Rolf Hilgenfeld

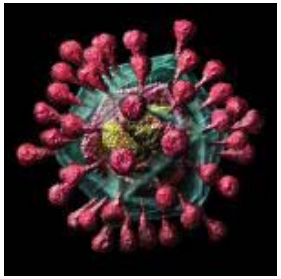
Universität zu Lübeck

Global threads by RNA viruses require global responses, beyond political borders

University of South Bohemia

in a World of Science without Borders

Ceske Budejovice, November 24-25, 2009



Global travelling and trade
lead to enhanced spread of viruses

All emerging viruses causing disease in humans in the past 15 years were RNA viruses

1994- West-Nile virus: N Africa, Romania, then USA (1999)

1997- H5N1: Hong Kong, Viet-Nam

1997- Nipah virus: Malaysia **NEW**

2000- Rift-Valley fever virus: crossed the Red sea…

2003- SARS coronavirus **NEW**

2003- Monkeypox: USA

2005- Marburg virus: Angola

2005- Japanese encephalitis: India

2006- Chikungunya virus: La Réunion, Indian Ocean, India

2008/2009- Enterovirus 71: China, Singapore **NEW**

2009- «Swine influenza» virus H1N1: Mexico, USA ⇒ global

Which role is plyed by climate change?

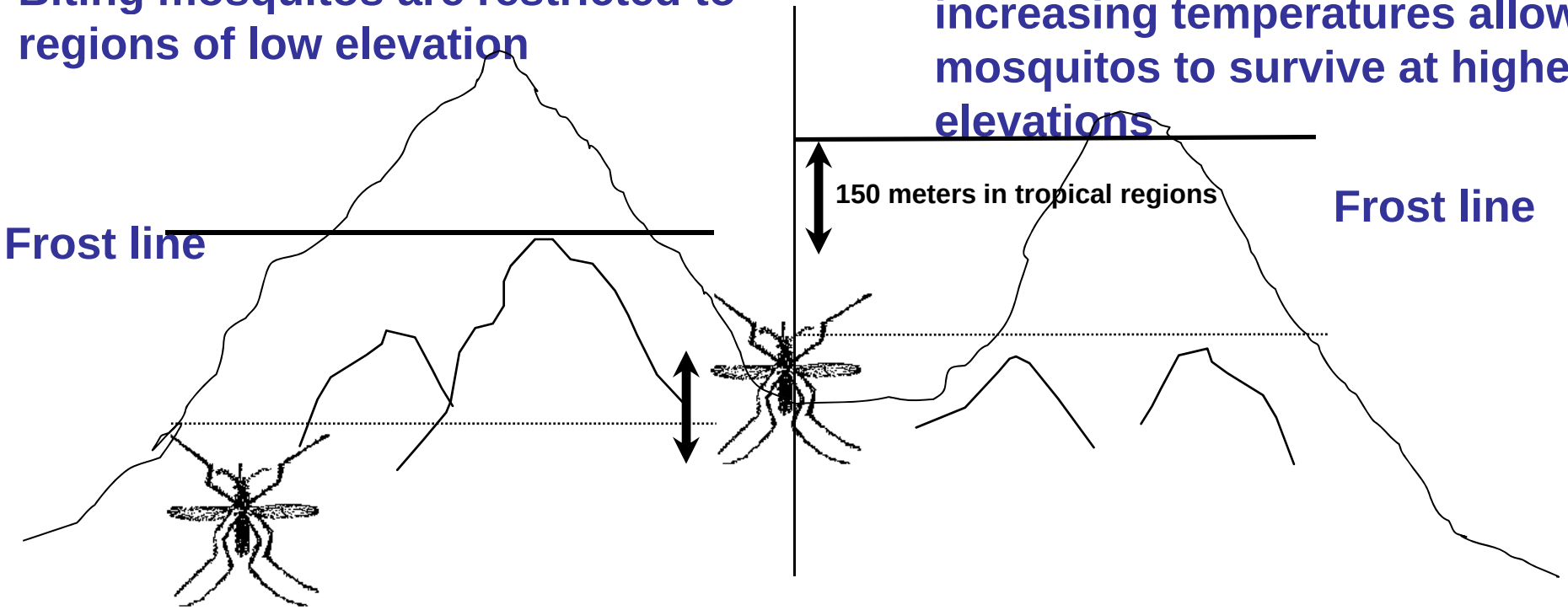
Today, mosquitos survive at higher elevations

before 1970:

Biting mosquitos are restricted to regions of low elevation

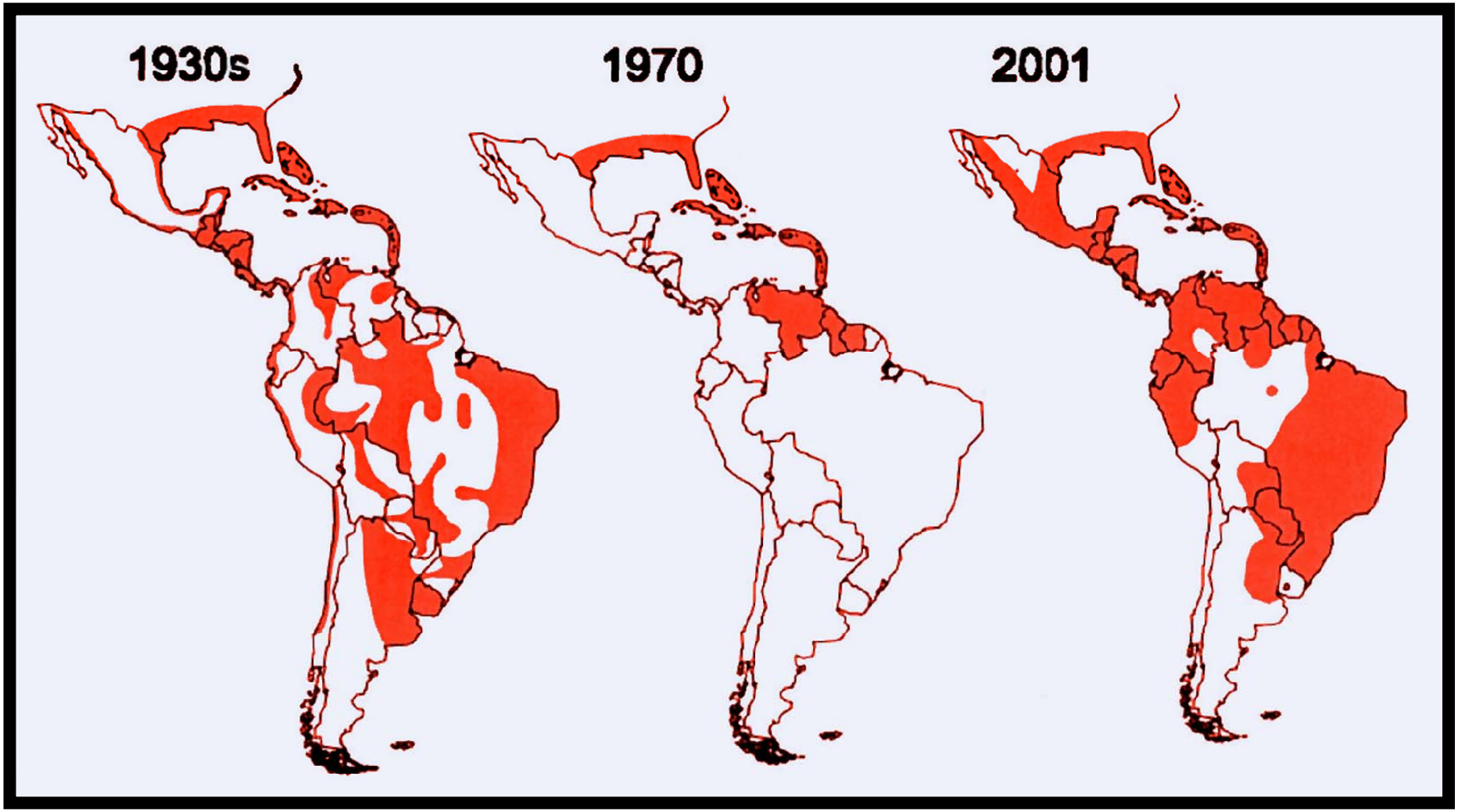
today:

