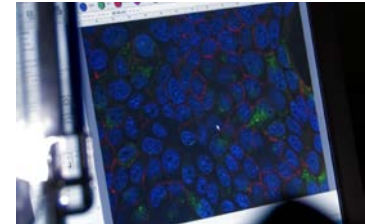
Why are highly pathogenic IAV able to replicate
in spite of high cytokine levels ?

Joint programme of activities: Role of the transcription factor NF- κ B

Essential impact of NF- κ B in H5N1 induced gene expression

Partner #3 and #6a

Schmolke et al. (2009), J Immunol.



H5N1 gene expression profile is shifted from a IFN type response to a predominant inflammatory response

Partner #3 and #6a

Viemann et al., (2011), J. Immunol.

Friesenhagen et al. (2013) J Innate Immun

IAV suppress type I IFN signalling by NF- κ B-mediated induction of SOCS3 expression

Partner #1, #3, #6a and RKI

Pauli et al. (2008), PLOS Pathogens

Partner #6a and PEI

Pauli et al. (2008), Retrovirology



Pathogenicity associated cytokines are not regulated by NF- κ B factor p50 in the mouse

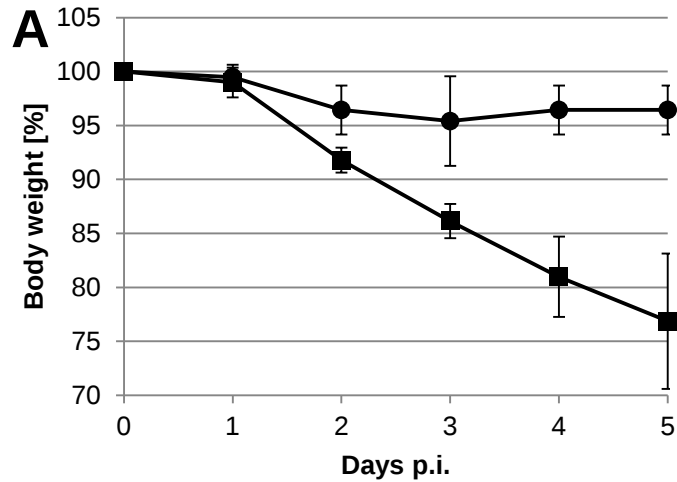
Partner ,#6a,#6b, FLI

Droeblner et al. (2008), J Virol.

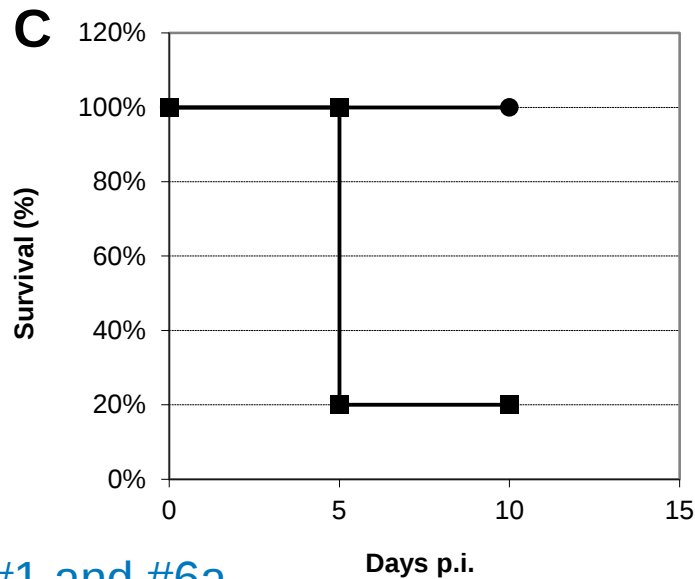
Rückle et al. (2012), J Virol.

