

Tollwut

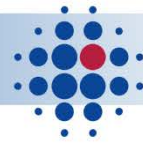


Forschungsergebnisse und Forschungsbedarf zu einer vernachlässigten Zoonose

Conrad Freuling

Zoonosenforschungsverbund Tollwut/Lyssaviren

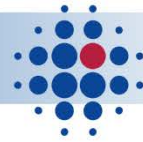




Tollwut

Eine der ältesten bekannten Zoonosen





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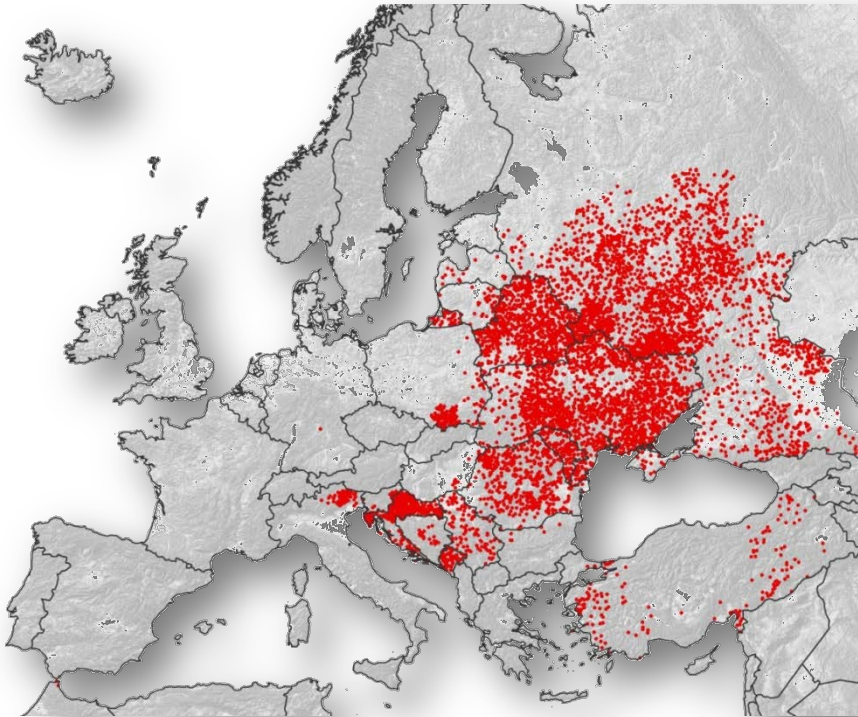
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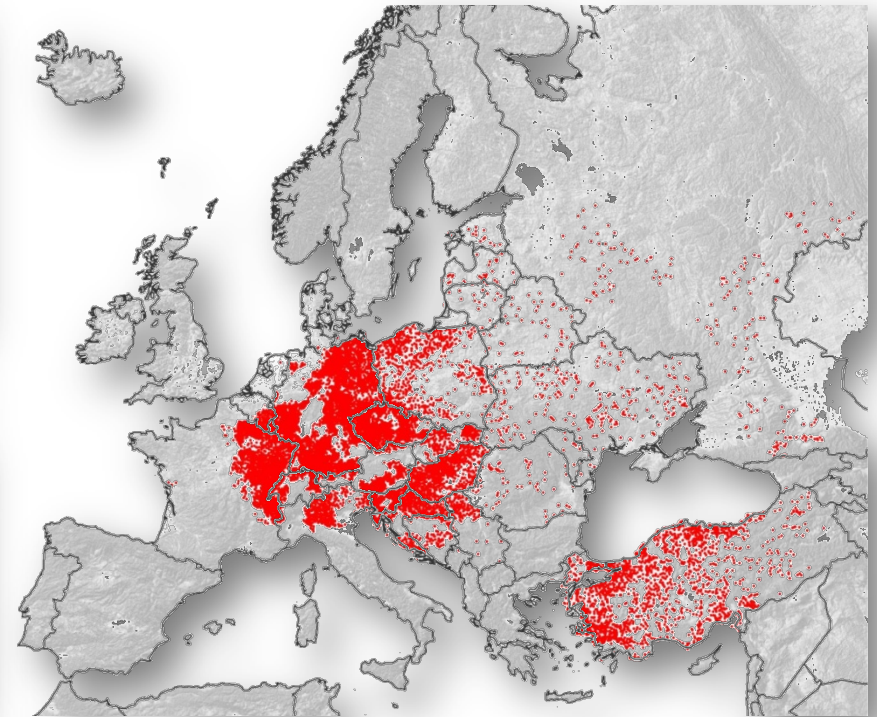
Tollwut

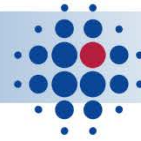
Erfolgreiche Bekämpfung in Europa

2012



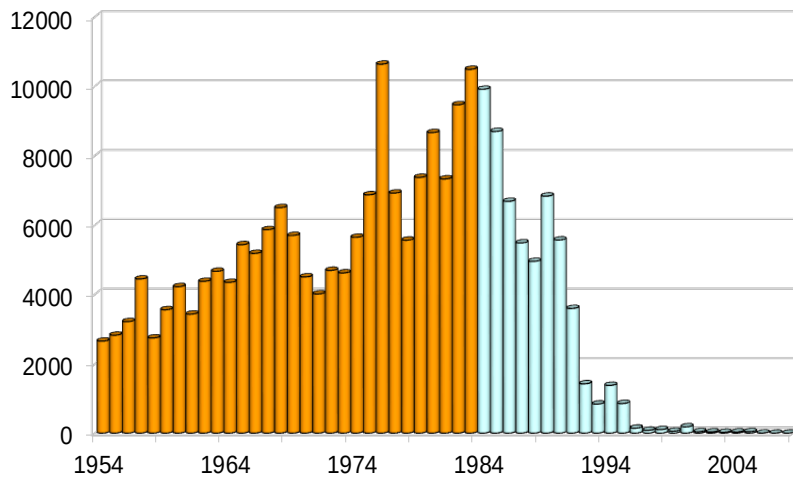
1983

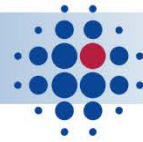




Tollwut

Deutschland ist tollwutfrei!

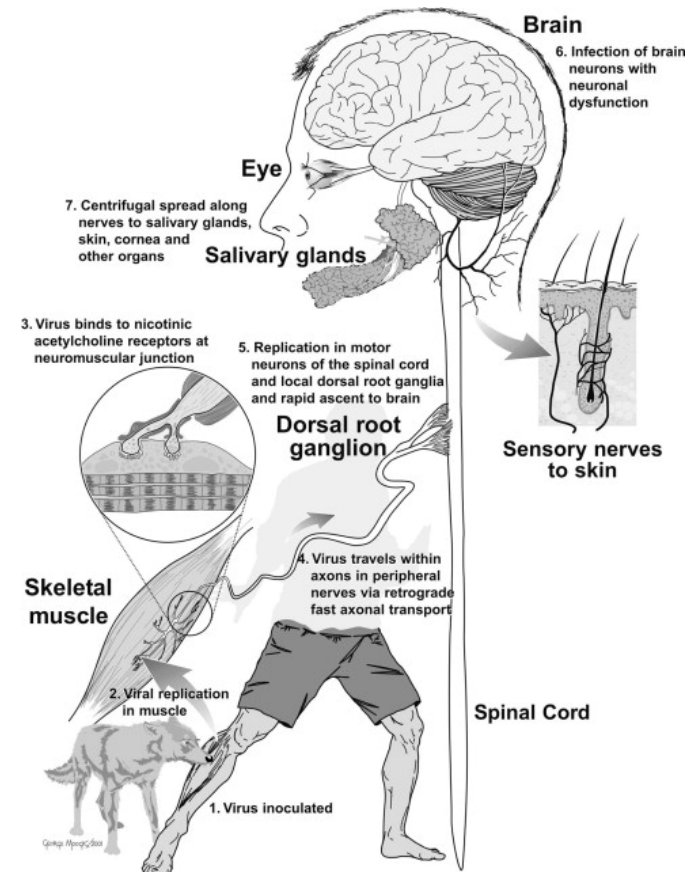


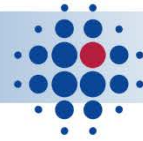


Tollwut

Eine “neglected zoonotic disease”

- Rabies
- Echinococcosis
- Taeniasis/cysticercosis
- Foodborne trematodiasis
- Human African trypanosomiasis
- Leishmaniasis
- Schistosomiasis