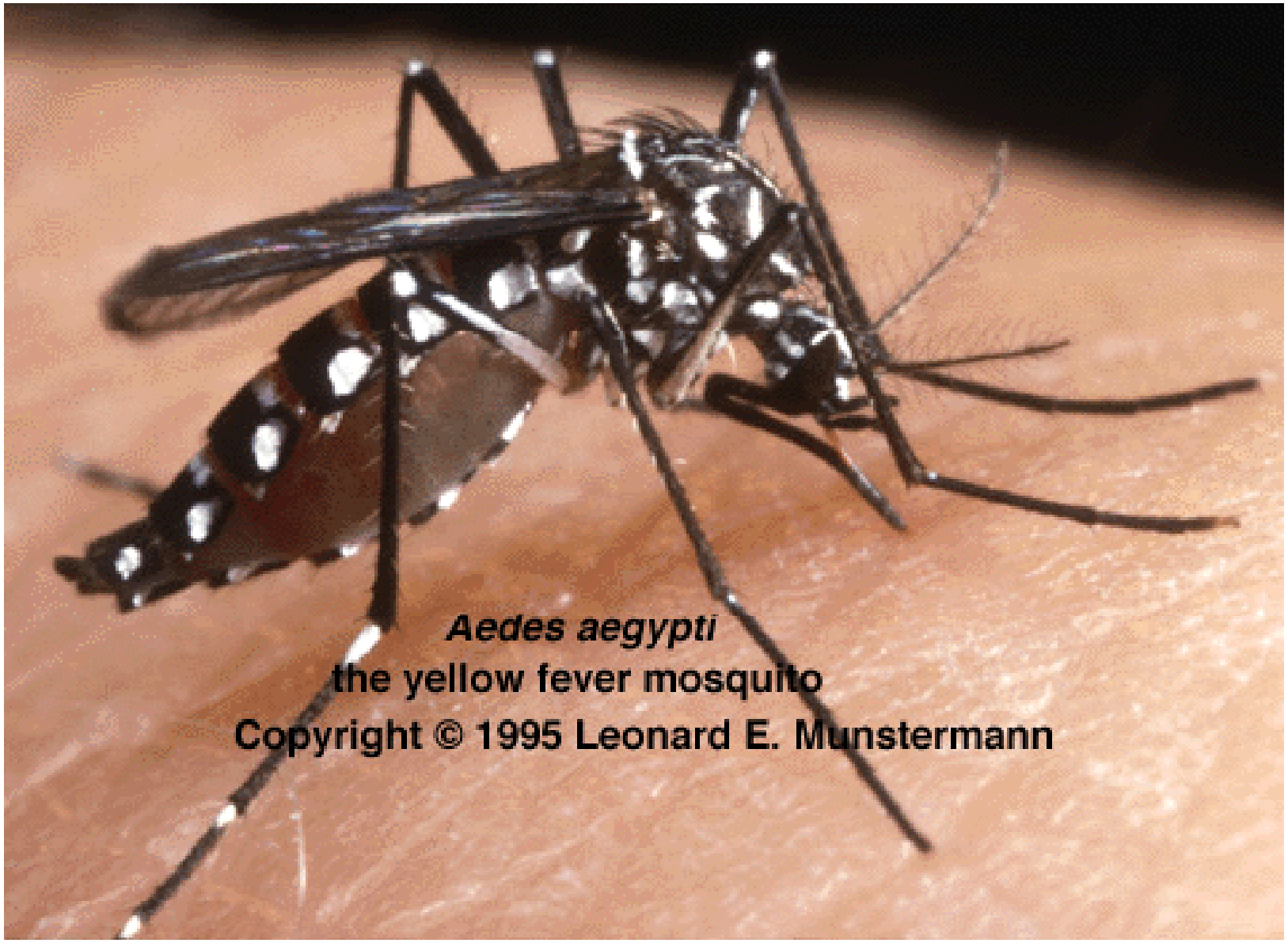
increasing temperatures allow mosquitos to survive at higher elevations