Conclusion: Only a small subset of cytokines are relevant for enhanced pathogenicity

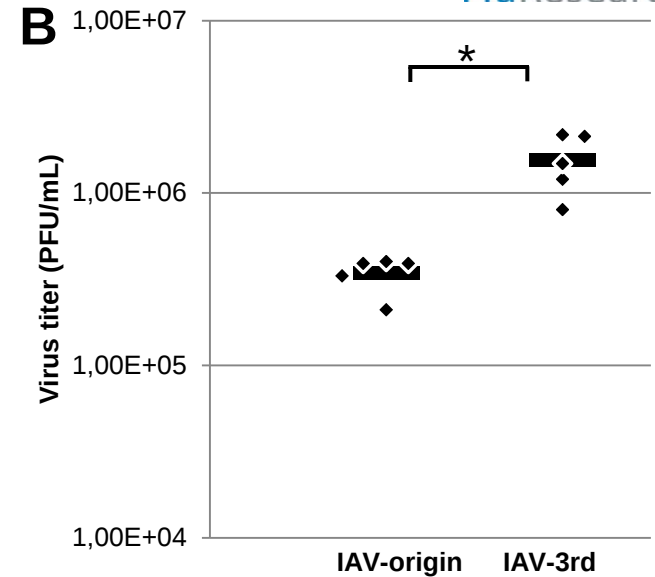
Increased pathogenicity of mouse-adapted pandemic H1N1v