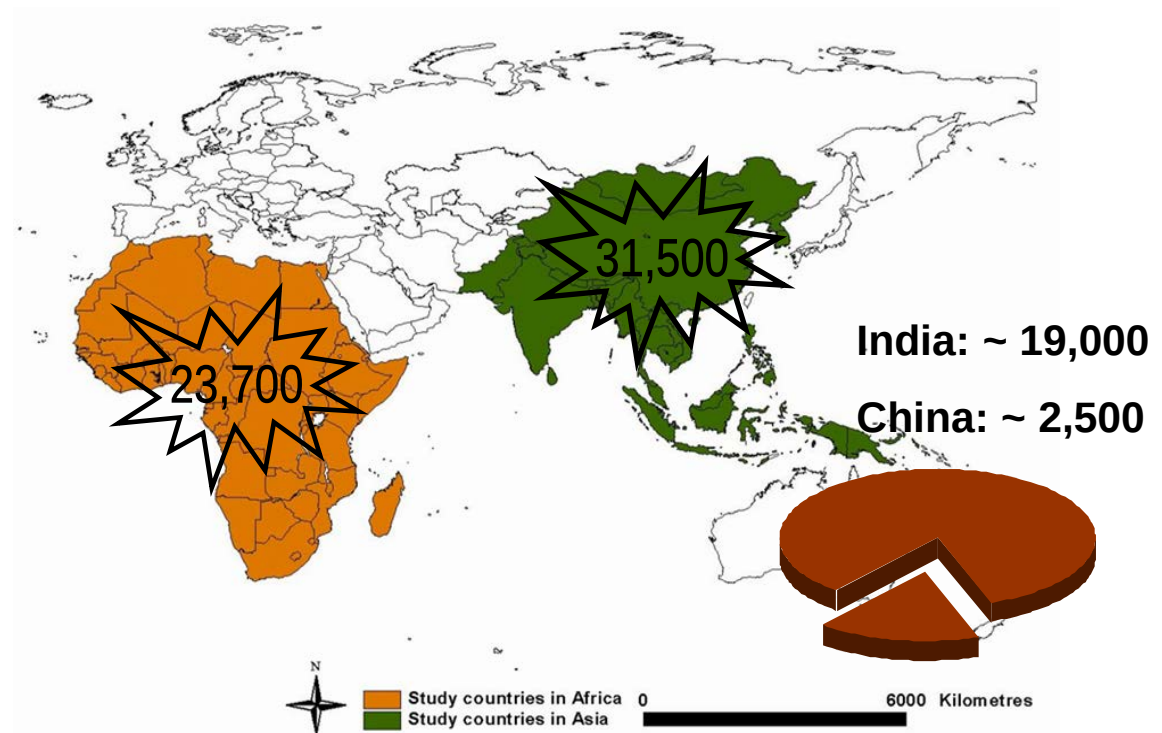




Tollwut

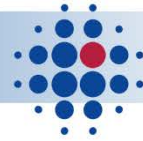
Eine “neglected zoonotic disease”