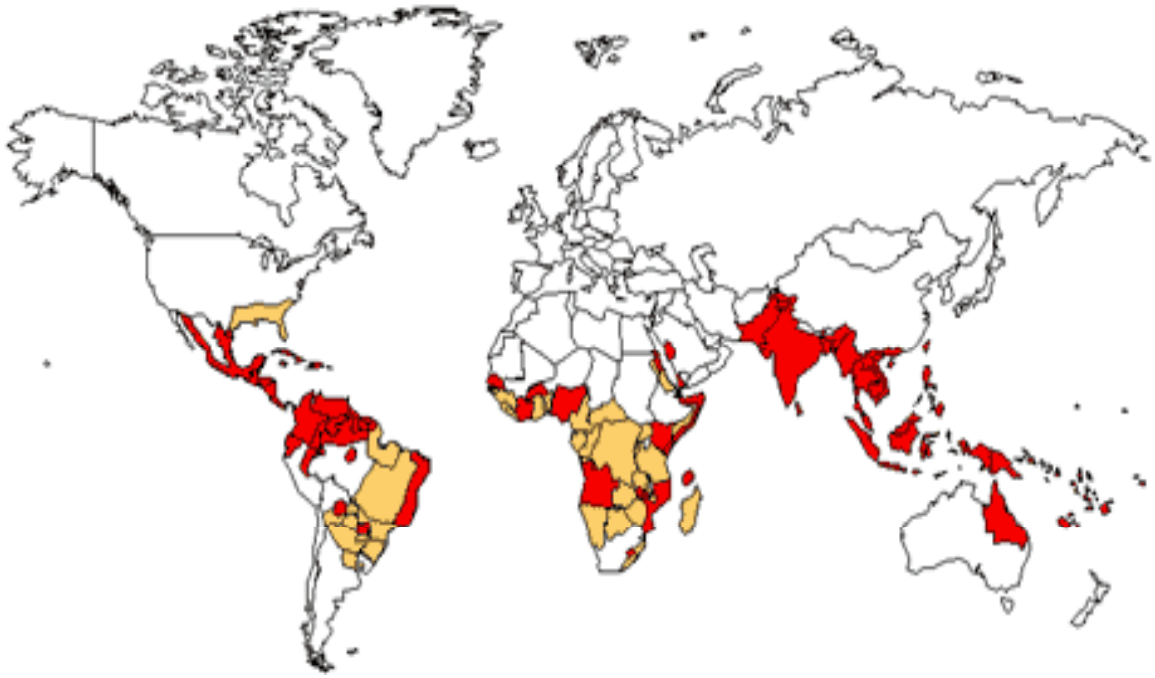
Aedes aegypti
requires > 10°C

Occurrence of infectious diseases in Central and South America




Aedes aegypti
the yellow fever mosquito
Copyright © 1995 Leonard E. Munstermann

Dengue Virus and West Nile Virus: Spread by Mosquitos



Verbreitungsgebiet von *Aedes aegypti*

Verbreitung von Dengue-Virus

Photo by Department of Medical Entomology, NIID

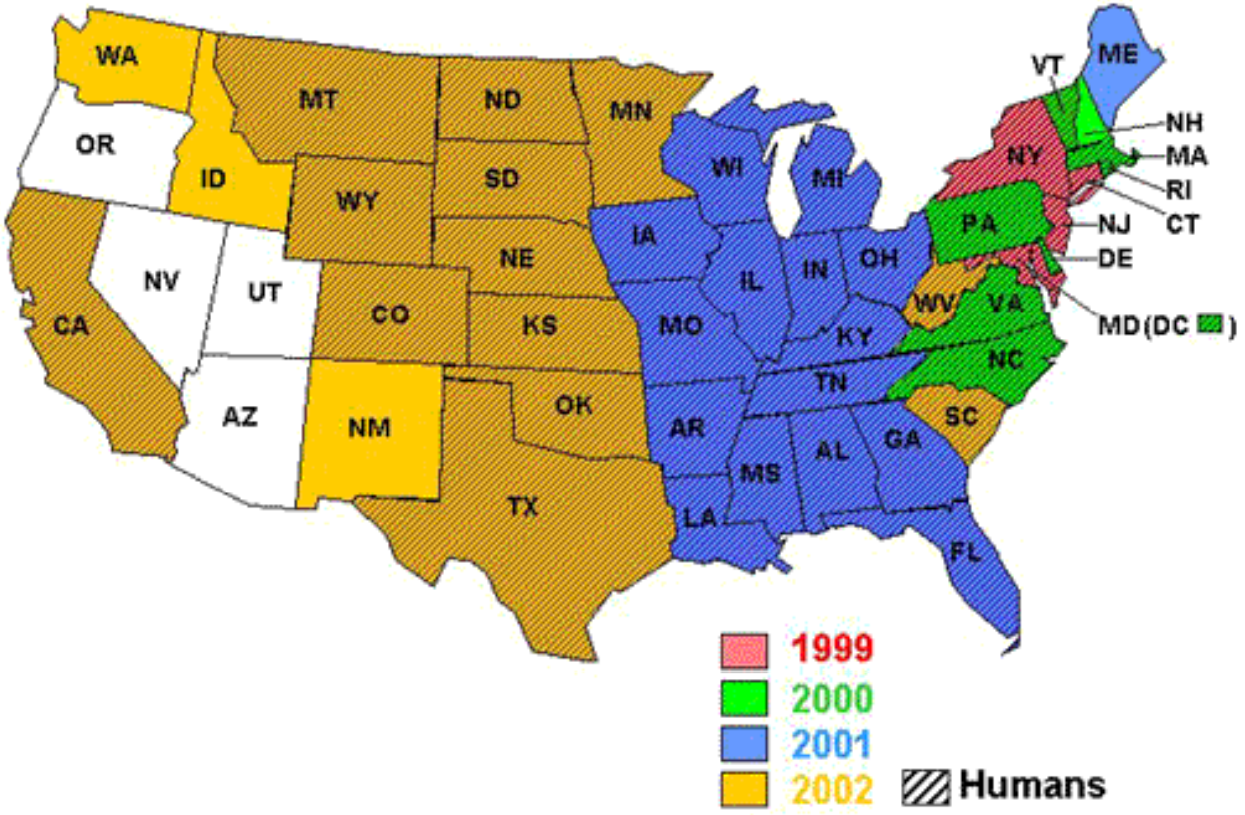
IASR

Infectious Agents Surveillance Report

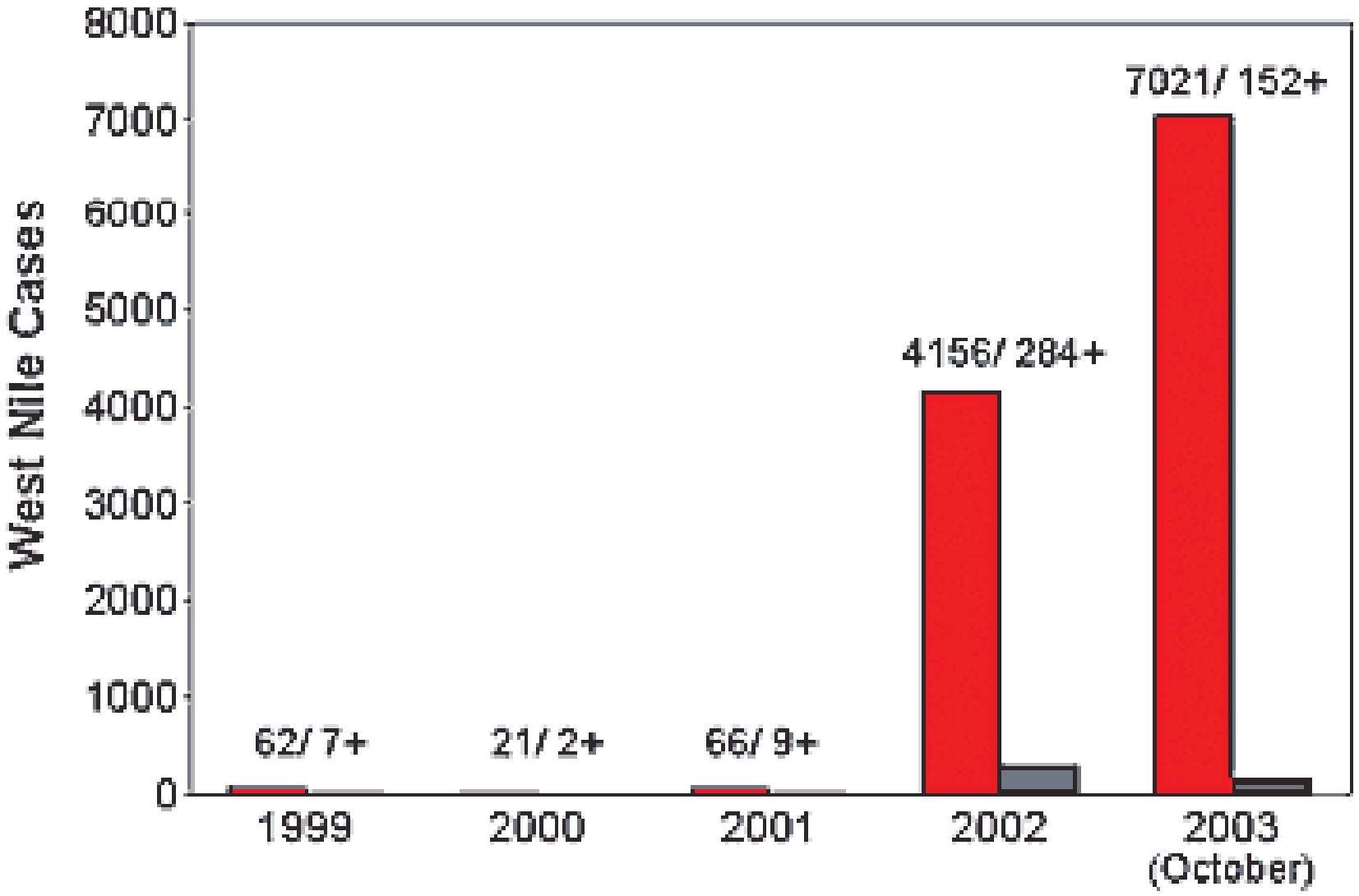
Aedes albopictus

Haemorhagic Dengue Fever

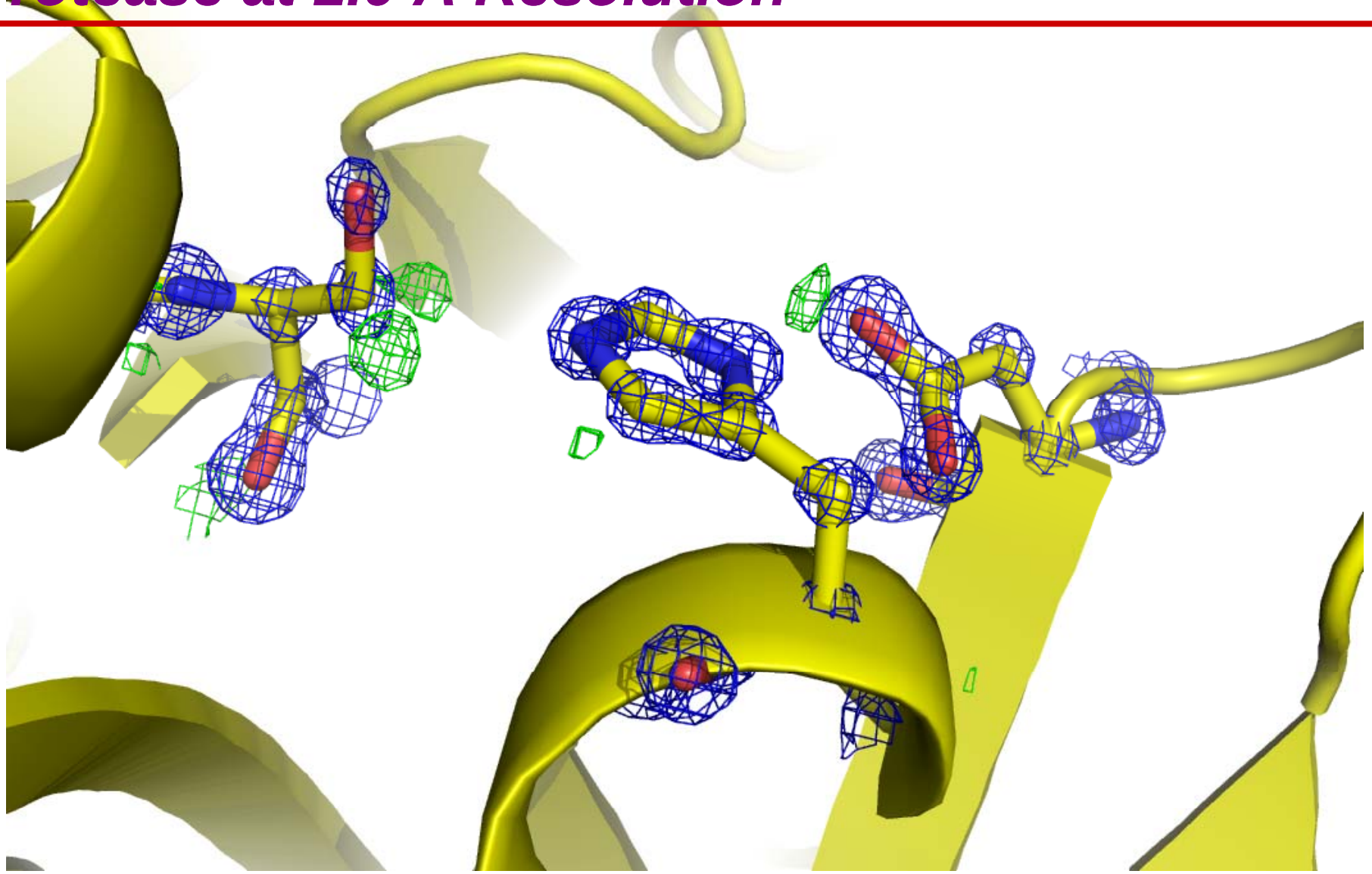
Geographical Distribution of West Nile Virus in the U.S. (1999 - 2002)