● IAV-origin ■ IAV-3rd



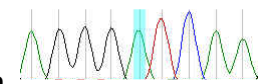
● IAV-origin ■ IAV-3rd



HA gene

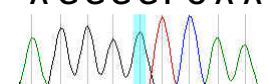
nucleotide substitution
at position 716

A G G G A T C A A



H1N1v-
origin

A G G G G T C A A



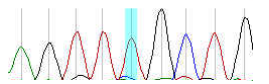
H1N1v-3rd

D222G

PA gene

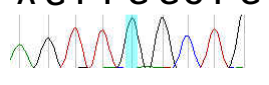
nucleotide substitution
at position 105

A G T T T G C T G



H1N1v-
origin

A G T T G G C T G



h1N1v-3rd

F35L

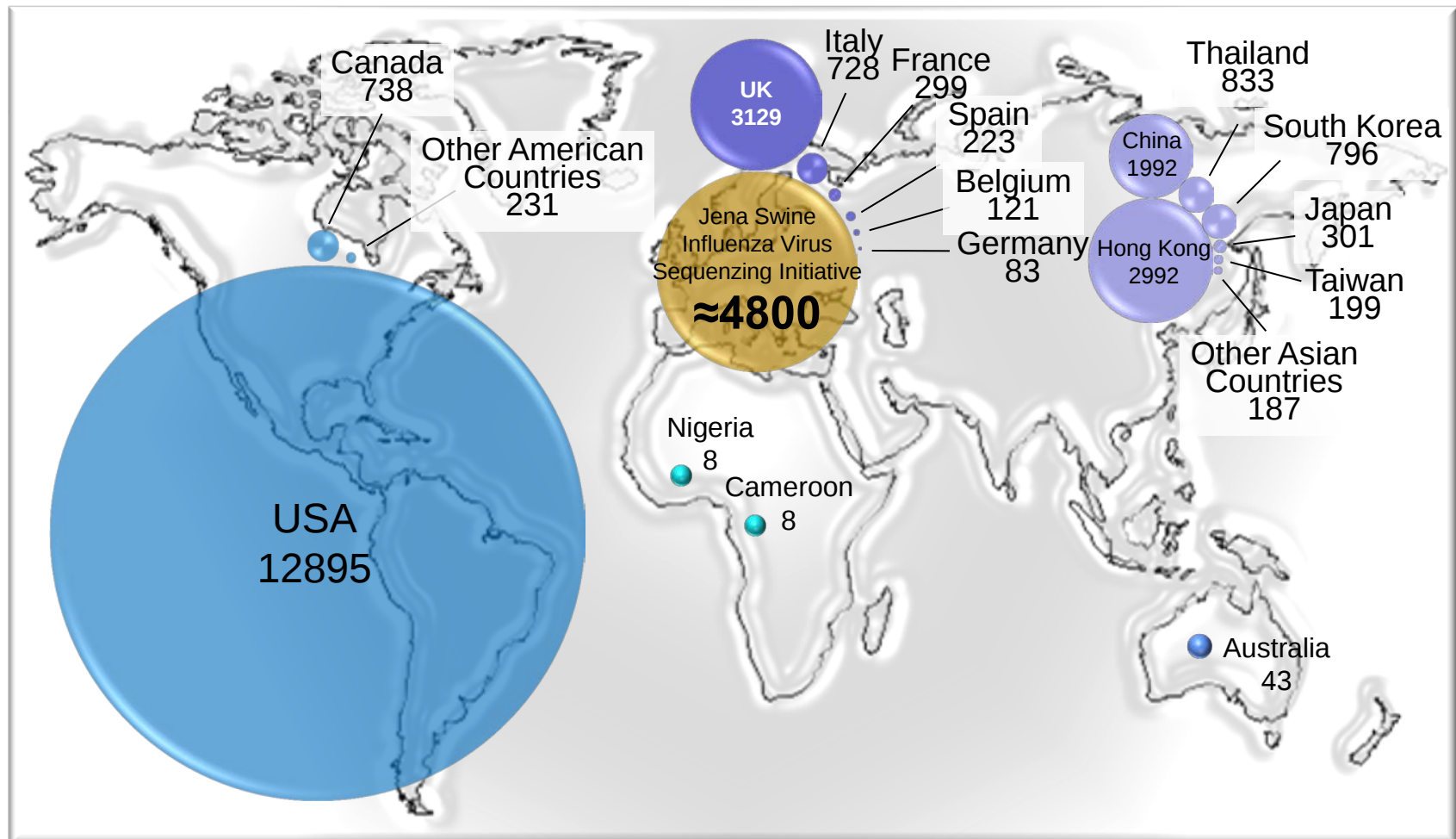


FluResearchNet.

Partners #10 Monitoring of swine influenza activity in Germany

Roland Zell (IVAT, Jena), Ralf Dürrwald (Rodleben)

- Swine influenza virus sequences deposited in GenBank: **26362** entries (as of 2 Oct. 2013)



Joint programme of activities: Novel approaches for antiviral intervention

NF- κ B inhibition as an antiviral approach against influenza viruses

Partner #1, #5, #6a and #6b

Ludwig and Planz (2008) Biol Chem

→Phase II clinical trial ongoing (Activaero GmbH)

The NF- κ B inhibitor SC75741 is a potent antiviral drug against influenza viruses in vitro and in vivo (including FluB, H5N1, H1N1v...)

Partner #6a and #6b

Ehrhardt et al. (2013), Cell Microbiol
Haasbach et al. (2013), Antiviral Res

Interaction blockers of the viral polymerase

Partner #4

Chase et al. (2008), J Virol
Mänz et al. (2011), J Biol Chem

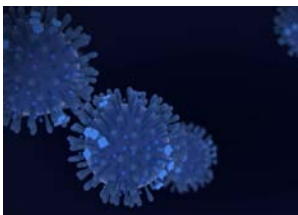


→Further development with PikePharma

Clinically approved MEK inhibitors act antiviral alone and in synergy with Tamiflu

Partner #5, #6a and #6b

Pinto et al. (2011), Antiviral Res
Haasbach et al. (2011), Antiviral Res
Haasbach et al. (2013) Antiviral Res.



→innovation award BioSTERN Region

Joint programme of activities: Novel approaches for antiviral intervention



Inhibitors of cytokine burst and immunomodulators as novel drugs against severe influenza

Type I IFN as an emergency drug against pandemic influenza

Partner #6b, #9 and associated partners

Kugel et al. (2008), J Virol

Haasbach et al. (2011), J Interferon Cytokine Res

→ clinical development by Amarillo Bioscience

PAR antagonists as modulators of the IFN response

Partner #6a and #6b (in collaboration)

