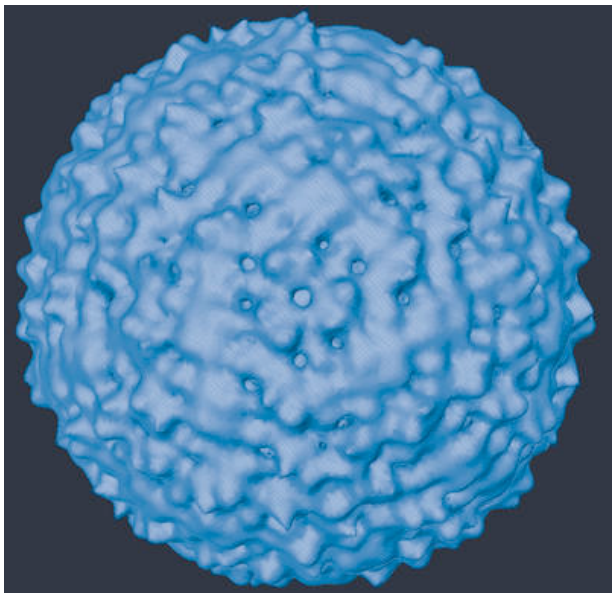
Contrasting Role of CCR5 in West Nile Virus and HIV Infection

Jean K. Lim, Ph. D.

National Institute of Allergy and Infectious Diseases

National Institutes of Health

WNV: Virologic characteristics



*Science; 2003 Oct 10

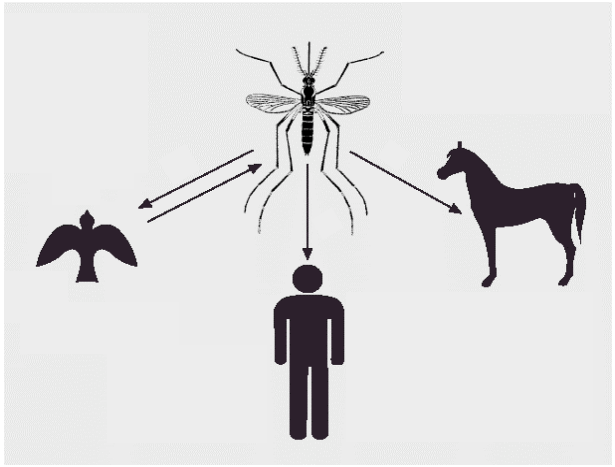
Virion – Enveloped virus, ~50nm sphere

Family – *Flaviviridae*

(includes JEV, Dengue, TBE, MVE)

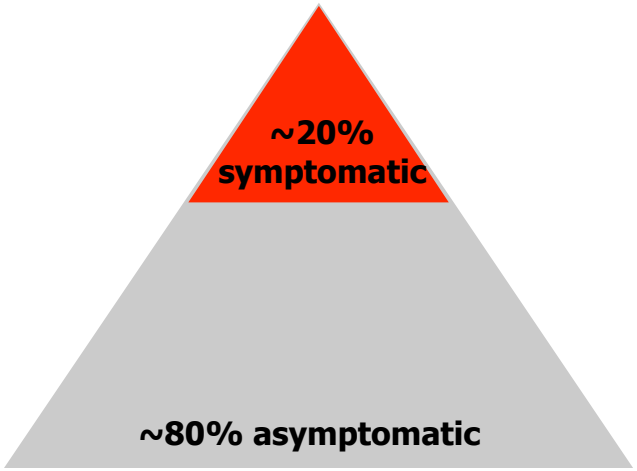
Genome – (+) single stranded RNA

WNV: Transmission and Clinical Manifestations



Reported WNV disease cases
United States, 1999-2005

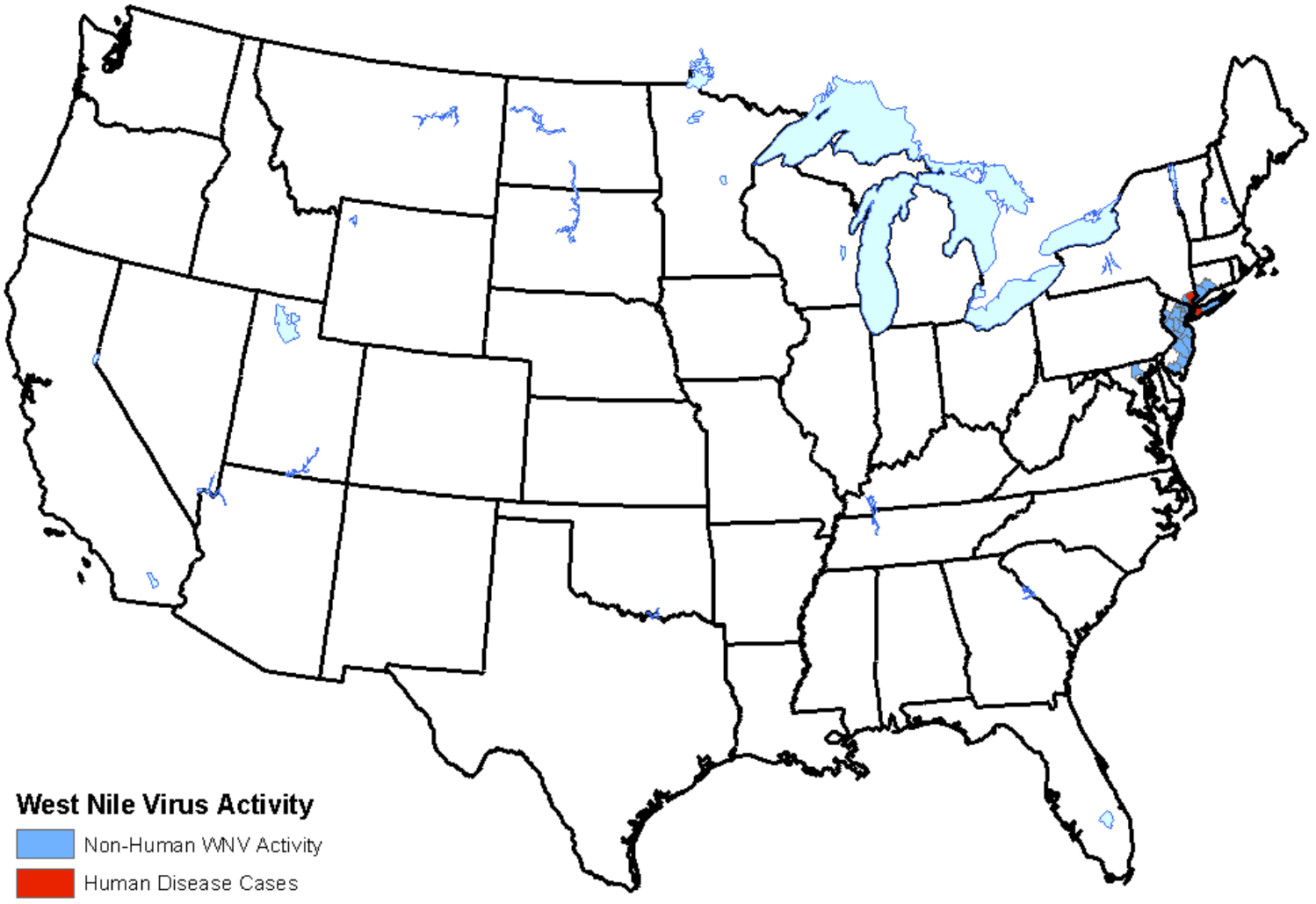
- Total Cases: 19,655
- Total Fatalities: 782 (~4.0%)