West Nile Virus Infections USA



Enabling Drug Design: West Nile Virus NS2B/NS3 Protease at 1.0 Å Resolution

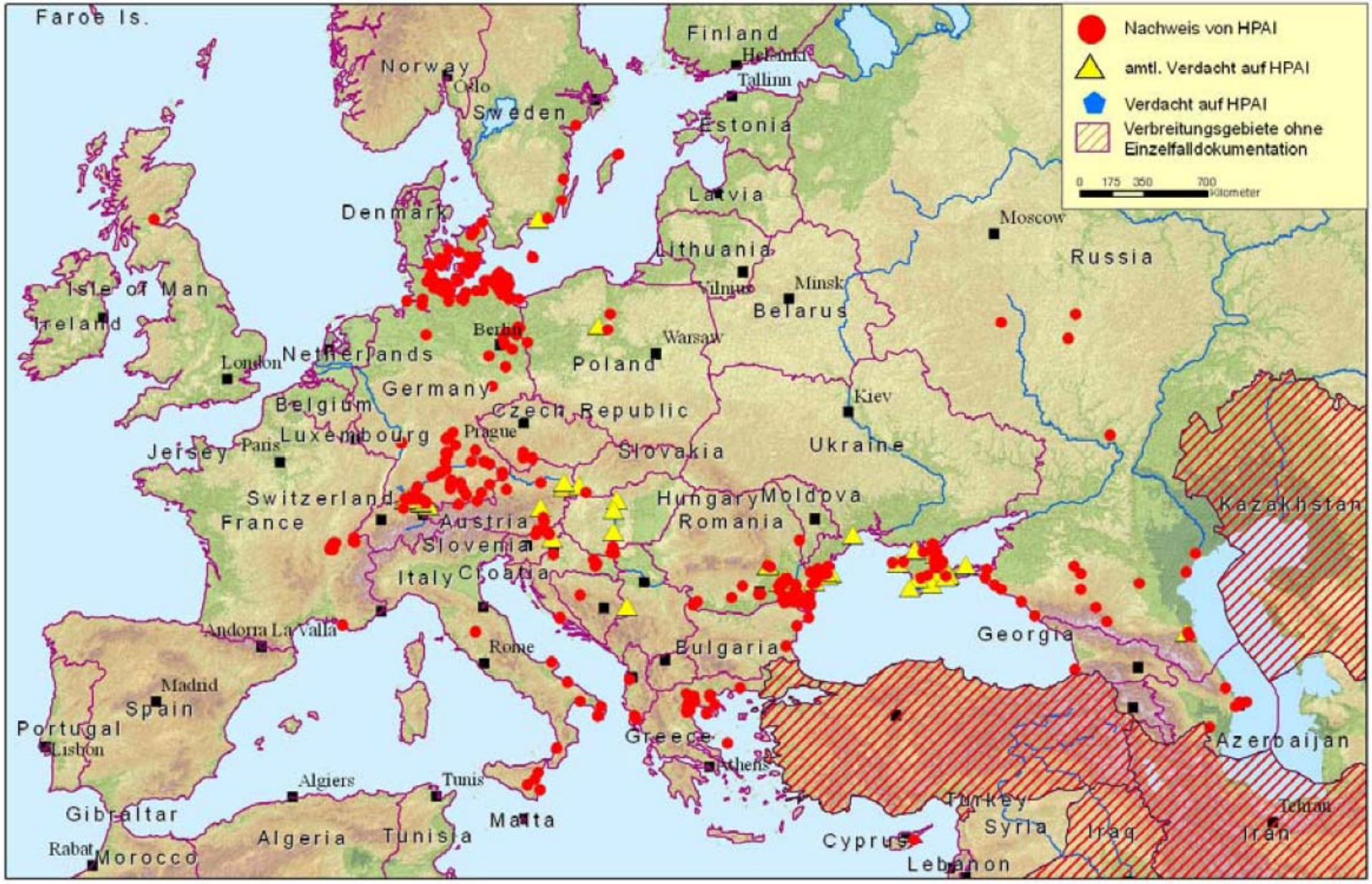


Caroline Haas, Holger Steuber (2009)

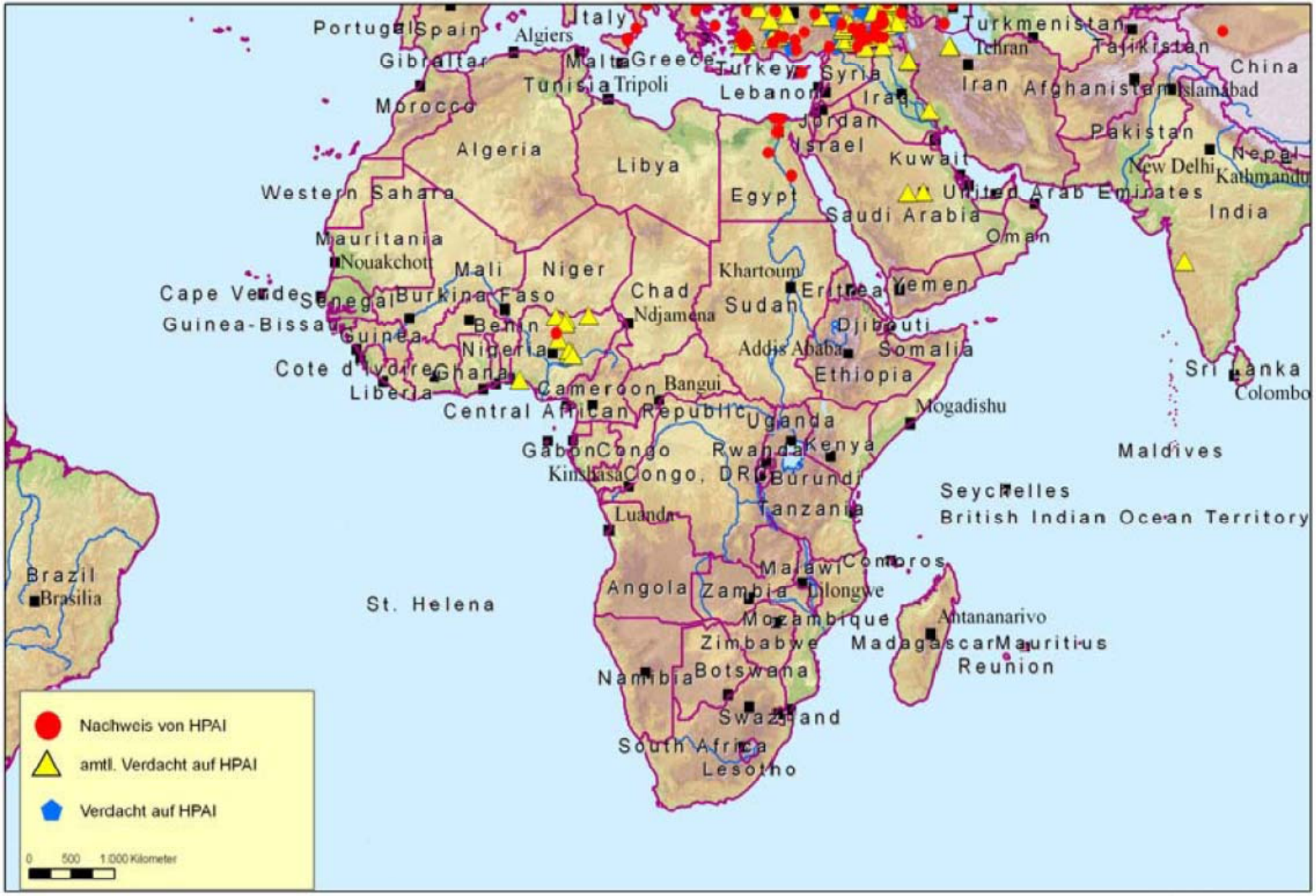
Mosquitos, birds, and the viruses they carry do not obey borders

The example of avian flu virus, H5N1 (2004-2007)


Tyumen 08/05
Novosibirsk 07/05
Kazachstan 07/05
Mongolia 06/05
Xinjiang 05/05
-10%
Qinghai 04/05
Vietnam 12/04
Streifengans (Anser indicus)



Aktueller Stand: Kumulative Fälle in Europa

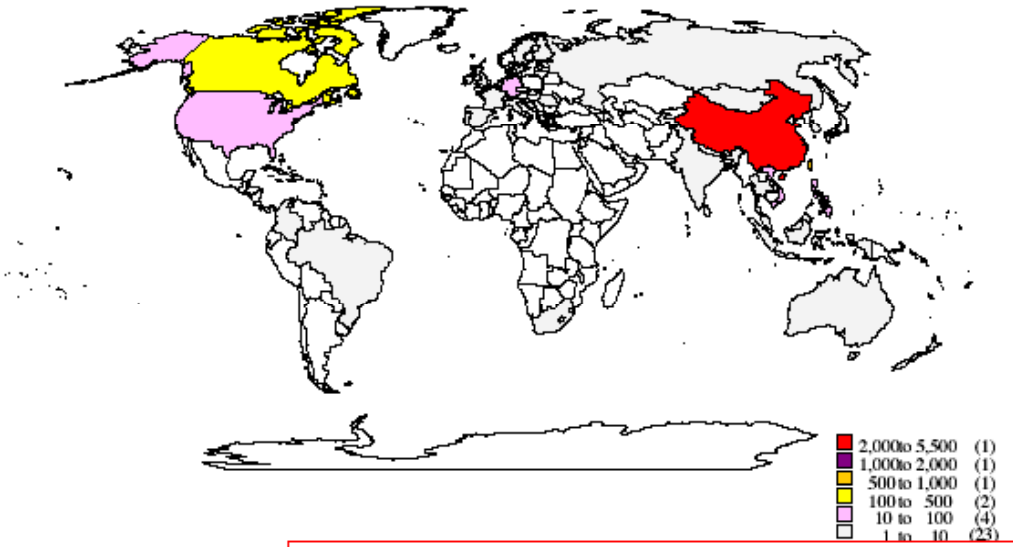


FLI Wusterhausen
Stand 20.02.06 16.30

SARS told several lessons:

- Zoonotic transmission of new viruses is always possible
- Hiding viral outbreaks does not work
- Democracies have a harder time to cope with viral outbreaks