■ Rabies



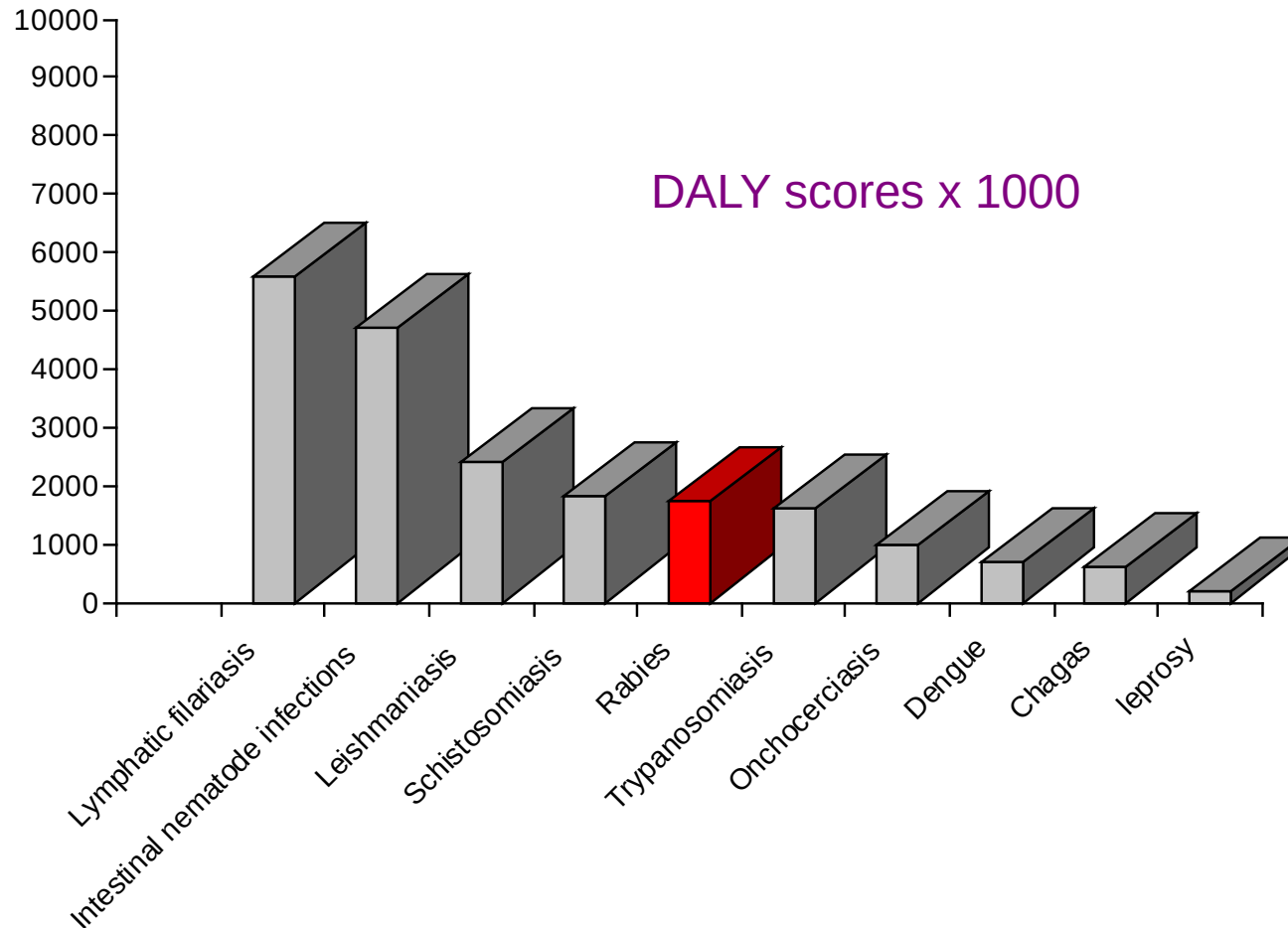
Knobel et al., Bulletin
WHO,

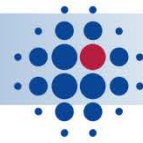
83: 360-368,2005



Tollwut

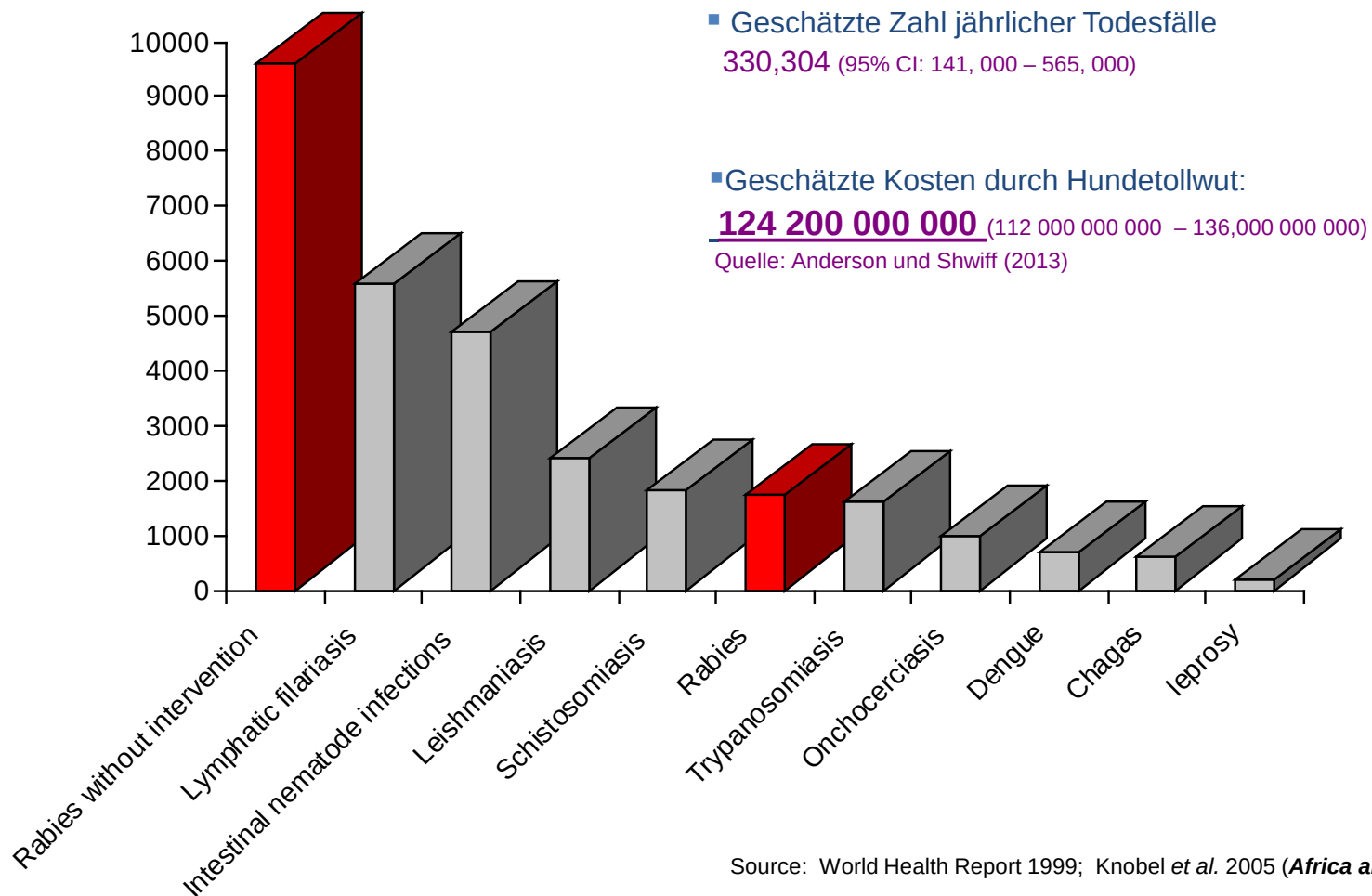
Bedeutung der “neglected zoonotic diseases”





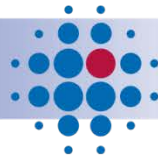
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Bedeutung der “neglected zoonotic diseases”





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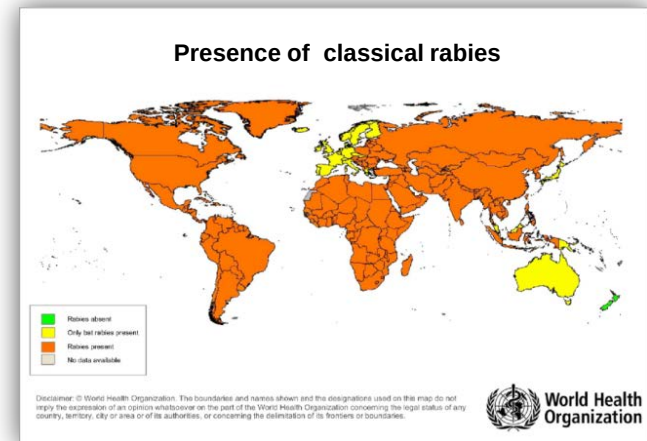
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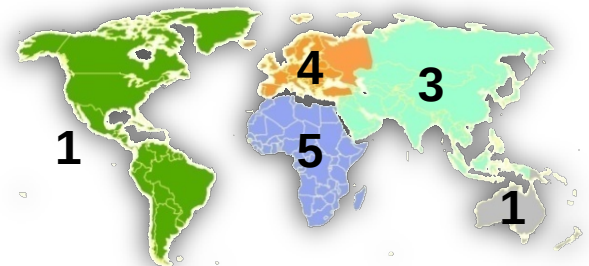
Die Erreger: Lyssaviren

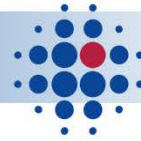
Reservoirspezies & geographische Verbreitung

Species	Spread	Reservoirs
RABV	worldwide	mammals
		chiroptera
LBV	Africa	Chiroptera
MOKV	Africa	???
DUVV	Africa	chiroptera
EBLV 1	Europe	chiroptera
EBLV 2	Europe	chiroptera
ABLV	Australia	chiroptera
ARAV	Asia	chiroptera
KHUV	Asia	chiroptera
IRKV	Asia	chiroptera
WCBV	Asia	chiroptera
SHIBV	Africa	chiroptera
BBLV	Europe	chiroptera
IKOV	Africa	chiroptera



Bat lyssaviruses





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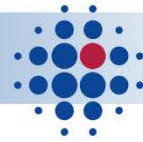
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Der Forschungsverbund Tollwut

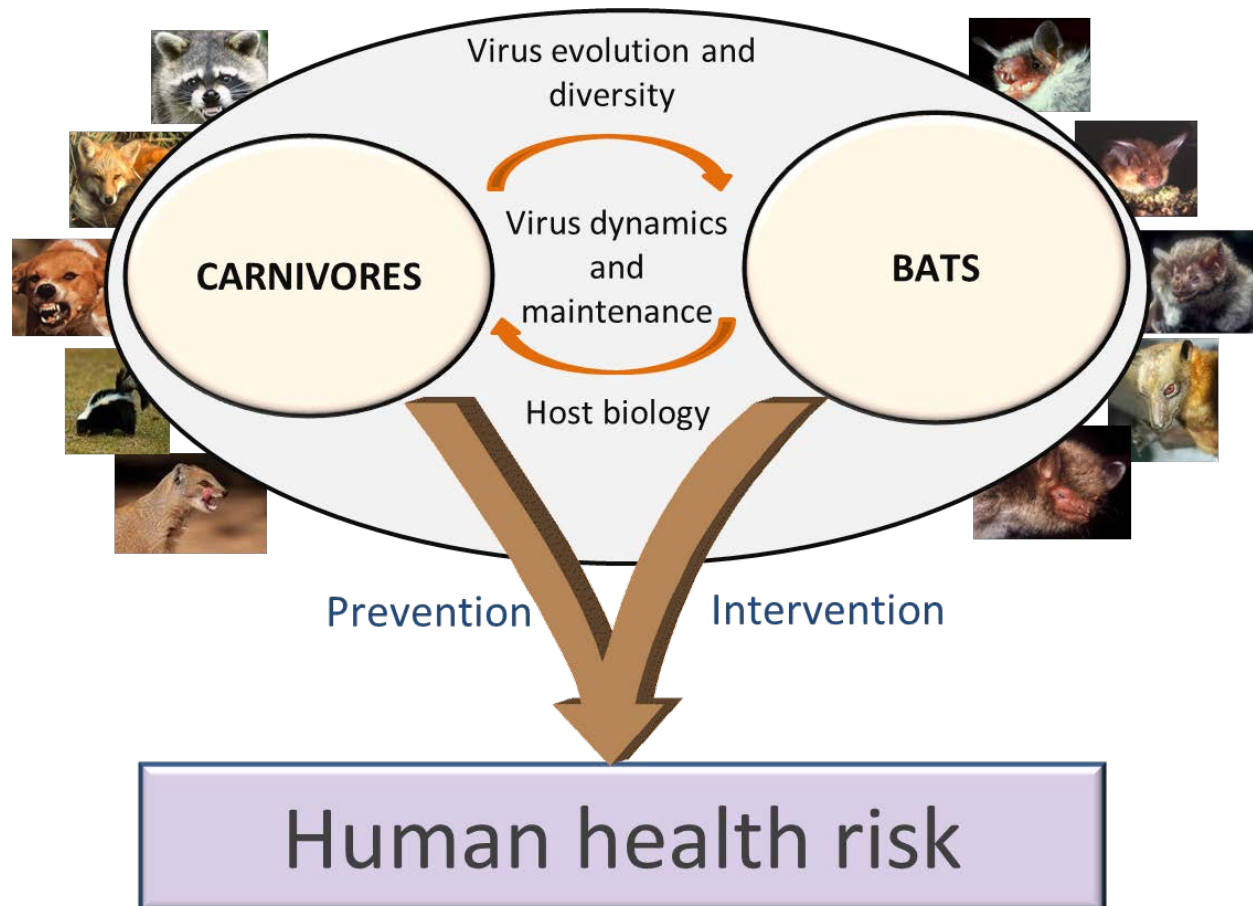
Bündelung nationaler und internationaler Kompetenzen