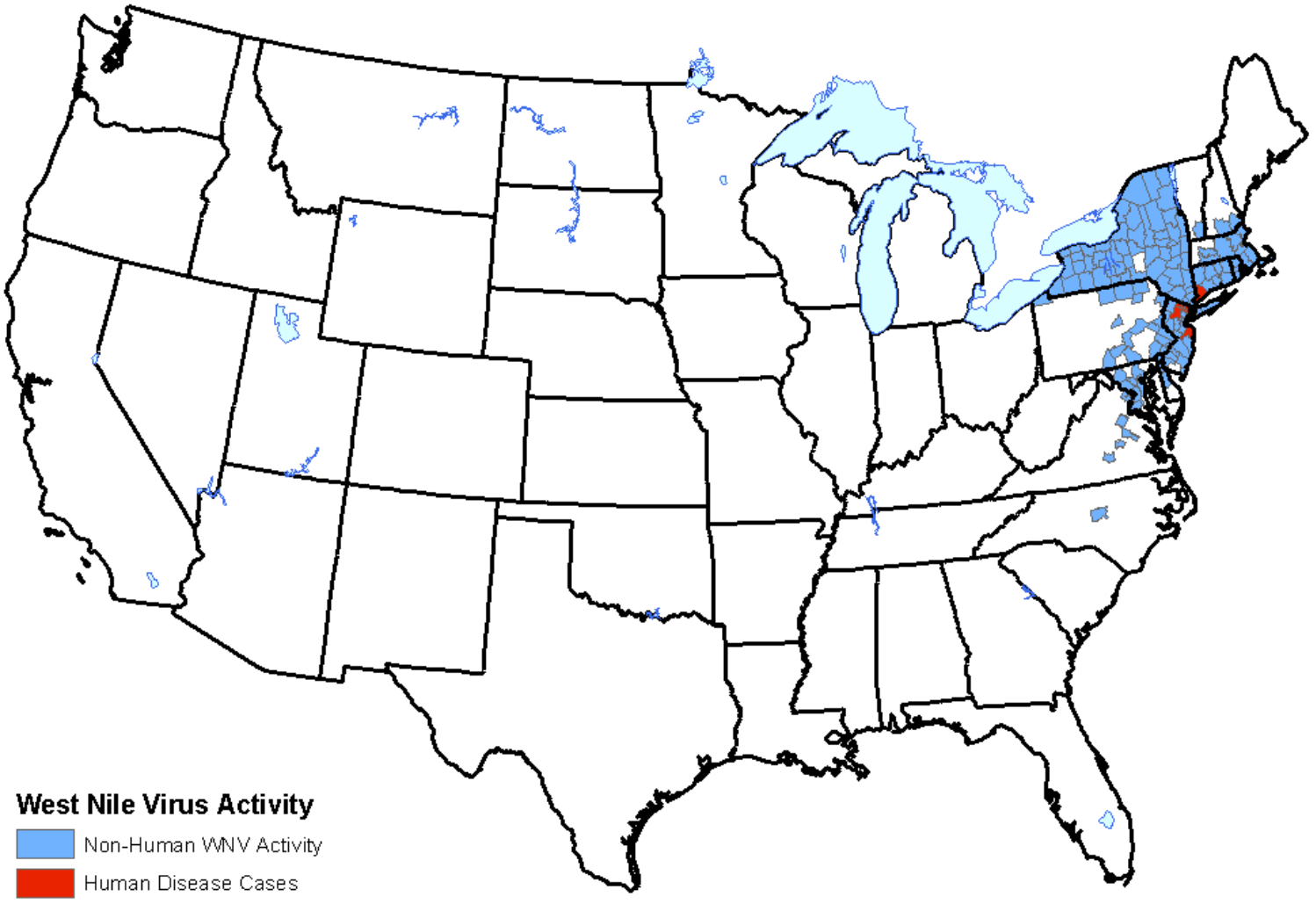
Symptomatic Disease

- West Nile Fever
- Meningitis
- Encephalitis
- Death

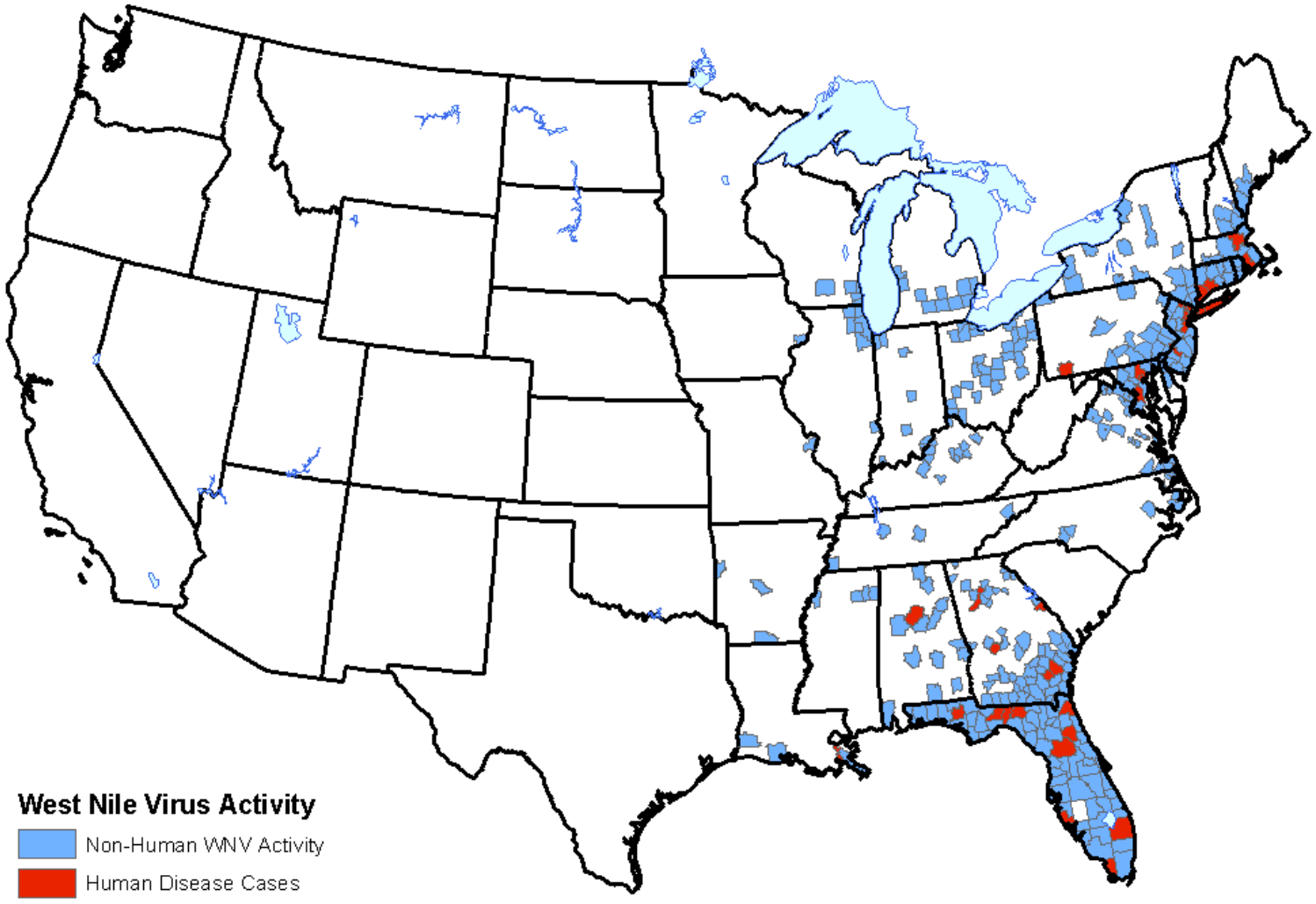
Spread of WNV in the US:1999



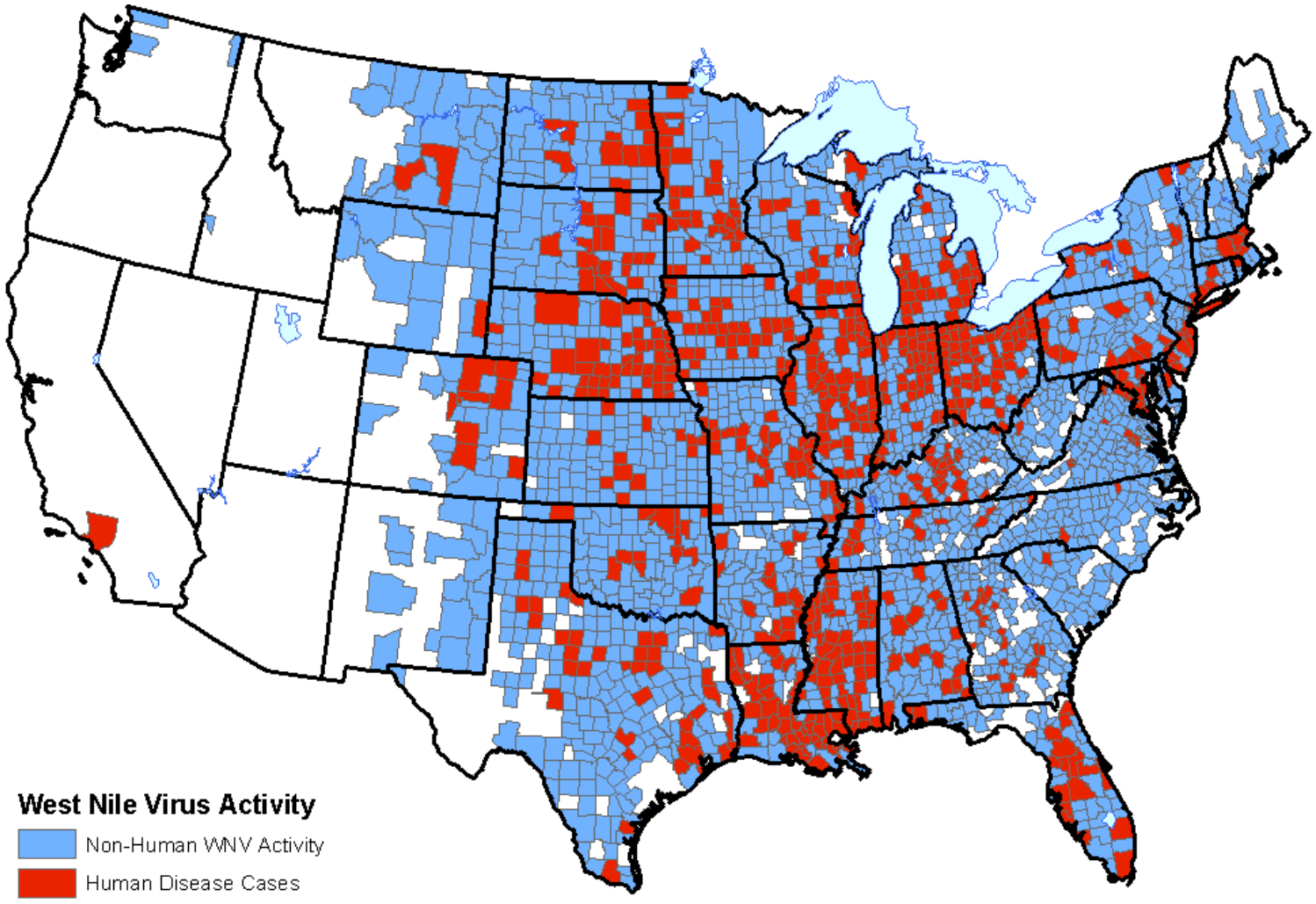