Distribution and cost of SARS



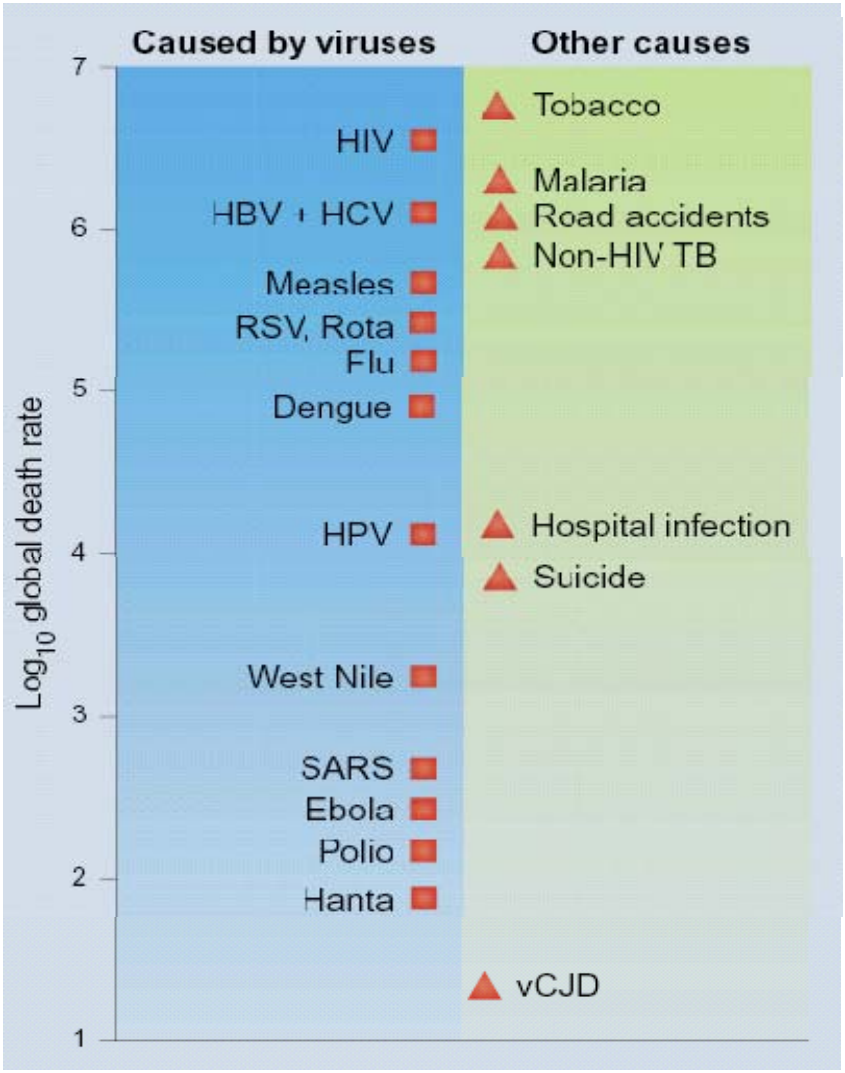
Cost of SARS:

Worldwide: 59 US$ billion
China, mainland: 17.9 US$ billion, 1.3% GDP
Hong Kong: 12 US$ billion, 7.6% GDP

	Cases	Deaths	Case-fatality ratio (%)
Worldwide	8422	916	11
China (inland)	5327	349	7
Hong Kong	1755	300	17
Taiwan	665	180	27
Canada	251	41	17
Singapore	283	33	14

As of August 7, 2003, 29 countries reported 8422 cases. WHO

Major causes of human death:

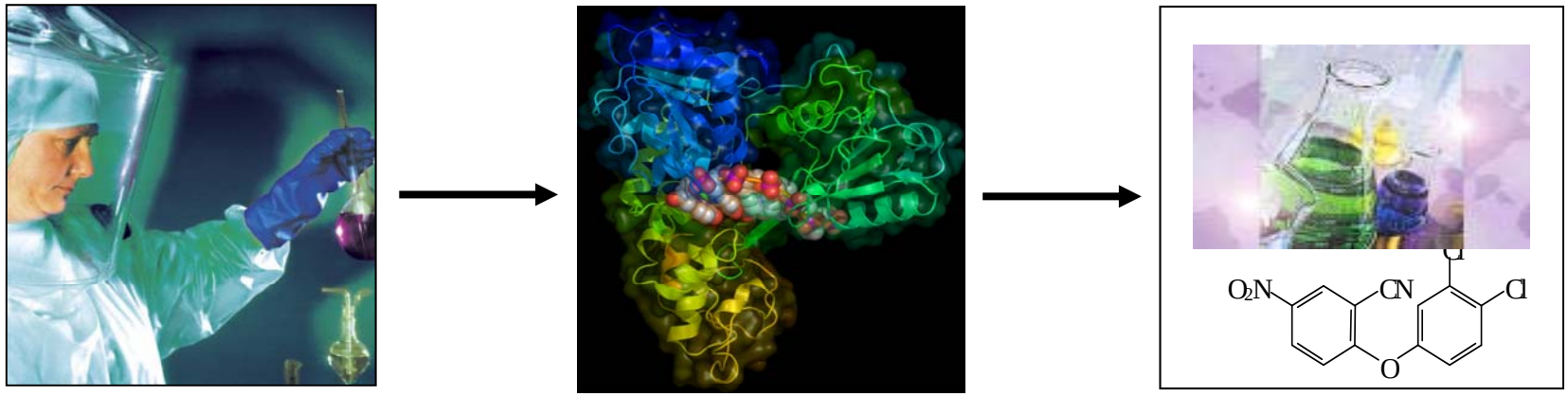


Most are RNA viruses.

An alarming situation !

VIZIER and SILVER:
Preparing Europe for the next outbreak

Goal : Identification of **new targets** from **RNA viruses** through a **structural characterization** of the replicative system



Structural Genomics project supported by the European Union

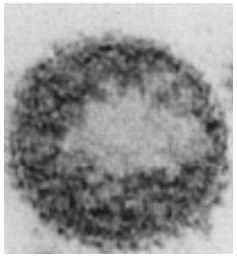
Successor (hopefully!): SILVER - **S**mall-molecule **i**nhibitor **l**eads **v**ersus **e**merging **R**NA viruses

Means : 21 “partners” (chemists, virologists, structural biologists)
>200 full time researchers involved
12 M€ funding by EC

Conclusion: Study all RNA viruses!

