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9-23-2008

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Richard J. Kuhn

Purdue University, kuhnr@purdue.edu

Bärbel Kaufmann

Purdue University

Shee Mei Lok

Purdue University

Mick Cherrier

Purdue University

Rushika Perera

Purdue University

See next page for additional authors

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Recommended Citation

Kuhn, Richard J.; Kaufmann, Bärbel; Lok, Shee Mei; Cherrier, Mick; Perera, Rushika; Sedlak, Dagmar; Nybakken, Grant E.; Chipman, Paul R.; Zhang, Wei; Diamond, Michael S.; Fremont, Daved H.; and Rossmann, Michael G., "Structural Studies of West Nile Virus in Complex with Neutralizing Antibodies." (2008). *Department of Biological Sciences Faculty Publications*. Paper 57. <http://docs.lib.purdue.edu/bioscipubs/57>

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Authors

Richard J. Kuhn, Bärbel Kaufmann, Shee Mei Lok, Mick Cherrier, Rushika Perera, Dagmar Sedlak, Grant E. Nybakken, Paul R. Chipman, Wei Zhang, Michael S. Diamond, Daved H. Fremont, and Michael G. Rossmann

Oral presentation

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Structural studies of West Nile virus in complex with neutralizing antibodies

Richard J Kuhn*¹, Bärbel Kaufmann¹, Shee Mei Lok¹, Mick Cherrier¹,
Rushika Perera¹, Dagmar Sedlak¹, Grant E Nybakken², Paul R Chipman¹,
Wei Zhang¹, Michael S Diamond², Daved H Fremont² and
Michael G Rossmann¹

Address: ¹Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA and ²Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

Email: Richard J Kuhn* - kuhnr@purdue.edu

* Corresponding author

from Infectious diseases of the nervous system: pathogenesis and worldwide impact
Paris, France. 10–13 September 2008

Published: 23 September 2008

BMC Proceedings 2008, 2(Suppl 1):S25

This abstract is available from: <http://www.biomedcentral.com/1753-6561/2/S1/S25>

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West Nile virus (WNV) is a positive strand RNA virus in the family Flaviviridae, which includes members such as dengue, Japanese encephalitis, tick-borne encephalitis, yellow fever and Hepatitis C. As with other members of the genus, it is arthropod transmitted and has recently established itself as an endemic virus in the United States. Although most infections are asymptomatic, clinical manifestations of WNV include encephalitis and death. We have been interested in investigating the nature of the immune response with particular emphasis on the role of antibodies in reducing the level of infection. We have used a combination of techniques, but primarily structure, as a tool to probe the nature of antibody-mediated virus neutralization. Our results suggest that neutralization of virus particles is more complex than originally envisioned, with multiple mechanisms utilized. Using a combination of X-ray crystallography and cryo-electron microscopy, several virus-antibody complexes have been determined at pseudo-atomic resolution. These studies suggest the following: 1) flavivirus particles exhibit dynamic motions or breathing that transiently expose cryptic epitopes; 2) although there are 180 potential binding sites for each monoclonal antibody the quasi-equivalent nature of the virion usually permits only a subset of sites to be utilized; 3) the availability of these sites, the epitope itself, and the

avidity of antibody directly influence the mechanism of neutralization; and 4) particles thought to be incapable of infecting cells, so-called immature viruses, may play a critical role in immune surveillance and reactivity. The structure of the flavivirus virion and complexes of monoclonal antibodies will be presented along with data to support mechanisms antibody-mediated flavivirus neutralization.