Spread of WNV in the US:2000



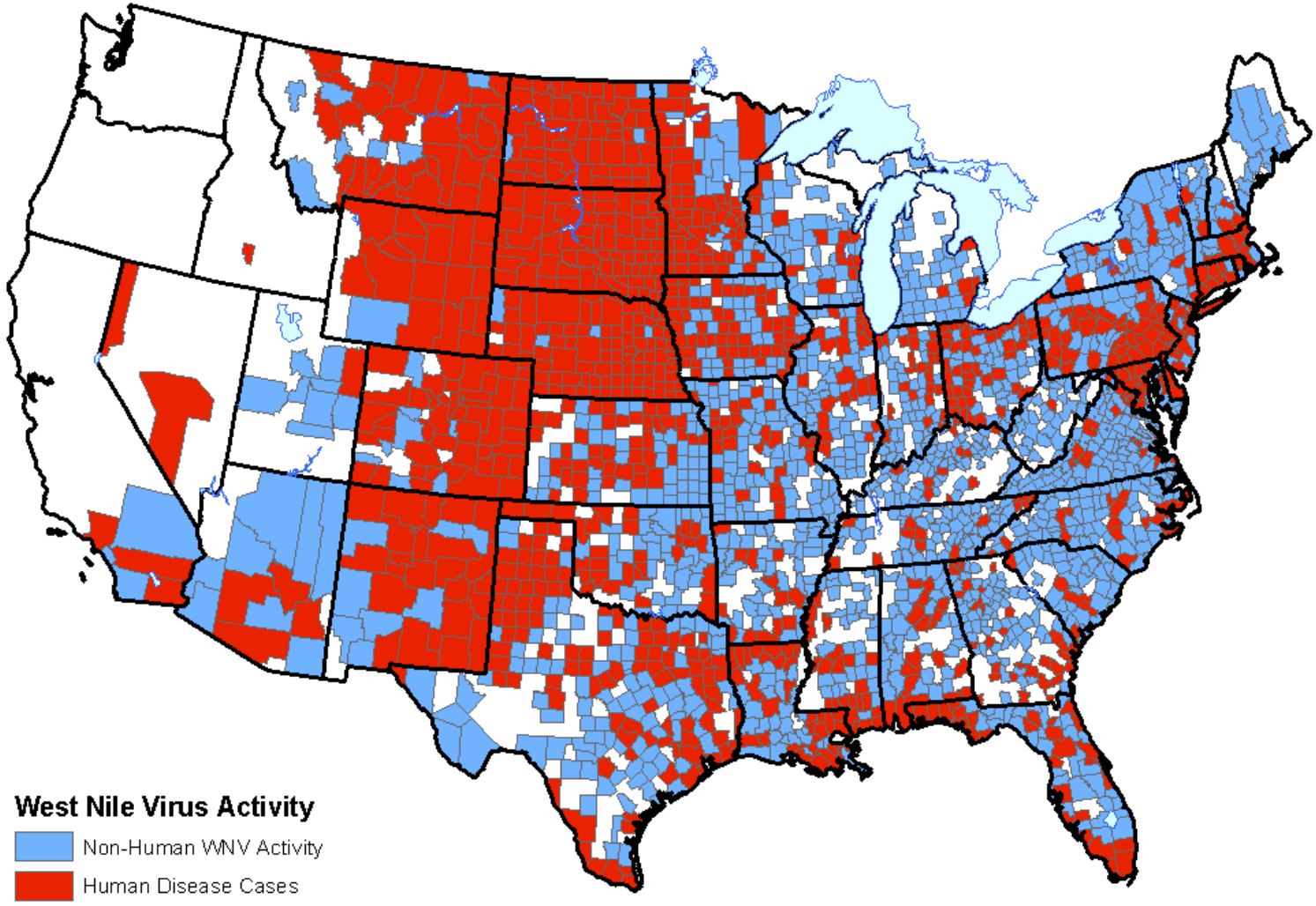
Spread of WNV in the US:2001



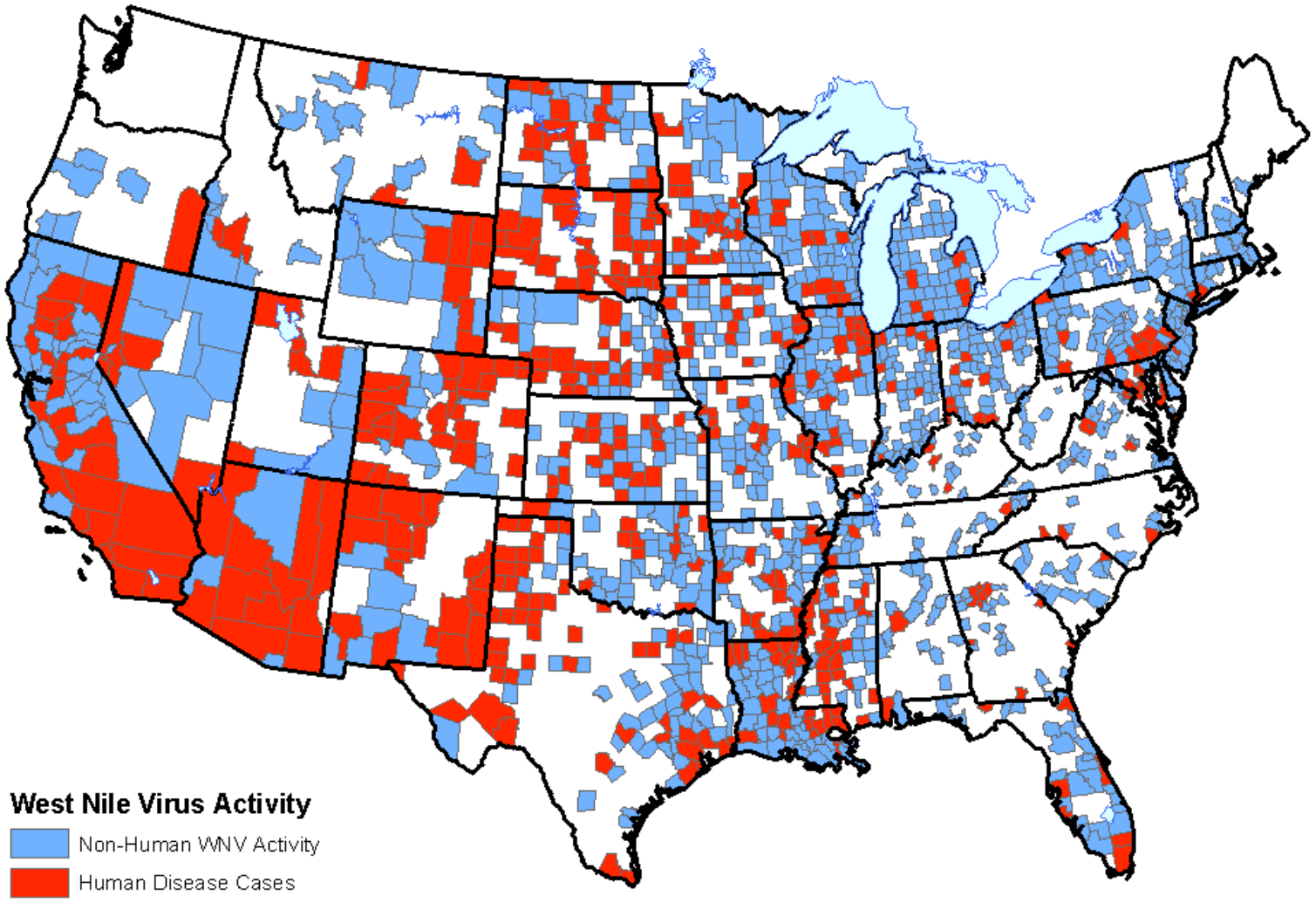
Spread of WNV in the US:2002



Spread of WNV in the US:2003



Spread of WNV in the US:2004



Reported WNV disease cases
United States, 1999-2005

Year	Total Cases	Fatalities
1999	62	7
2000	21	2
2001	66	9
2002	4,156	284
2003	9,862	264
2004	2,539	100
2005	2,949	116
Total	19,655	782 (4.0%)

Are chemokines and chemokine receptors important for WNV pathogenesis?