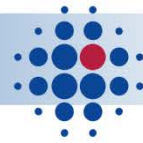




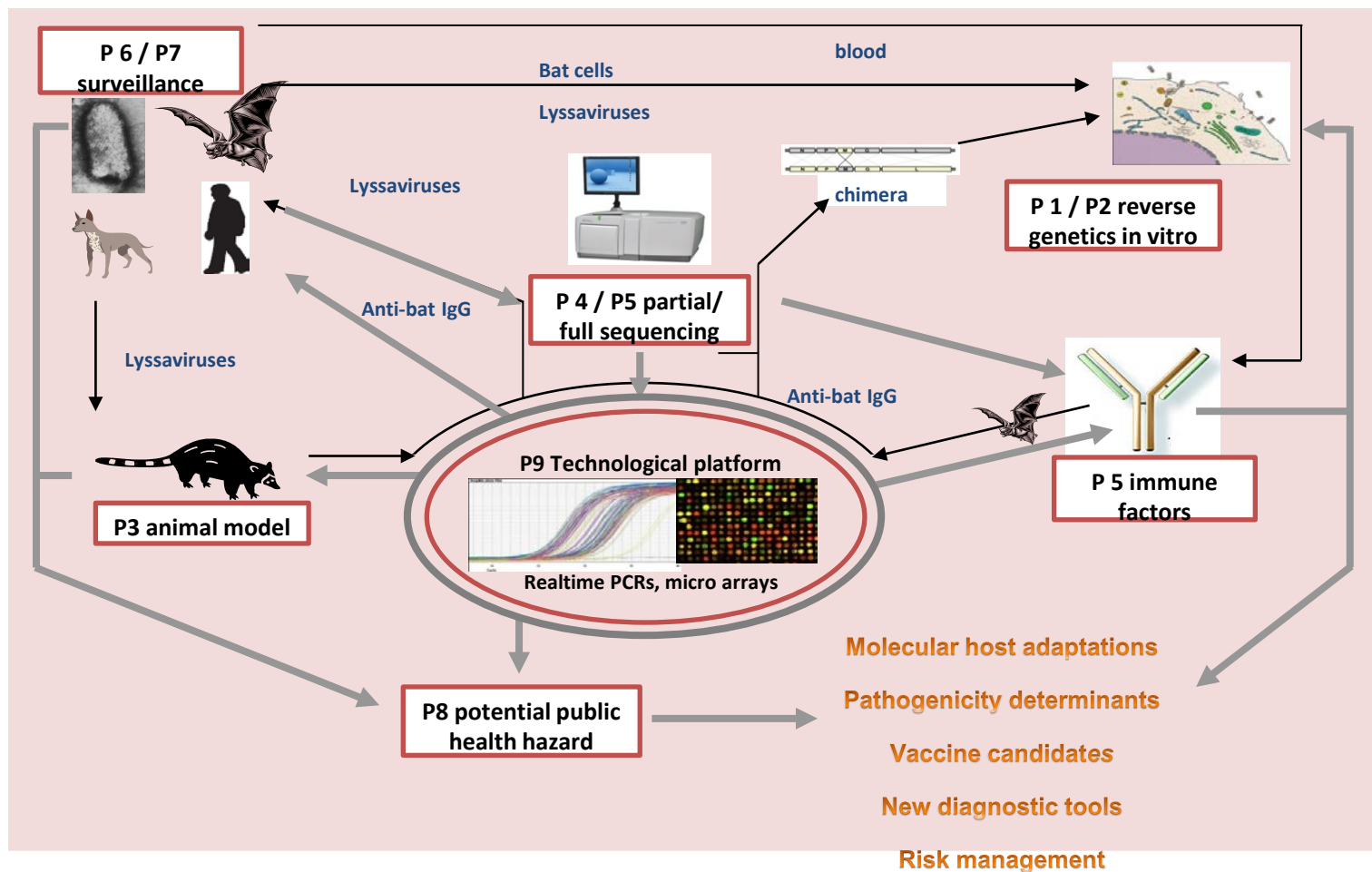
Der Forschungsverbund Tollwut

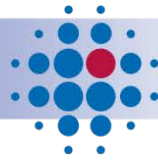
Lyssavirus Research Network





Der Forschungsverbund Tollwut Vernetzung





Work package leaders



Co-ordinator

Thomas Müller

Deputy

Conrad Freuling



WP1

WP2

WP3

WP4

WP5

WP6

WP7

WP8

WP9

Stefan
Finke

Karl-Klaus
Conzelmann

Adriaan
Vos

Dirk
Höper

Bernd
Köllner

Christian
Drosten

Conrad
Freuling

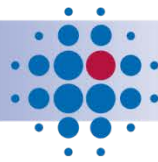
Stefan
Ross

Martin
Beer

Bernd
Hoffmann



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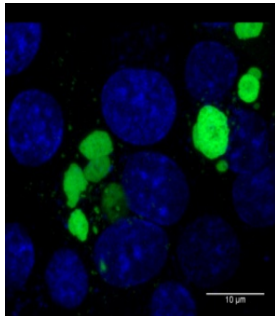
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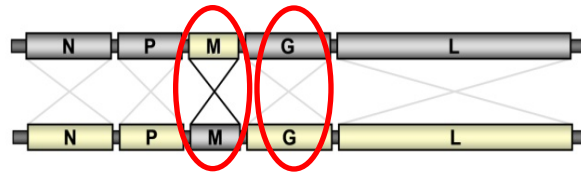
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WP 1

Lyssaviral envelope proteins and their contribution to host range and pathogenicity

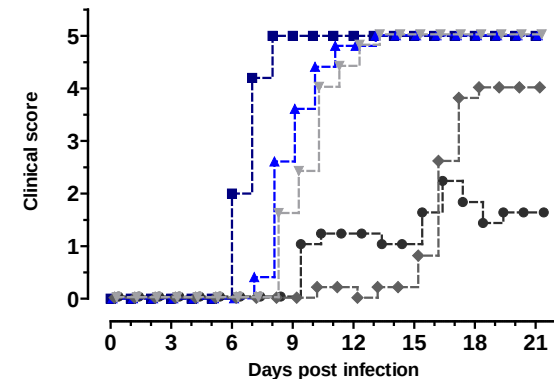
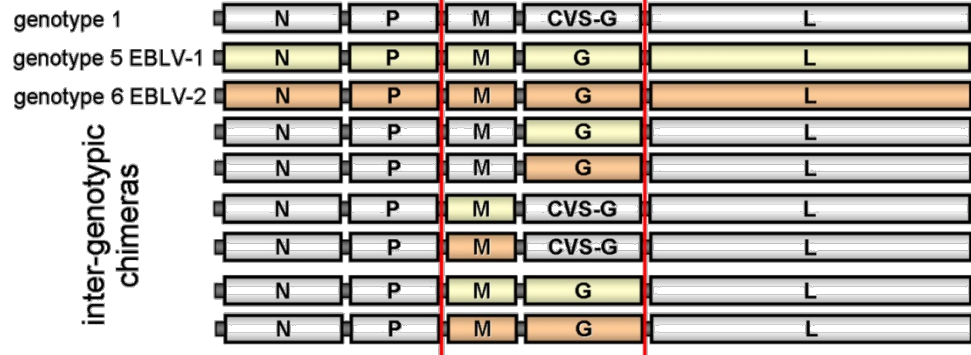


RABV backbone



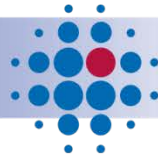
- Identification of G-dependant pathogenicity & transmission
- Identification and characterization of M-dependant viruselimination