Feld et al. (2008), J Immunol

Shpacovitch et al. (2011), Immunology

Khoulache et al. (2013), J Clin Invest

p38 MAPK inhibitors act beneficial in mice without blocking viral replication

Partner #3 and #6a

Börgeling et al. (2014), J Biol Chem

GM-CSF restores epithelial barrier function in the lung

Partner #12

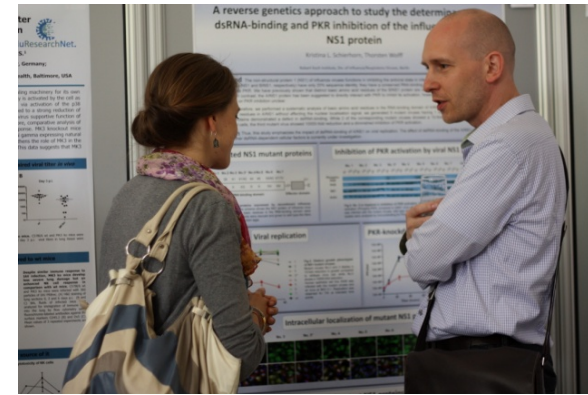
Unkel et al. (2012), J Clin Invest

Partner #12 with #1, #5, and #11

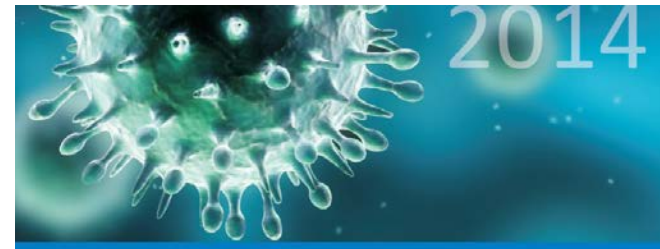
Hoegner et al. (2013) PLoS Pathogens

→ „compassionate use programm“ successful, further development in DZL

International Influenza Meeting



4th International Influenza Meeting 2014



Venue and date

University of Münster
Schlossplatz 2 | 48149 Münster, Germany
21–23 September, 2014

Organizer

FluResearchNet and National Research Platform for Zoonoses
Prof. Dr. Stephan Ludwig
c/o Institute of Molecular Virology
Von-Esmarch-Str. 56 | 48149 Münster
E-Mail: flu.2014@uni-muenster.de

Topics

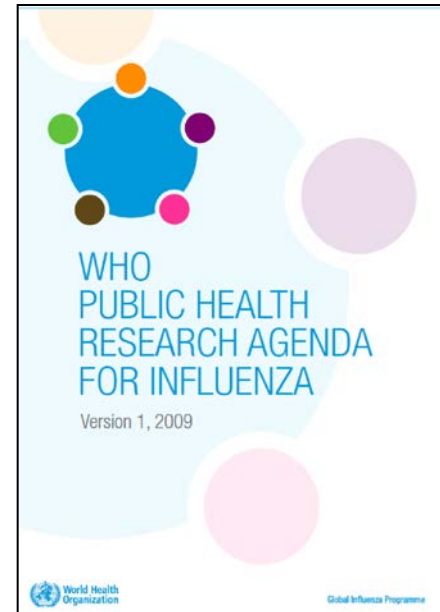
- Influenza and the lung
- Innate immunity
- Pathogenesis
- Vaccines and antivirals
- Virus cell interaction
- Free topics

For future information
please visit the website
of the FluResearchNet.

WHO Global Consultation on the Public Health
Research Agenda for Influenza
Geneva, CH, 17-20 Nov 2009

WHO technical consultation: Research needs
for the battle against respiratory viruses
Geneva, CH, 6-7 Nov 2012

Wilton Park conference WP1260 on Dual-use
biology: how to balance open science with security
Wilton Park, UK, 15-18 Sep 2013



Forschungs(förderungs)bedarf für die vernetzte Influenza Forschung

Molekulare Pathogeneseforschung

Zelluläre Restriktionsfaktoren, Co-Infektionen (DFG, EU)

Validierungsforschung

Evaluierung und Validierung von kommerzialisierbaren Ergebnissen (BMBF)

Integriertes Monitoring und Surveillance Programm mit evidenzbasierter Risikoabschätzung

Surveillance der Influenza Aktivität bei Mensch und Tier, Identifizierung und funktionelle Evaluierung viraler Pathogenitätsdeterminanten (BMBF)

One Health approaches to influenza

- Enhanced surveillance
 - clinical human and veterinary disease
 - combination of clinical and laboratory surveillance
 - co-ordination of local, regional, national and international surveillance programs
 - genetic and antigenic variation of viruses.
- Rapid, 'real time' dissemination of surveillance data.
- Understanding patterns of transmission: human-to human (and animal), animal-to-animal (and human).
- Understanding pathogenesis of disease in animals and humans.

Dwyer and Kirkland (2011) NSW Public Health Bulletin, Vol. 22,124-126



Danke für die Aufmerksamkeit!

www.fluresearchnet.de