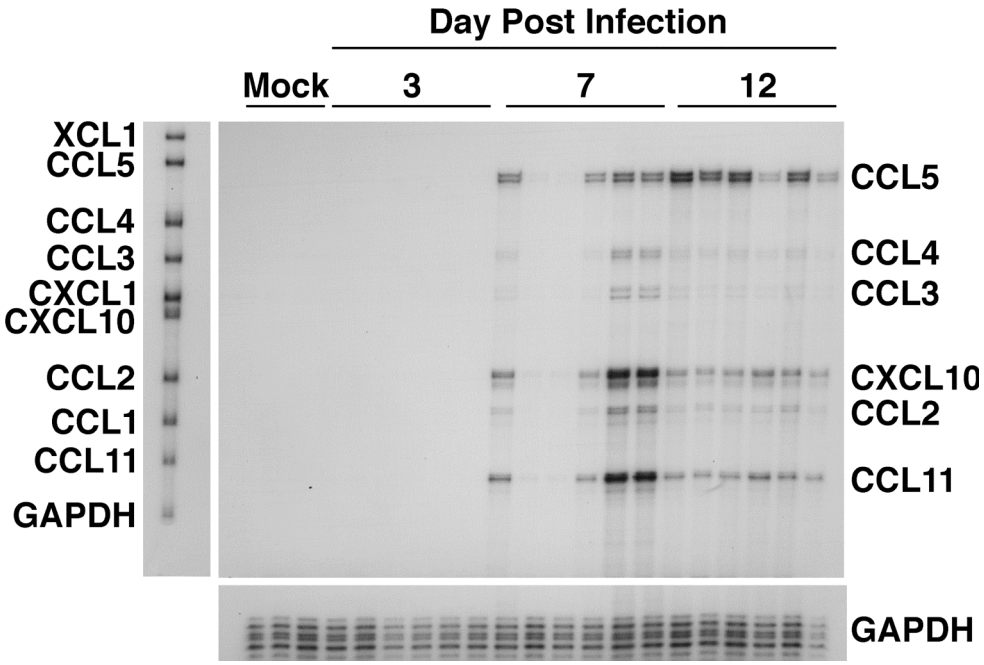
Chemokine Receptor CCR5 promotes leukocyte trafficking to the brain and survival in West Nile virus infection

William G. Glass, Jean K. Lim, Rushina Cholera,
Alexander G. Pletnev, Ji-Liang Gao, Philip M. Murphy.