RABV backbone





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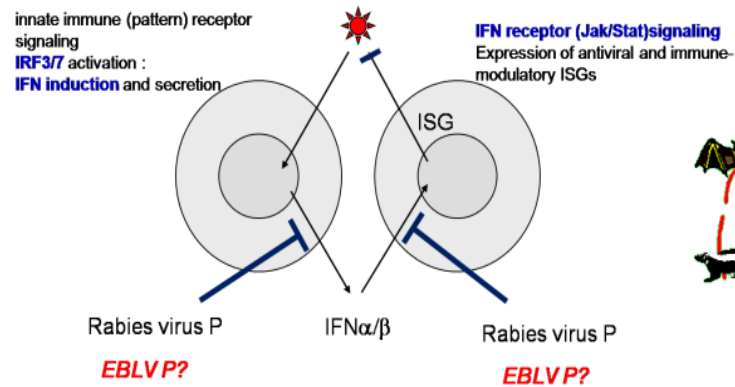
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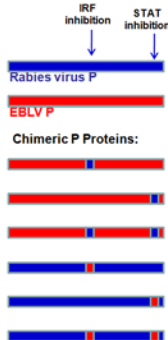


WP 2

The phosphoprotein – a key virulence and host range factor of rabies-like viruses



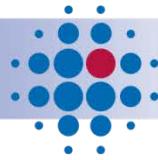
IRF and STAT
domain
mutations



- P is rabies virus IFN antagonist
 - Inhibits IRF3/7 activation and thus IFN induction
 - Inhibits JAK/STAT signaling and thus IFN-mediated antiviral response
- IFN-beta induction only blocked by RABV and EBLV-1
- Funktional species barrier for phylogroup 2 and 3 members



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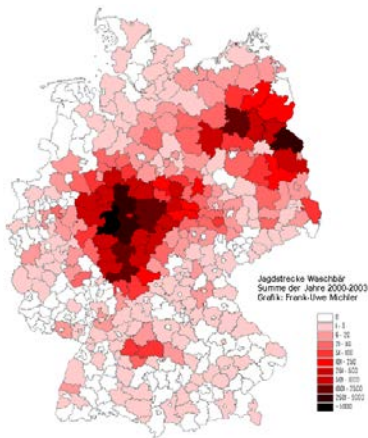
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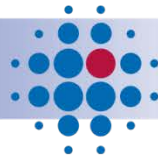
WP 3

Potential emerging rabies hosts - raccoon





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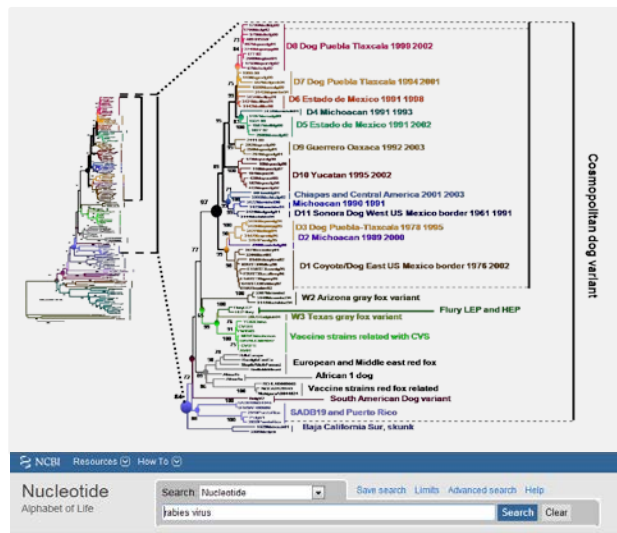
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WP 4

Whole genome sequencing, virus-host adaptation, and molecular epidemiological analyses of lyssaviruses



- Identification of an independent cycle in herbivores
- Complete genome analyses of field and vaccine samples (70)
- Viral quasispecies analysis in cell culture adapted viruses and field viruses
- Combining host and viral phylogeny for RABV in Greenland

Display: RefSeqs Summary, 20 per page. Sorted by None

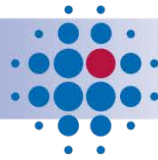
Found 11298 nucleotide sequences. Nucleotide (11297) EST (1)

Results: 1 to 20 of 11297

1. [Rabies virus strain_4102C108.glycoprotein \(G\) gene, partial cds, and G-L intergenic spacer, partial sequence](#)
1,305 bp linear cRNA
GU123662.1 GI:262480439
[Related sequences](#)
2. [Rabies virus strain_7578C105.glycoprotein \(G\) gene, partial cds, and G-L intergenic spacer, partial sequence](#)
1,305 bp linear cRNA
GU123661.1 GI:262480437
[Related sequences](#)
3. [Rabies virus strain_6979C105.glycoprotein \(G\) gene, partial cds, and G-L intergenic spacer, partial sequence](#)
1,305 bp linear cRNA
GU123660.1 GI:262480435
[Related sequences](#)



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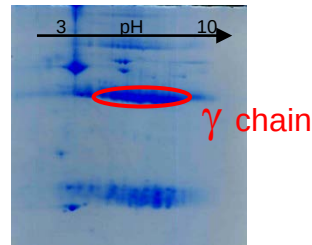
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WP 5

Humoral and cellular adaptive immune reactions of raccoons & European bats against „emerging viruses“



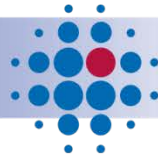
Poly- and monoclonal antibodies specific to immunoglobulines from



- Characterisation of immunoglobulines
 - Poly and monoclonal anti-bat-IgG
 - Poly and monoclonal anti-raccoon-IgG
- ELISA for IgG
- Transcriptom analysis
- Interferon Kappa and Omega (bats)
- Permanent cell lines (bats)



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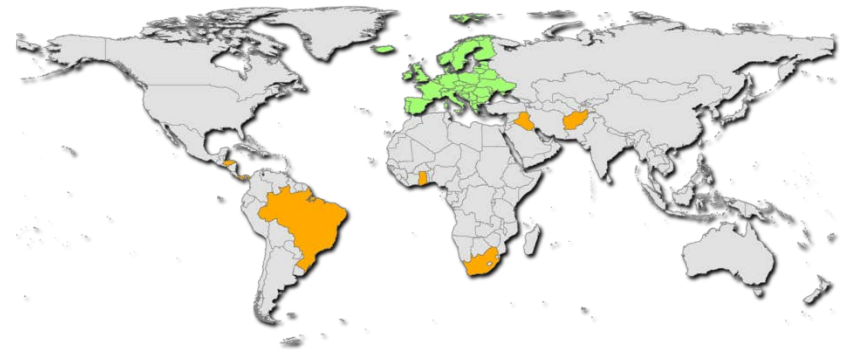
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universitäts
klinikum **bonn** Institut für Virologie

WP 6

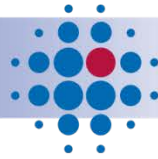
Bat-borne Lyssaviruses as neglected causes of viral encephalitis in Africa and Brazil

- ecological and virological species barriers
- prevalence of LVs in fruit-eating bats
 - Isolation of LBV in an apparently healthy bat
- Generation of bat cell lines from *E. helvum*
- Detection of a novel bat-Rhabdovirus
- transmissibility to humans and livestock by cell culture models





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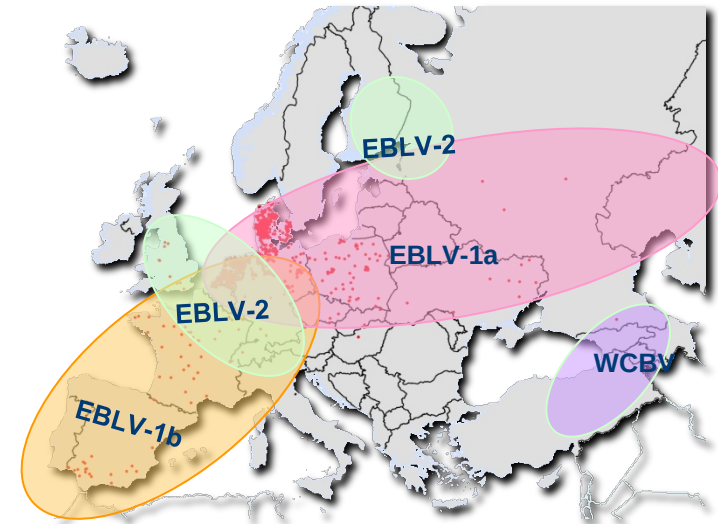
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WP 7

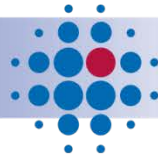
Establishing passive and active surveillance of bat related lyssaviruses in indigenous bat species in Europe

- Detection of a Bokeloh bat lyssavirus, a novel lyssavirus
- Enhanced passive surveillance: additional cases for EBLV-1, 2 and BBLV
- Active surveillance: few positives