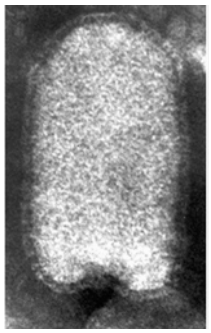
MONONEGAVIRALES

Bornaviridae ***Filoviridae*** ***Rhabdoviridae*** …



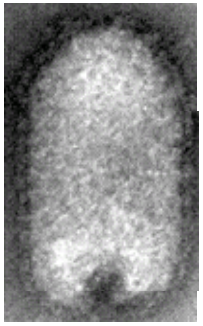
Bornavirus

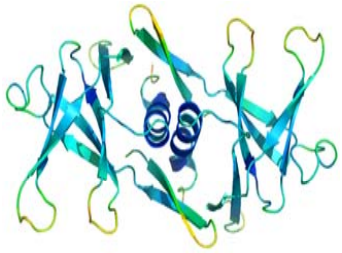
Ebola virus

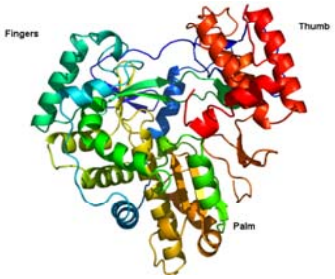


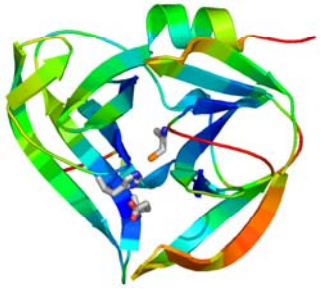
EPIDEMIC

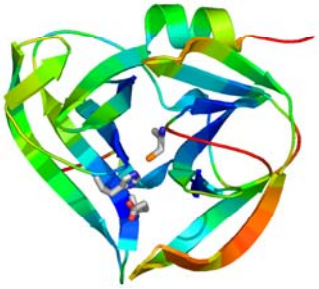
New virus







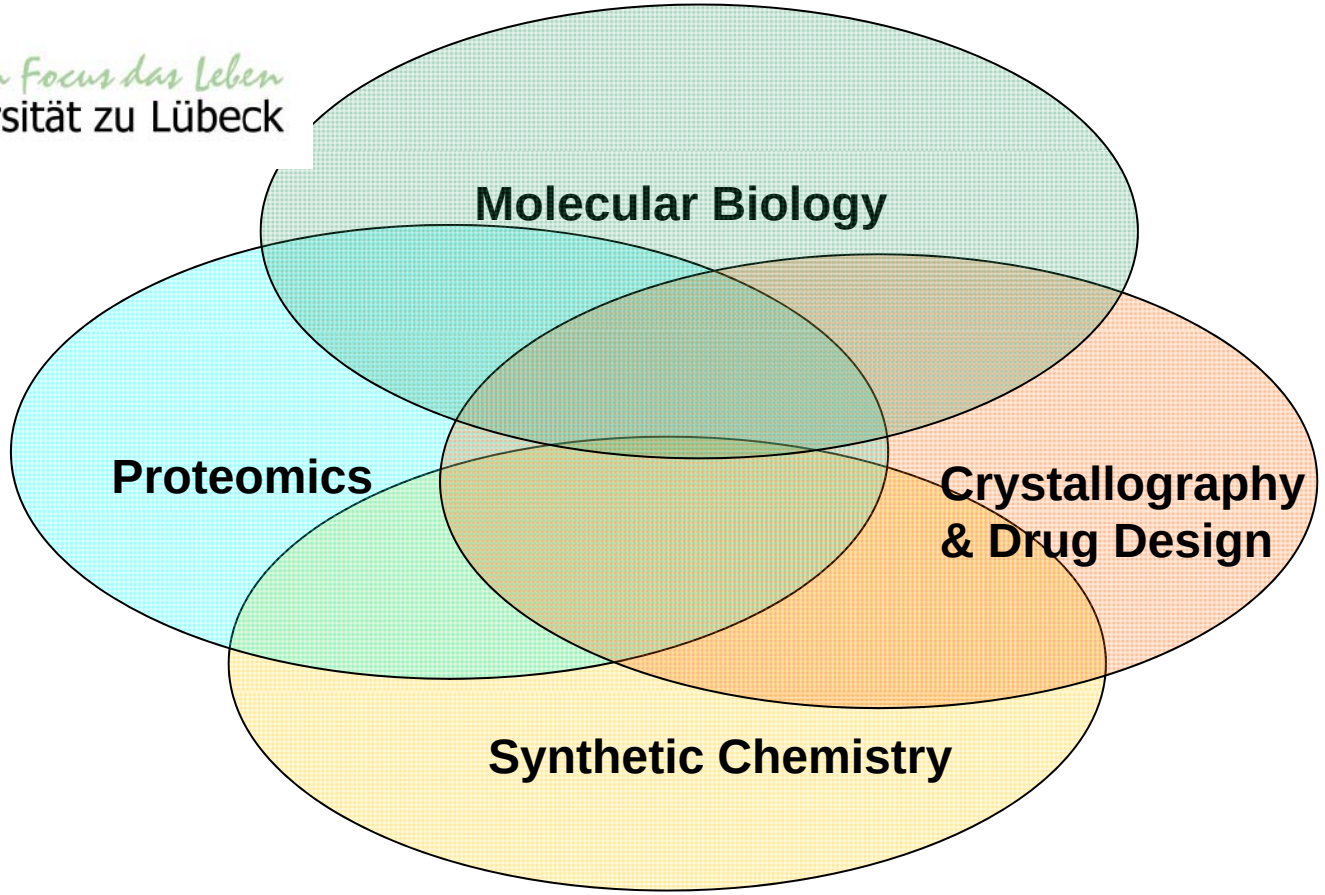




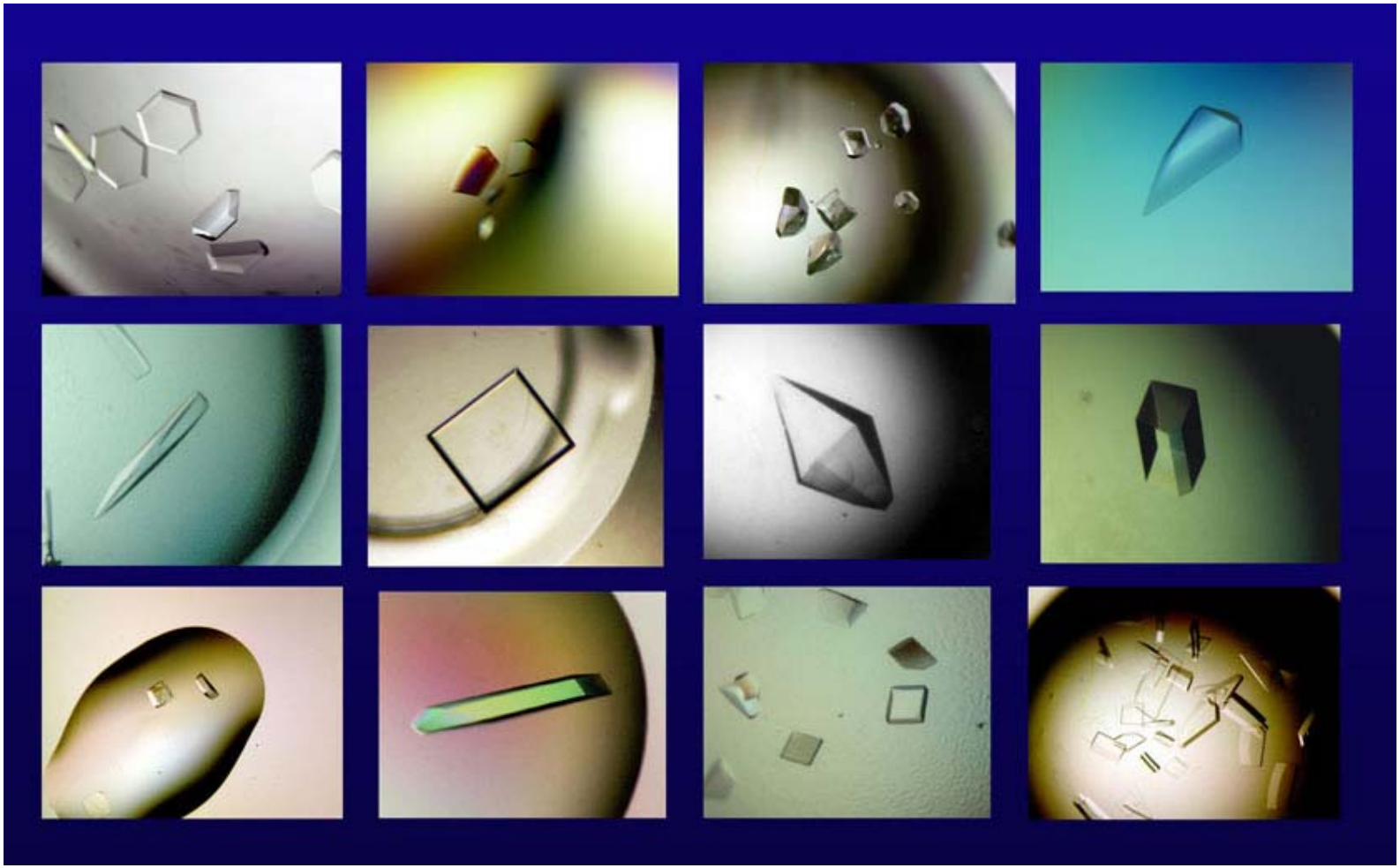
Save years…

Interdisciplinary approach to antiviral drug discovery

Im Focus das Leben
Universität zu Lübeck



SARS-CoV and other coronaviruses, coxsackievirus and other enteroviruses, influenzavirus, Lassa virus, HIV



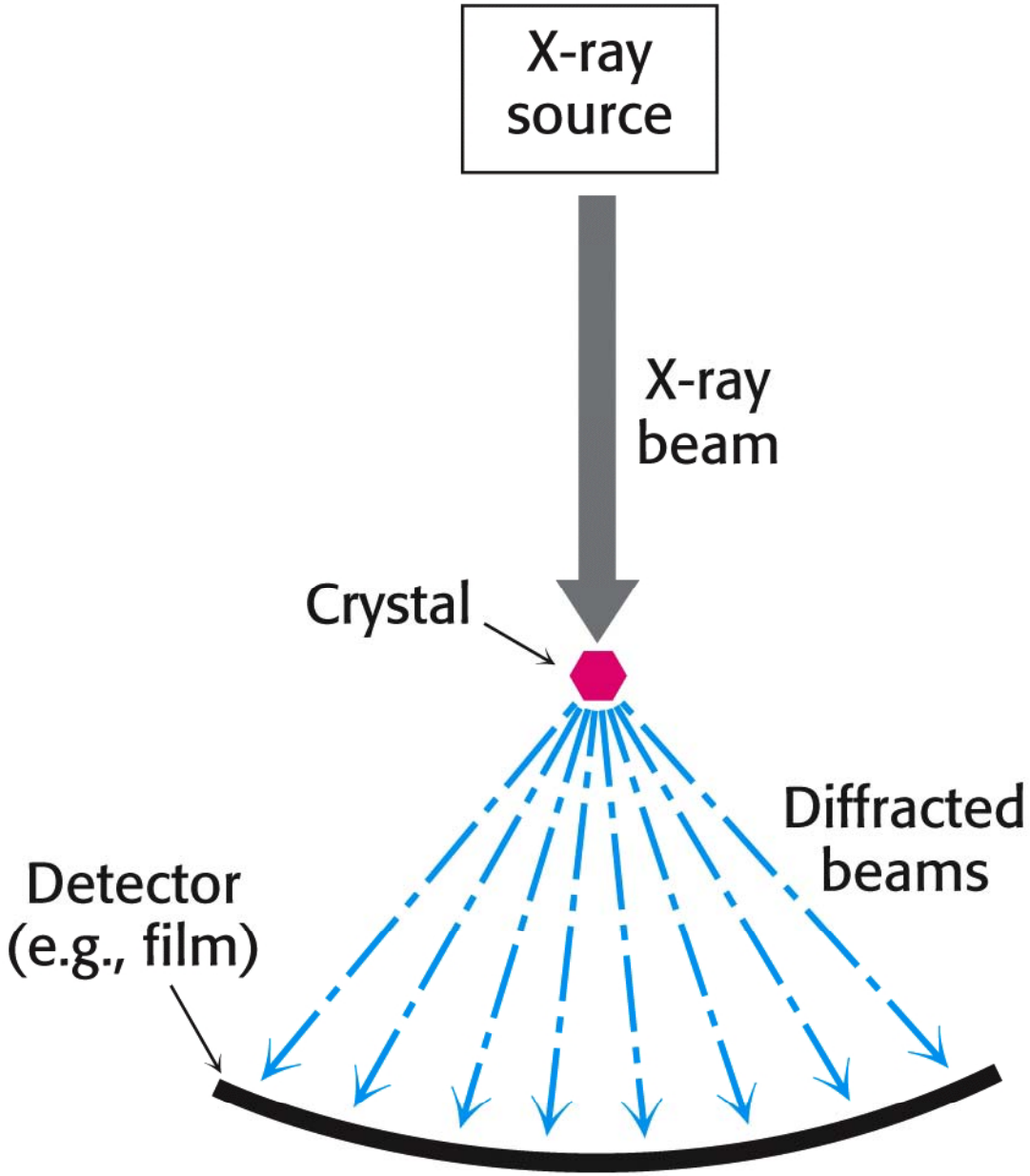
Collaboration with the University of South Bohemia:

Dr. Ivana Smatanova, Prof. Dalibor Stys,
Institute of Physical Biology, Nove Hrady

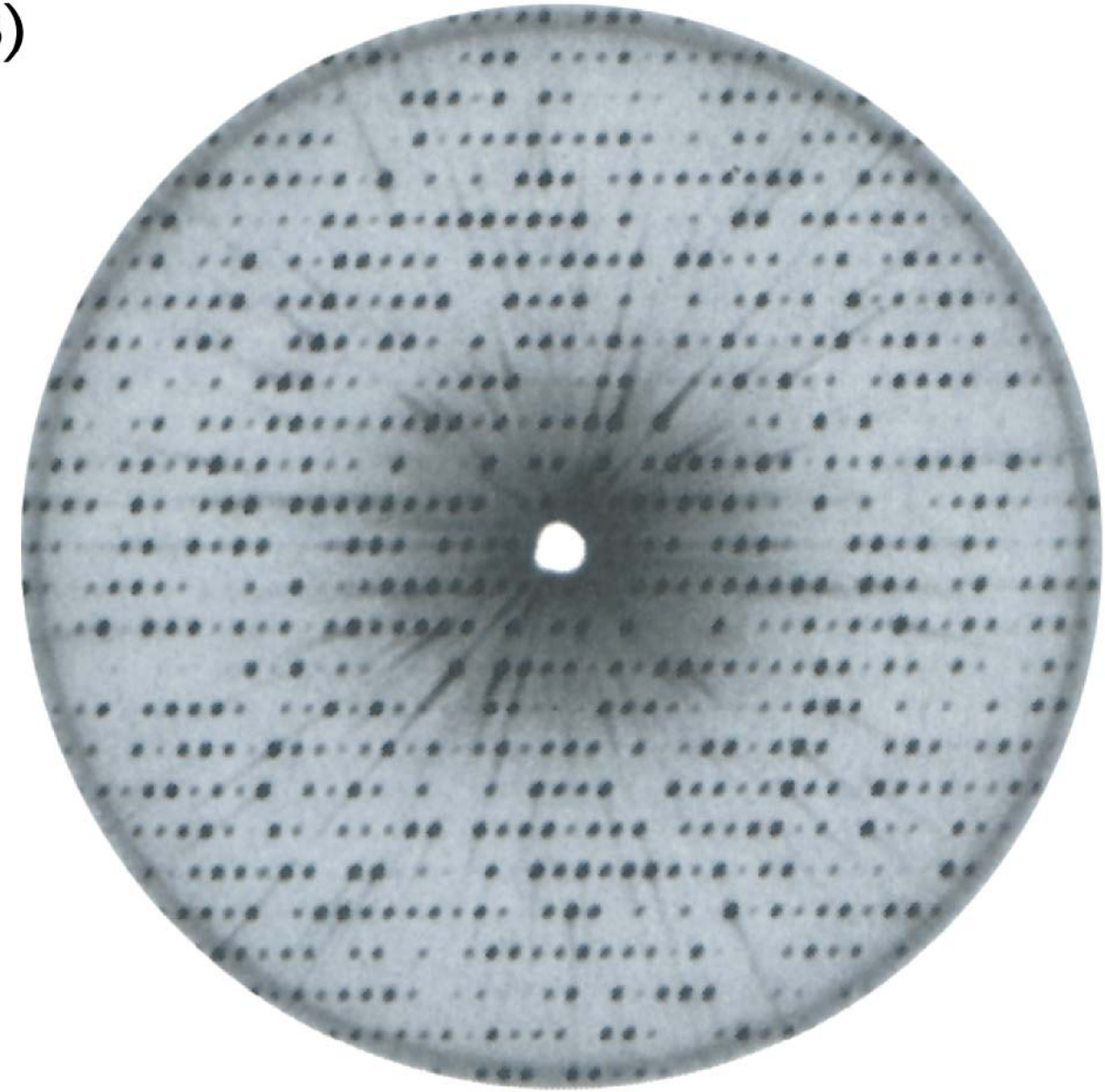
New techniques for crystalliation of proteins

Biannual FEBS Course on “Advanced Methods of Protein Crystallization“

Pokeweed antiviral protein

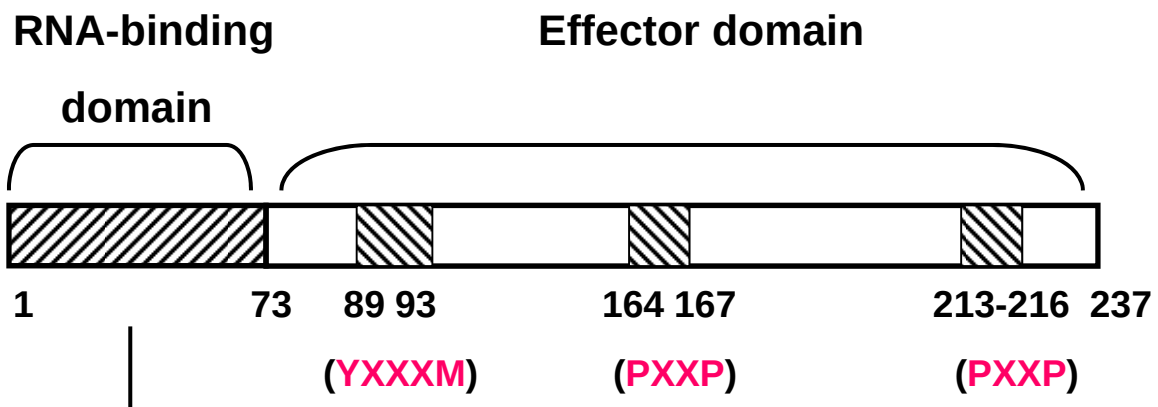

X-ray source
X-ray beam
Crystal
Diffracted beams
Detector (e.g., film)

(B)



A new target for anti-influenza drugs: The interactions between NS1 and host proteins (PI3-Kinase, CPSF30, TRAM25, PKR...)

Interactions of NS1 with dsRNA and host proteins



Sequester dsRNA

2'-5' oligo (A) synthetase/ RNase L pathway

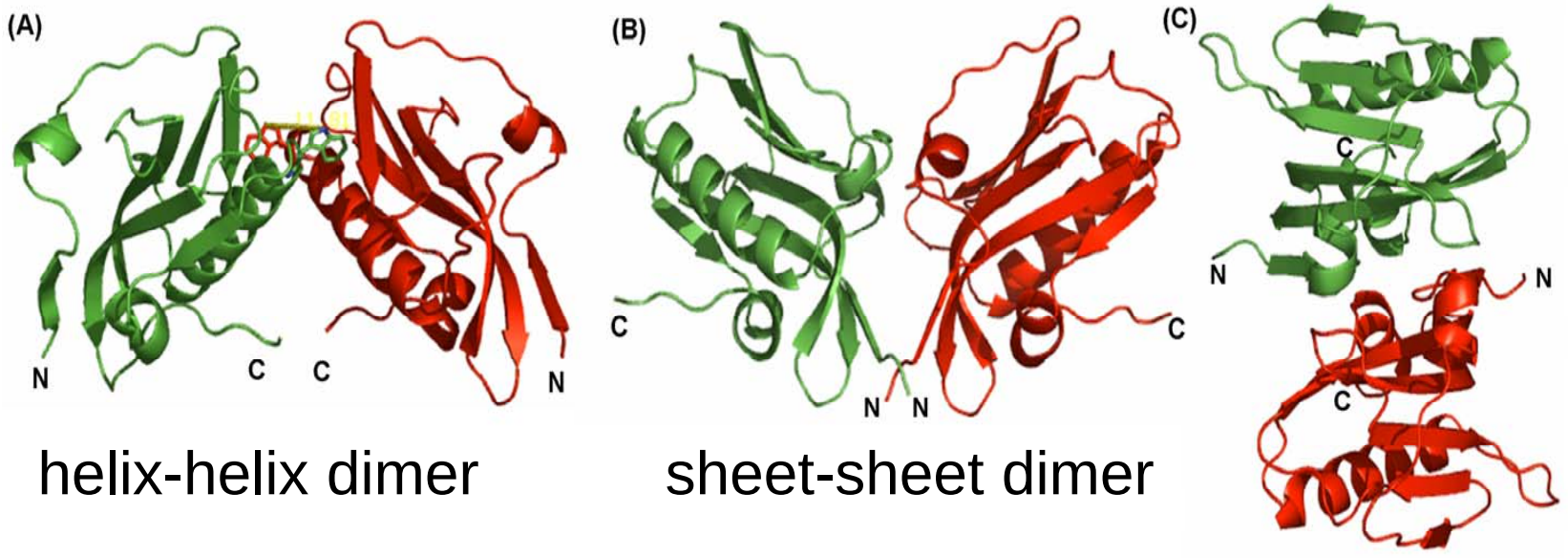
PNAS, 2006. 103. 7100–7105

p85 of PI3K → PI3K/AKT pathway

PNAS, 2006.103.14194-14199
J Virol, 2007. 81. 3058-3067
J Gen Virol, 2007. 88.13-18