J Exp Med, Oct 17, 2005

mouse

WNV induces expression of CCR5 ligands in the mouse brain



RNAse Protection Assay

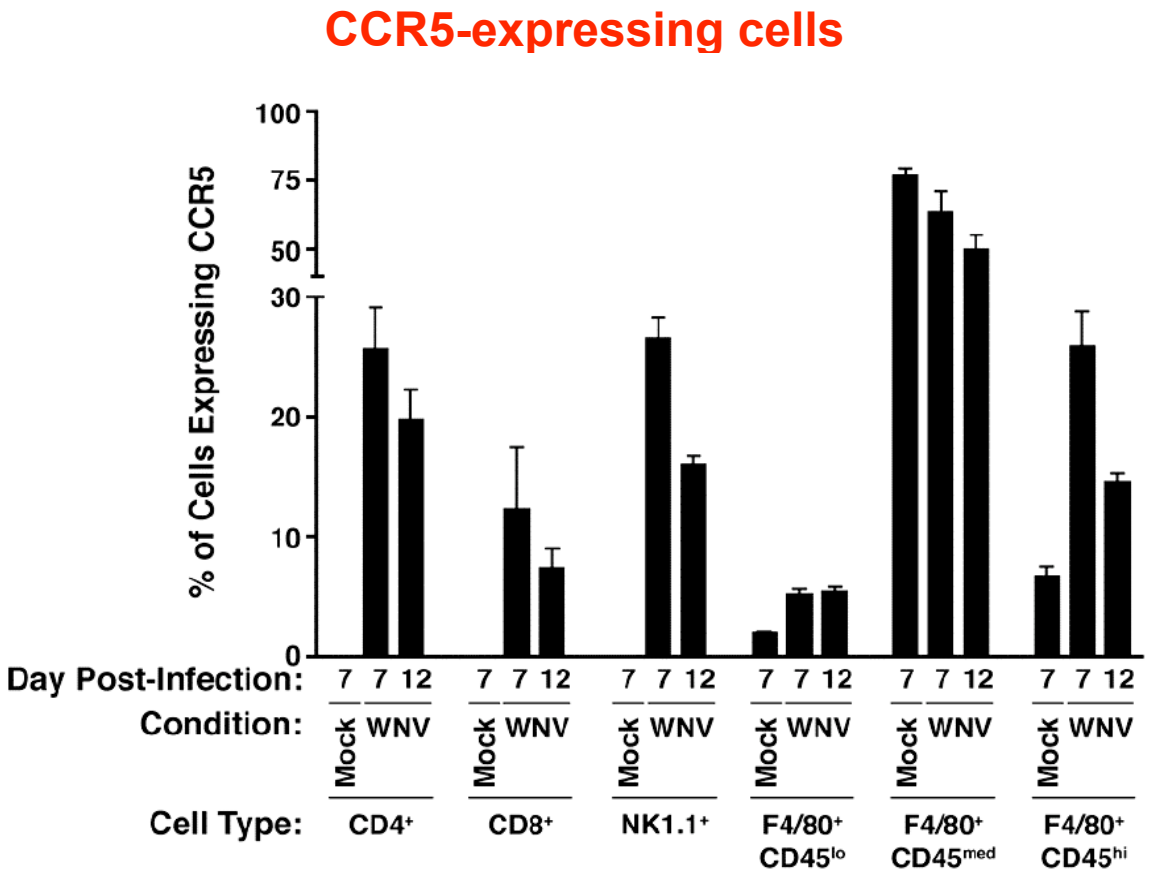
Receptor candidates

CCR5

CXCR3
CCR2
CCR3

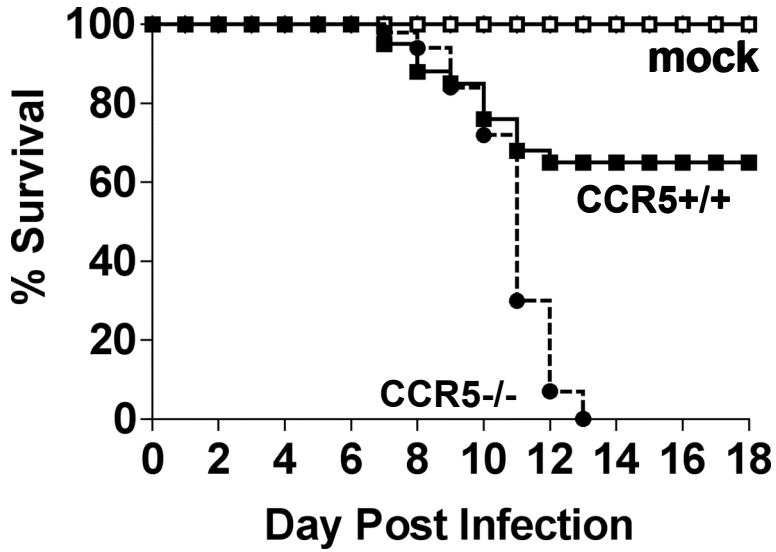
mouse

WNV induces the influx of CCR5-expressing cells into the mouse brain

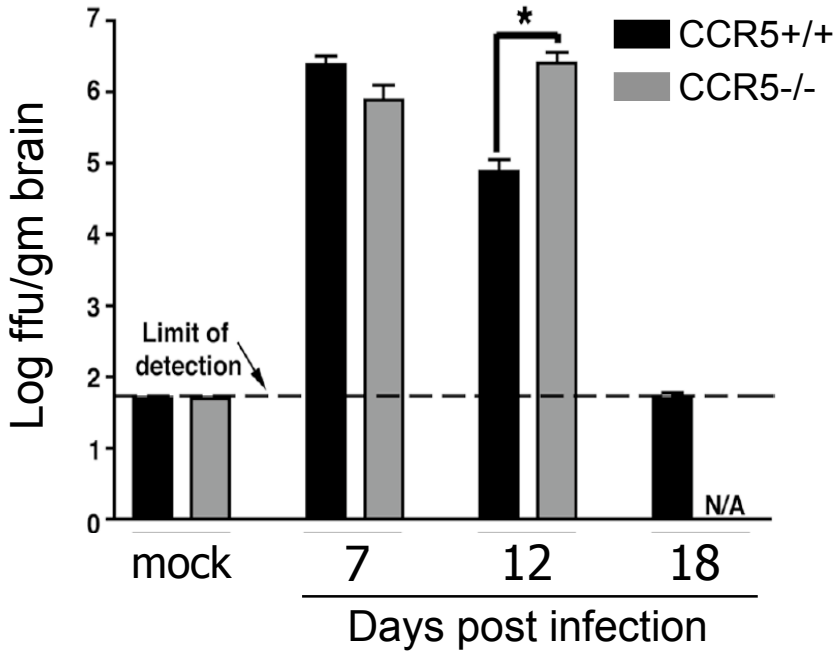


CCR5-deficient mice are unable to clear virus from the CNS and uniformly succumb to WNV infection