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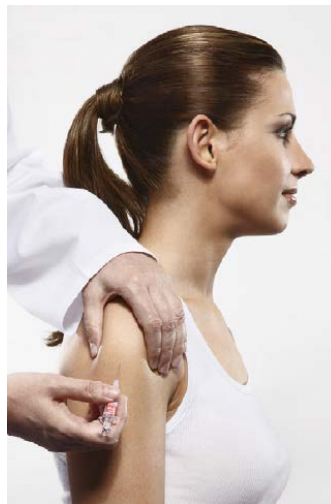
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WP 8

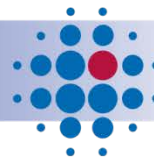
The potential public health hazard of rabies – perception by the general population
& the medical community in Germany



- Rabies assessment Germany
 - Knowledge on rabies limited
 - Both general public and human medicine
 - Exposition rate halved after rabies-free declaration
 - Annually ca 20.000 doses of RABV vaccines
 - Not possible to further assess



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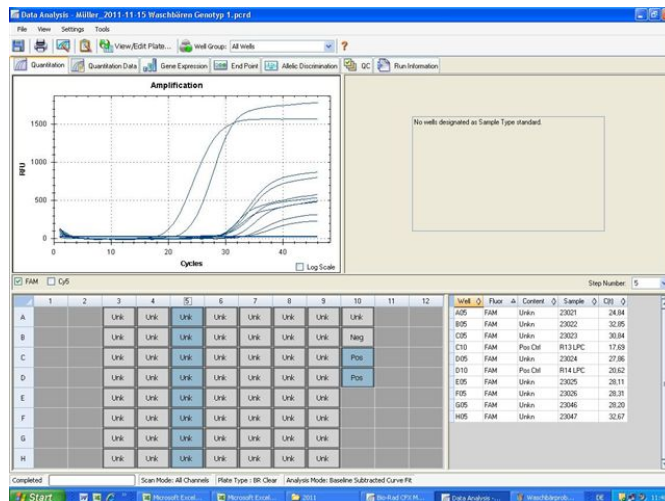
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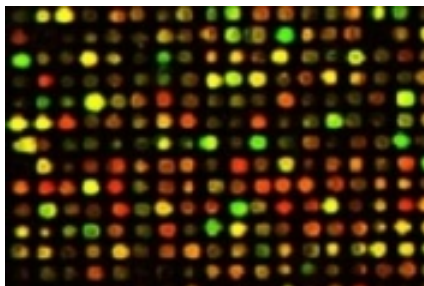
WP 9

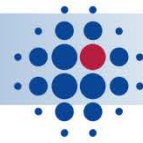
Development and validation of molecular methods for genome detection and characterization of all lyssaviruses



Technology platform

- Development and establishment of fully validated, standardized and applicable real-time RT-PCR and microarray systems
- Ring trials
- Pan-Lyssa (N-and L-Gene)





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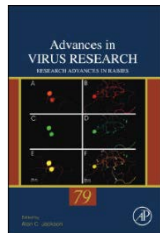
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Lyssavirus

Publikationen innerhalb des Verbundes



OPEN ACCESS freely available online

Diversity and Epidemiology of Mokola Virus

Jon Kopelav¹, Nicolette Wiegand¹, Jessica Coenen¹, Wanda Markter¹, Dennis Marston¹, Anthony R. Fooks², Conrad M. Freuling³, Thomas F. Müller⁴, Claude T. Sabet⁵, Louis H. Nat⁶

¹Department of Virology and Plant Pathology, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa, ²NIH, Division of Zoonotic and Infectious Diseases, National Center for Infectious Diseases, Division of Field Epidemiology, Centers for Disease Control and Prevention, Atlanta, Georgia, ³Department of Virology, Animal Health Research Laboratory, University of Veterinary Medicine, Vienna, Austria, ⁴Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁵Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁶Department of Virology, University of Veterinary Medicine, Vienna, Austria



Lyssavirus distribution in naturally infected bats from Germany

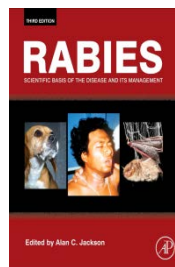
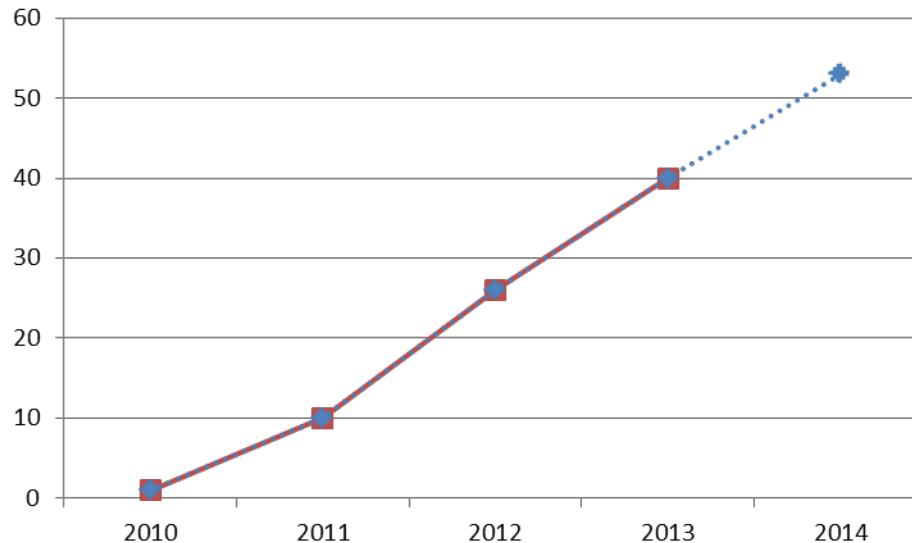
J. Schatz¹, J.P. Triller², T.C. Mettenleiter¹, A. Aue³, D. Stiel⁴, T. Müller¹, C.M. Freuling^{1,5}

¹Department of Virology, Friedrich-Loeffler-Institut, Greifswald, Germany, ²Department of Virology, University of Veterinary Medicine, Vienna, Austria, ³Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁴Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁵Department of Virology, University of Veterinary Medicine, Vienna, Austria

A Step Forward in Molecular Diagnostics of Lyssaviruses – Results of a Ring Trial among European Laboratories

Malina Fischer¹, Kerstin Wernke¹, Conrad M. Freuling², Thomas Müller³, Oshan Aylan⁴, Bernard Brechler⁵, Florence Clouet⁶, Sonia Vázquez-Morén⁷, Peter Hostnik⁸, Anika Haavilainen⁹, Mats Isaksson¹⁰, Engbert A. Kool¹¹, Jean Mooney¹², Mihai Turcu¹³, Thomas B. Rasmussen¹⁴, Sandra Revilla-Fernández¹⁵, Marcin Smieszek¹⁶, Anthony R. Fooks¹⁷, Dennis A. Marston¹⁸, Martin Beer¹⁹, Bernd Hoffmann²⁰

¹Institute of Diagnostic Virology, Friedrich-Loeffler-Institut, Greifswald, Germany, ²Institute of Molecular Biology, Friedrich-Loeffler-Institut, Greifswald, Germany, ³Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁴Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁵Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁶Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁷Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁸Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ⁹Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁰Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹¹Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹²Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹³Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁴Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁵Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁶Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁷Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁸Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ¹⁹Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ²⁰Institute of Virology, University of Veterinary Medicine, Vienna, Austria



Novel Lyssavirus in Natterer's Bat, Germany

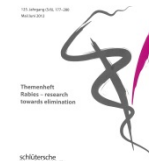
Conrad M. Freuling, Martin Beer, Franz J. Conrath, Stefan Fink, Bernd Hoffmann, Barbara Keller, Jeannette Kient, Thomas C. Mettenleiter, Elke Muhlebach, Jens P. Tielke, Peter Wochowicz, and Thomas Müller

A virus isolated from a Natterer's bat (*Myotis nattereri*) in Germany was differentiated from other lyssaviruses on the basis of the nucleotide sequence of a panel of monoclonal antibodies. Phylogenetic analysis supported the assumption that the isolated virus, which had dynamics, may represent a new member of the genus *Lyssavirus*.

bat (*M. nattereri*) and *M. daubentonii* and has only sporadically been found in Europe and in Germany (?). The transmission of EBLV-1 and EBLV-2 in bats is Europe is still only poorly understood. (5) We report lyssavirus infection in a Natterer's bat.