Crystal structure of H5N1 NS1 effector domain

Influenza A/Vietnam/1203/2004
3 different dimers occur in the crystal:



helix-helix dimer

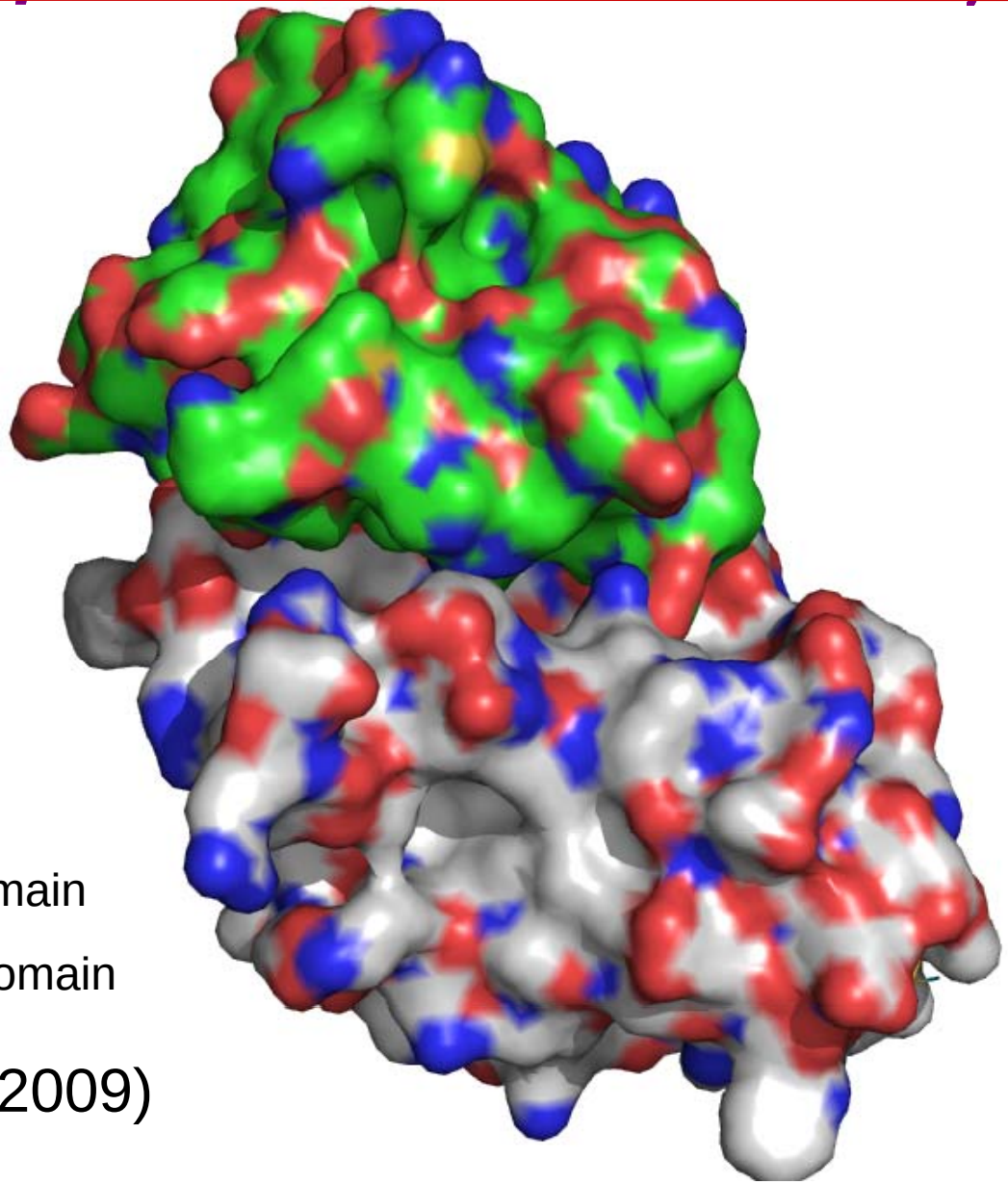
sheet-sheet dimer

novel dimer

variable dimerization may be relevant to multifuntional interactions of NS1

Shuai Chen, Yibei Xiao, Can Shen (2009)

Interaction between the SH2-binding motif of NS1 and the p85 subunit of PI3-kinase β

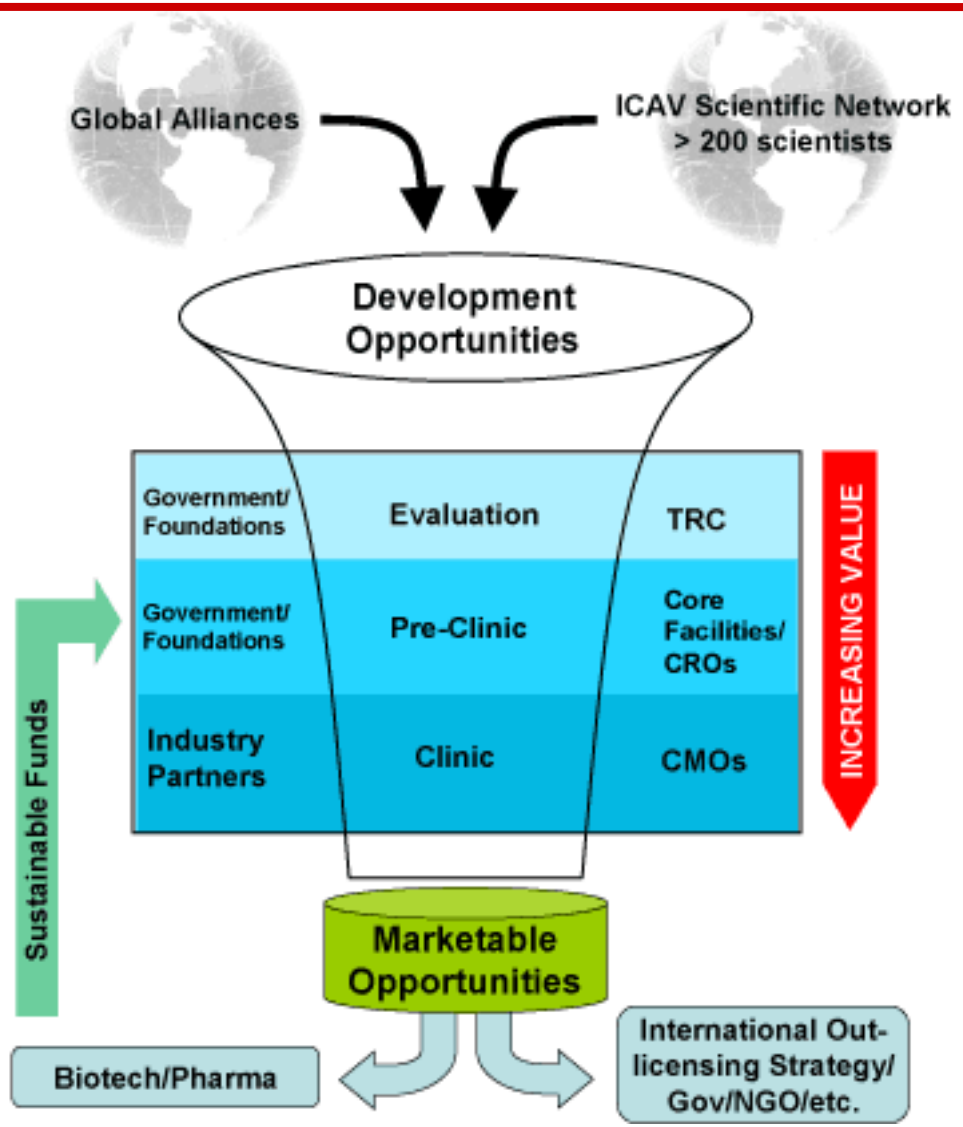


Green: p85 N-SH2 domain

White: NS1 effector domain

J. Tan, S. Chen (2009)

How can development of antivirals be financed? The International Consortium on Antivirals (ICAV)



Jeremy Carver, CEO
Michel Chrétien

Jacques Chirac
Jean Chrétien

www.icav-citav.ca

International Consortium on Antivirals (ICAV)

Vision

Global access to affordable anti-viral therapies for neglected and emerging viral diseases.

Mission

Through the international collaboration of scientists, governments and industry, ICAV accelerates the discovery and development of novel anti-viral therapies. ICAV will ensure the delivery of these therapies to those most in need.

Objective

The delivery of one novel anti-viral drug to market every five years.

THE END

Thank you!

Im Focus das Leben

Universität zu Lübeck