The Study
In November 2009, a bat was found on the ground in Ditzelsdorf, Lower Saxony, Germany (52°21'13.93"N, 9°51'31.50"E). The bat was morphologically identified as a Natterer's bat (*M. nattereri*). It was given necropsy and was autopsied with subsequent virus isolation. In February 2010, the bat began to act aggressively, directly approaching any moving object, vigorously trying to bite, and screaming frequently. This agitated state lasted 7 days and was followed by general weakness, lethargy, and paralysis. After the first 3 days of the clinical course, the bat stopped drinking and eating. Ten days after recognition

BERLINER UND MÜNCHENER
TIERÄRZTLICHE
WOCHENSCHRIFT



PHILOSOPHICAL
TRANSACTIONS
OF
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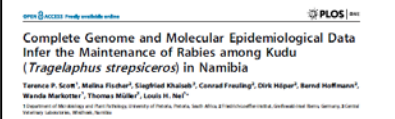
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Research
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The elimination of fox rabies from Europe: determinants of success and lessons for the future

Conrad M. Freuling¹, Kate Hampson², Thomas Sellens³, Ronald Schödl⁴, Francis X. Meaker⁵, Thomas C. Mettenleiter⁶ and Thomas Müller⁷

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Complete Genome and Molecular Epidemiological Data Infer the Maintenance of Rabies among Kudu (*Tragelaphus strepsiceros*) in Namibia

Tamara P. Scott¹, Malina Fischer², Singhal Khushf³, Conrad Freuling⁴, Dirk Höper⁵, Bernd Hoffmann⁶, Wanda Markter⁷, Thomas Müller⁸, Louis H. Nat⁹

¹Department of Virology and Plant Pathology, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa, ²Institute of Virology, University of Veterinary Medicine, Vienna, Austria, ³Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁴Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁵Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁶Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁷Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁸Department of Virology, University of Veterinary Medicine, Vienna, Austria, ⁹Department of Virology, University of Veterinary Medicine, Vienna, Austria

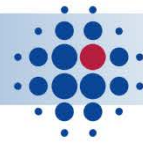
Twenty years of active bat rabies surveillance in Germany: a detailed analysis and future perspectives

J. Schatz¹, B. Ohlendorf², P. Buss³, G. Felz⁴, D. Dolch⁵, J. Teubner⁶, J. A. Encarnação⁷, R.-U. Mehl⁸, M. Fischer⁹, B. Hoffmann¹⁰, L. Kwasnitschka¹¹, A. Balke-Buschmann¹², T. C. Mettenleiter¹³, T. Müller¹⁴, and C. M. Freuling¹⁵



Control and prevention of canine rabies: The need for building laboratory-based surveillance capacity

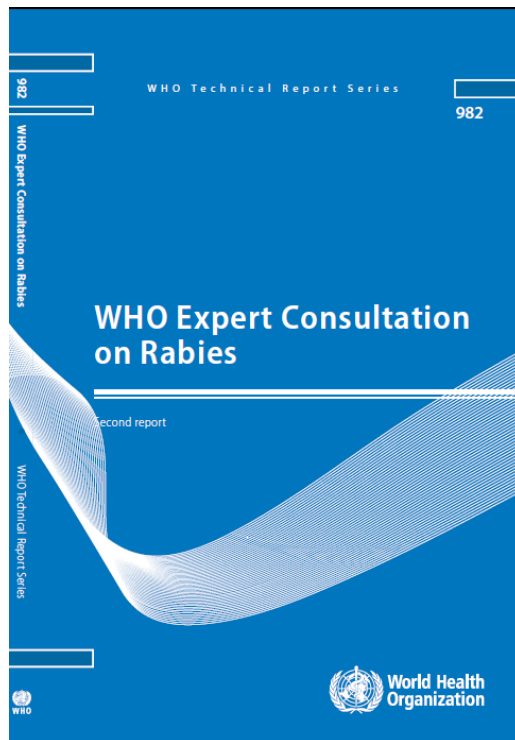
Ashley C. Banyard¹, Daniel L. Horton², Conrad Freuling³, Thomas Müller⁴, Anthony R. Fooks^{5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}



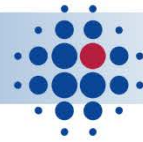
Lyssavirus

Herausforderungen und Forschungsbedarf

- WHO definierter Forschungsbedarf



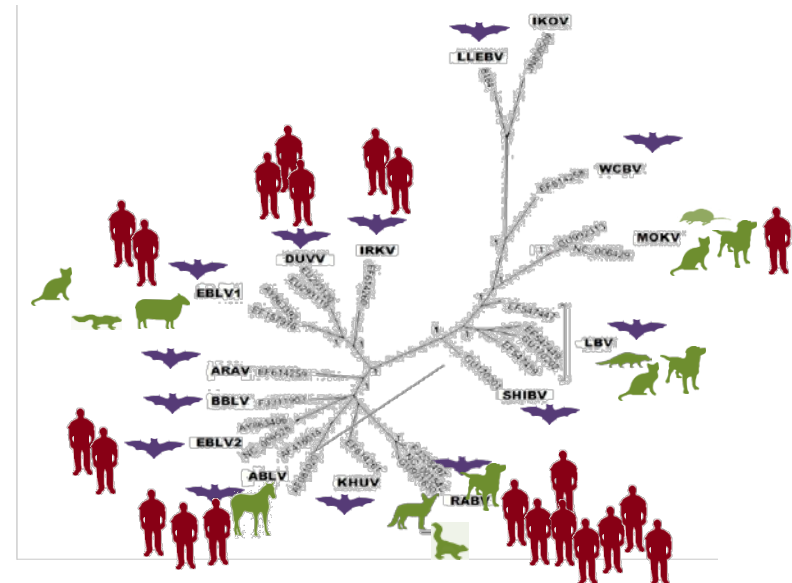
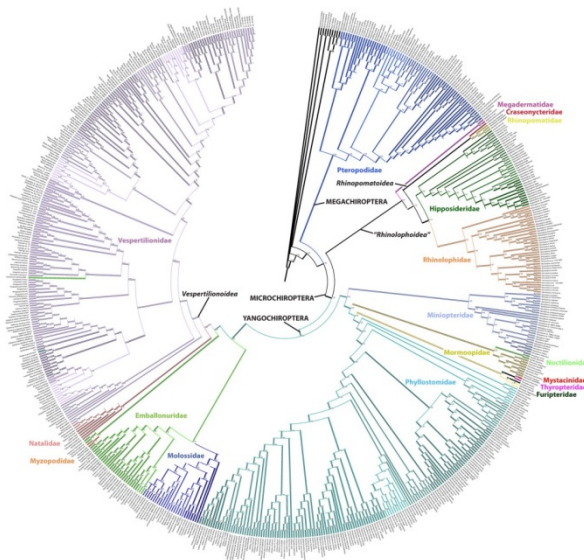
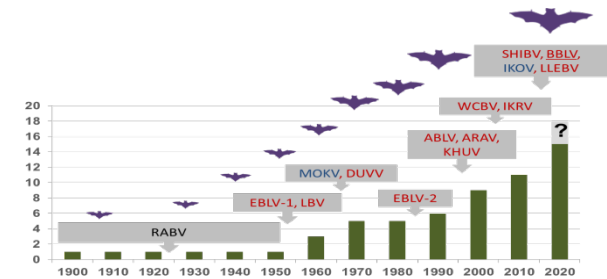
- Diagnostics
- Epidemiology
- Characterization of viral isolates
- Biological medical products
- Human rabies prophylaxis
- Pathobiology
- Host ecology

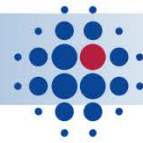


Lyssavirus

Herausforderungen und Forschungsbedarf

- Unbekannte Diversität der Lyssaviren
 - Fledermäuse sind die wahren Reservoirre
 - Aufbau einer permanenten Surveillance
 - Kopplung mit anderen Surveillanceaktivitäten

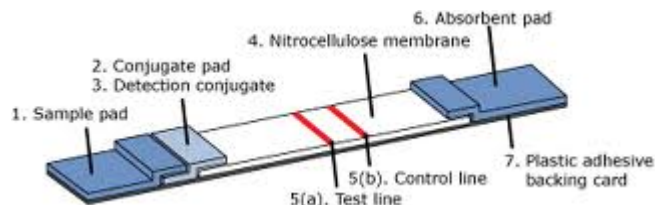


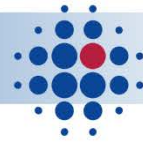


Lyssavirus

Herausforderungen und Forschungsbedarf

- Alternative dezentrale Nachweisverfahren
 - Logistische Probleme vor allem in Afrika
 - fehlende Infrastruktur, Laborkapazitäten
 - Mangelnde Surveillance
 - z.B. Lateral Flow Devices



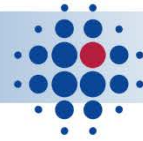


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Herausforderungen und Forschungsbedarf

- Invasive Spezies mit Vektorkompetenz
 - Z.B. Waschbär
 - Köder-Impfstoff-
 - Fehlende Strategien der Bekämpfung

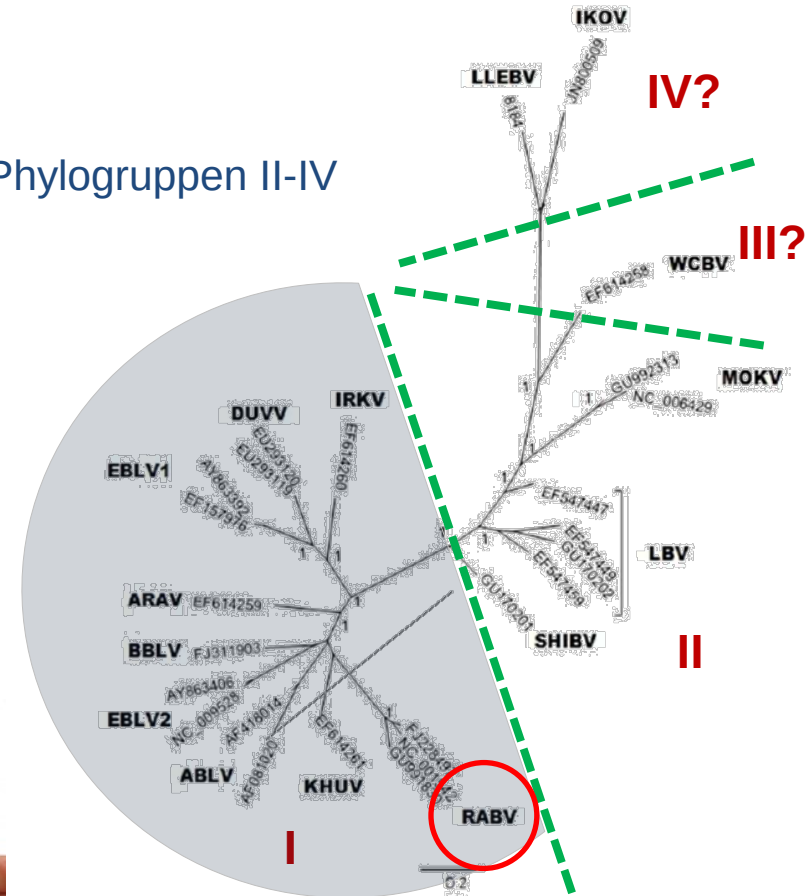


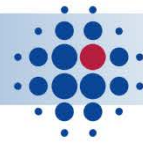


Lyssavirus

Herausforderungen und Forschungsbedarf

- Infektionsrisiko für Mensch & Tier
 - Kein Kreuzschutz für Lyssaviren der Phylogruppen II-IV
 - Unbekannter Schutz für BBLV

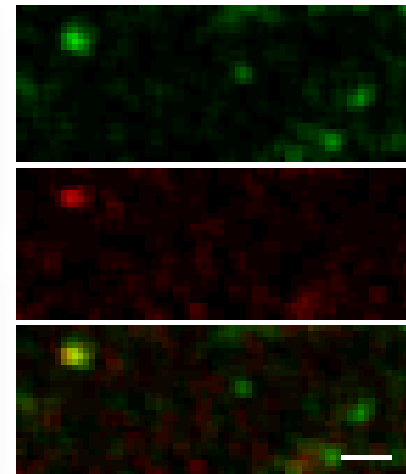
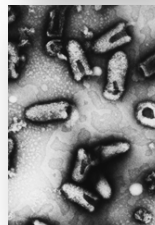
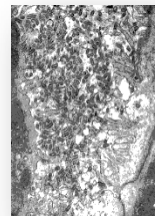
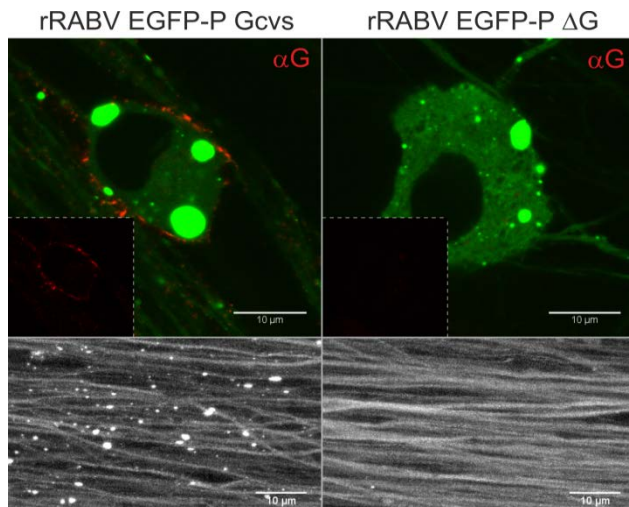




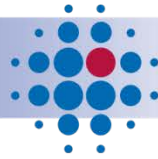
Lyssavirus

Herausforderungen und Forschungsbedarf

- Virale Neuroinvasion und Pathogenese
 - Tollwutvirus als Modell um Mechanismen zu erkennen
 - Angriffsmöglichkeiten für antivirale Moleküle



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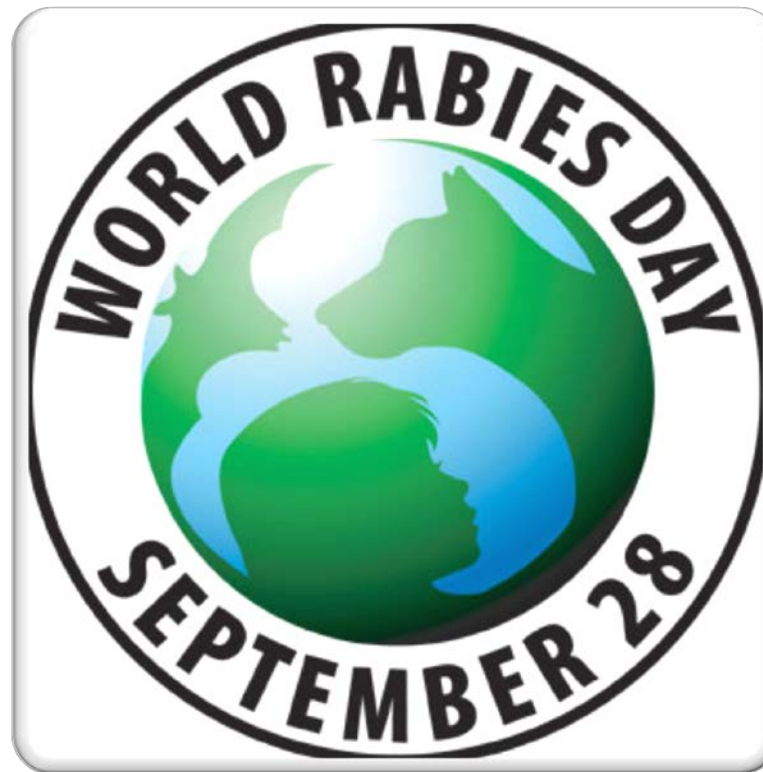
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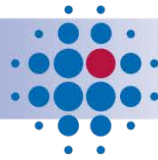
Working together to make rabies history

Internationale Initiative





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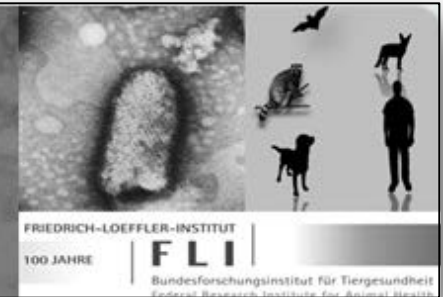
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Danksagung

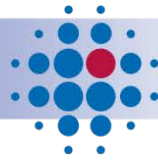
LYSSAVIRUS RESEARCH NETWORK

"LYSSAVIRUS - A POTENTIAL PUBLIC HEALTH RISK"

BMBF grant 01KI1016A



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