Survival Analysis

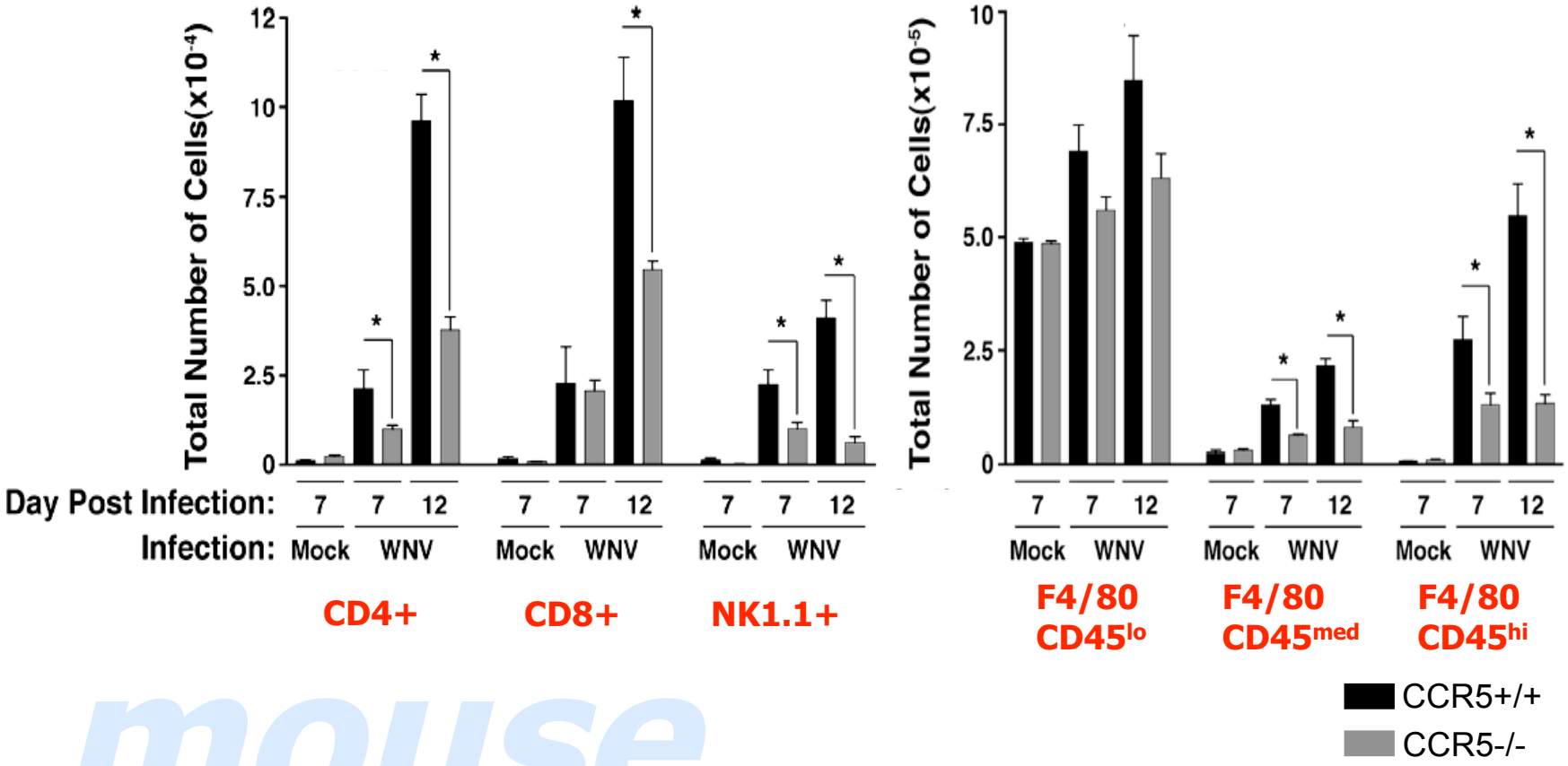


CNS Viral Load



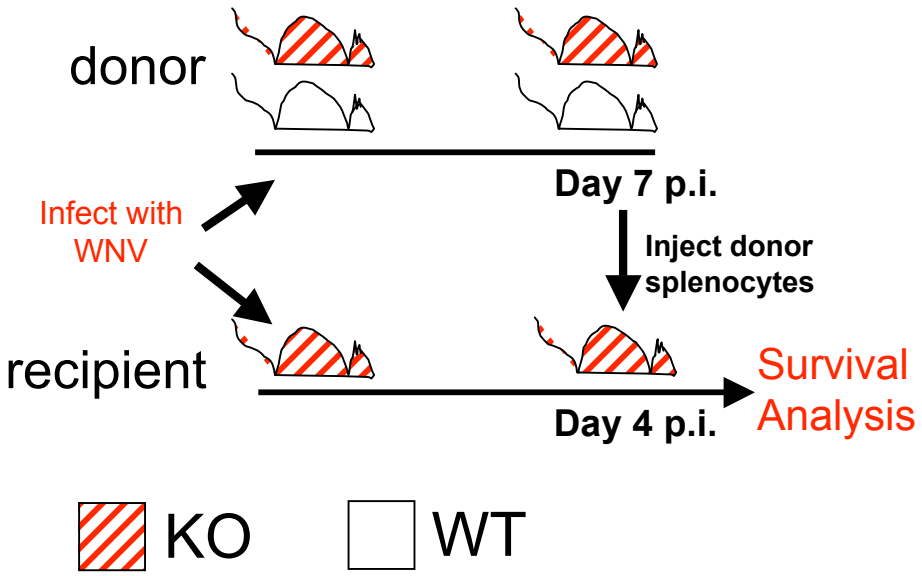
mouse

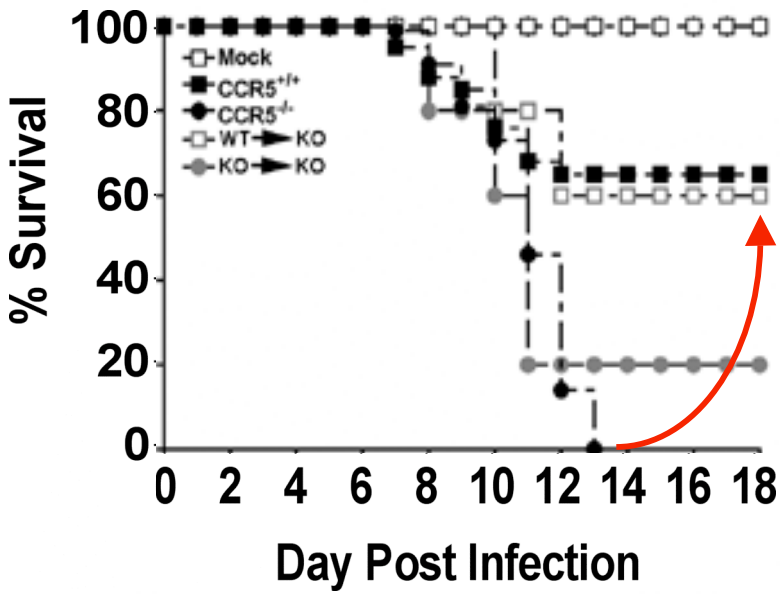
Mechanism: Loss of CCR5 results in decreased leukocyte trafficking to WNV-infected brain



mouse

Adoptive transfer of WNV-infected *ccr5* $^{+/+}$ splenocytes rescues *ccr5* $^{-/-}$ mice from fatal WNV infection





Summary: CCR5 plays a critical and non-redundant role in the mouse model of WNV infection. Loss of CCR5 results in decreased recruitment of leukocytes to the infected CNS and is uniformly fatal.

mouse

Is CCR5 a critical host factor in human WNV disease?

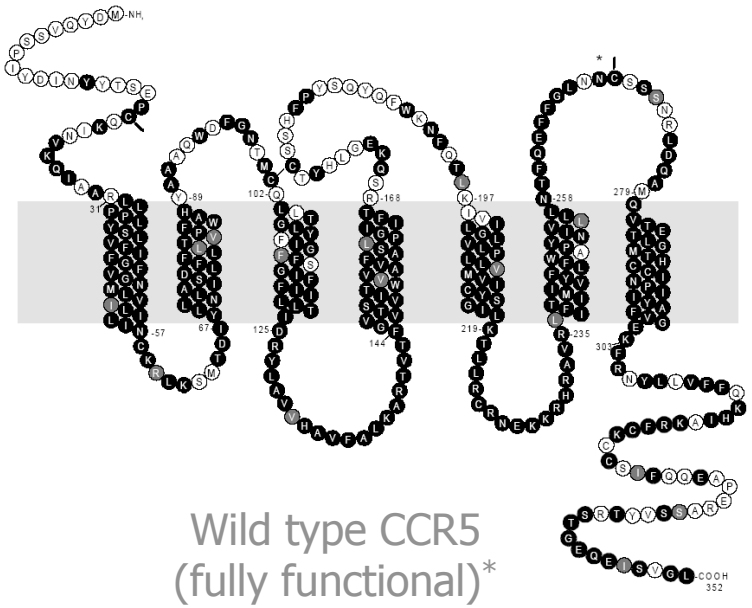
CCR5 deficiency increases risk of symptomatic West Nile Virus Infection

William G. Glass, David H. McDermott, Jean K. Lim, Sudkamon Lekhong, Shuk Fong Yu, William A. Frank, John Pape, Ronald C. Cheshier, and Philip M. Murphy.

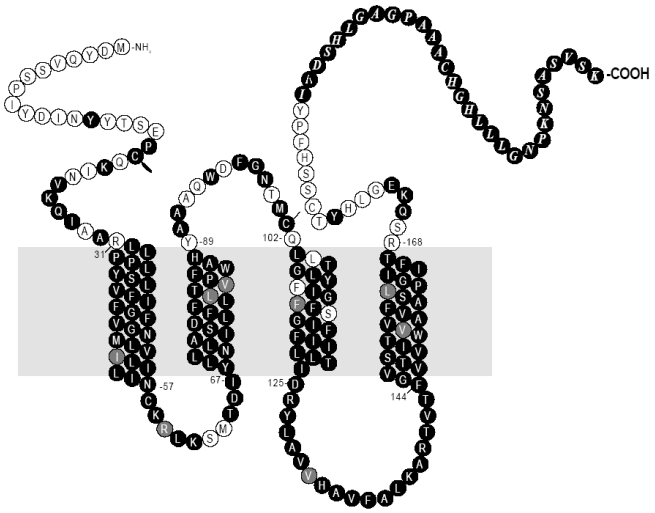
J Exp Med, Jan 17, 2006

man

Experimental Approach



Wild type CCR5
(fully functional)*



CCR5Δ32
(loss-of-function)*

Hypothesis:

CCR5Δ32 homozygosity is increased in WNV-symptomatic study groups

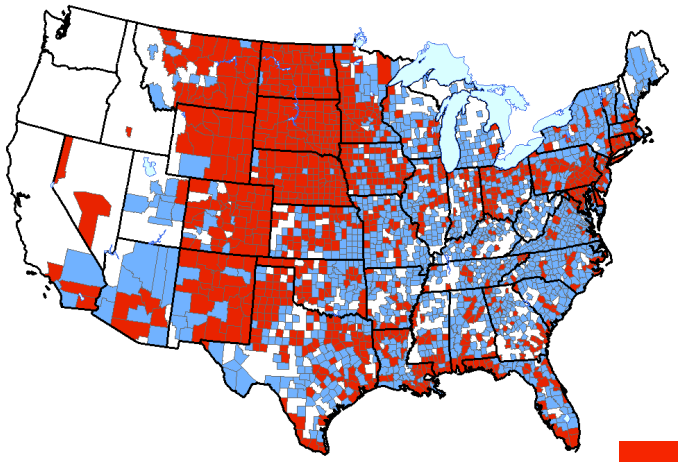
*figure from McNicholl et.al. 1997

Four study cohorts

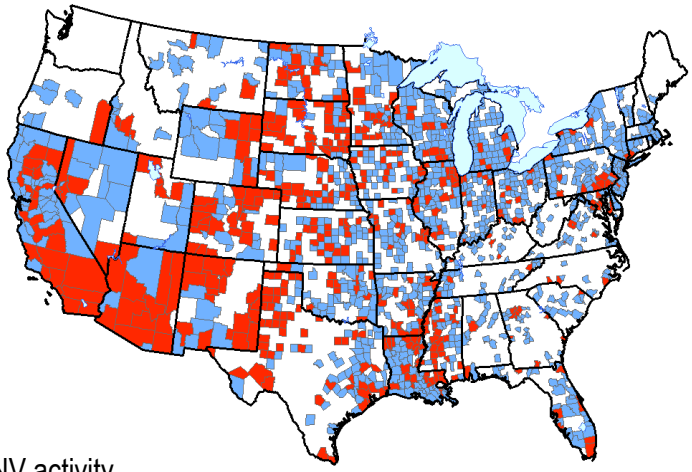
	WNV-positive		WNV-negative	
	Arizona	Colorado	Arizona	RBD*
Cohort size:	N=247	N=148	N=143	N=1318

* Random Blood Donors

WNV activity in the US: 2003



WNV activity in the US: 2004



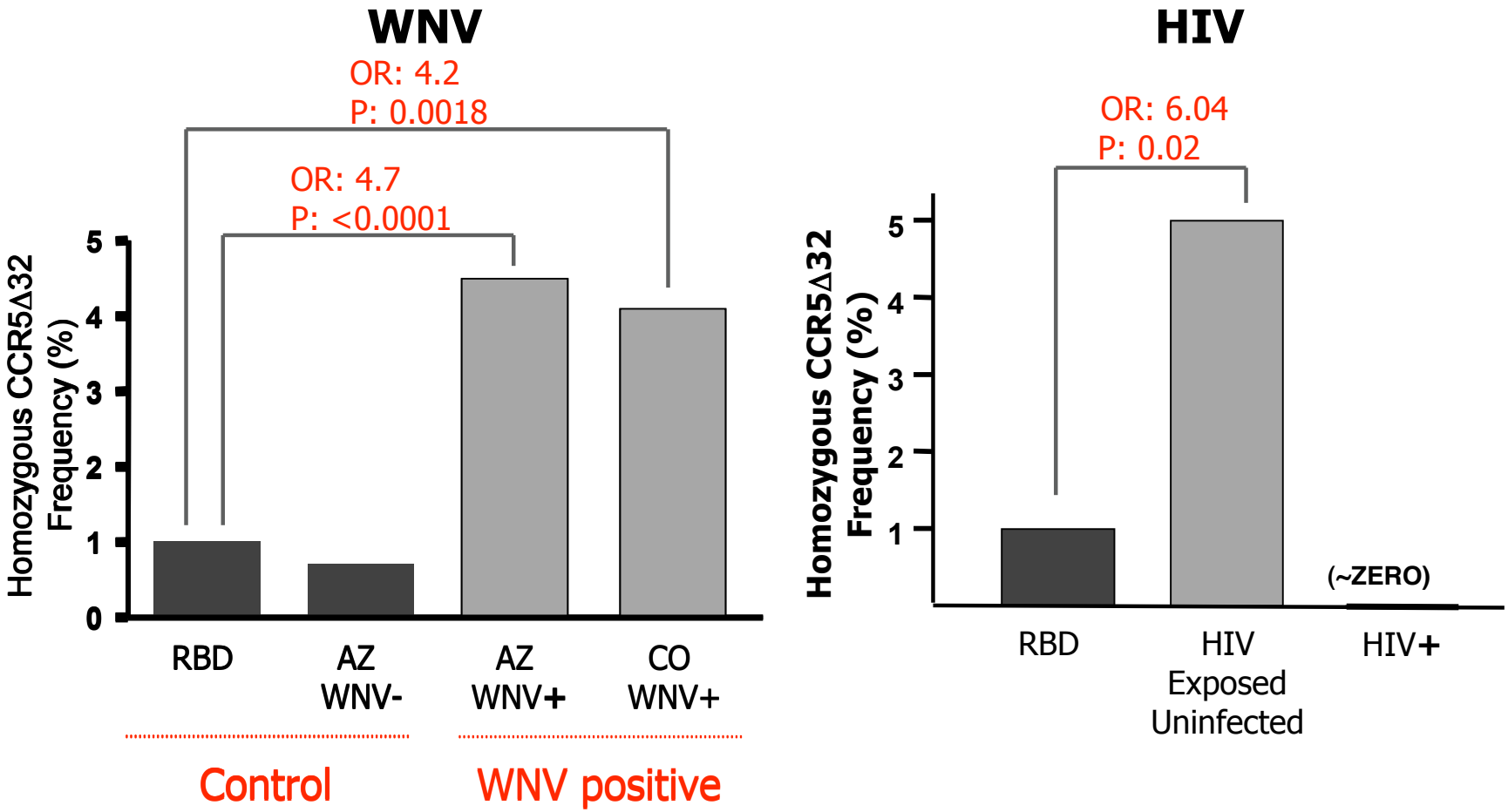
Human WNV activity

Non-Human WNV activity

*maps taken from CDC/USGS website

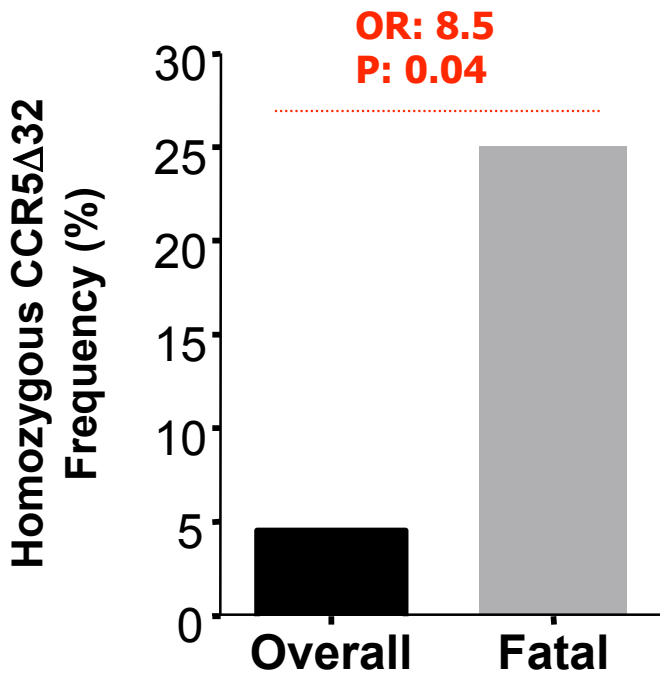
man

CCR5 deficiency is a strong risk factor for symptomatic WNV infection



* HIV data taken from Zimmerman et. al. *Mol Med* 1997

CCR5Δ32 homozygosity is associated with death from WNV infection



Summary and conclusions

1

CCR5 plays a critical role in host defense in WNV infection, in contrast to its harmful role in HIV and other diseases.

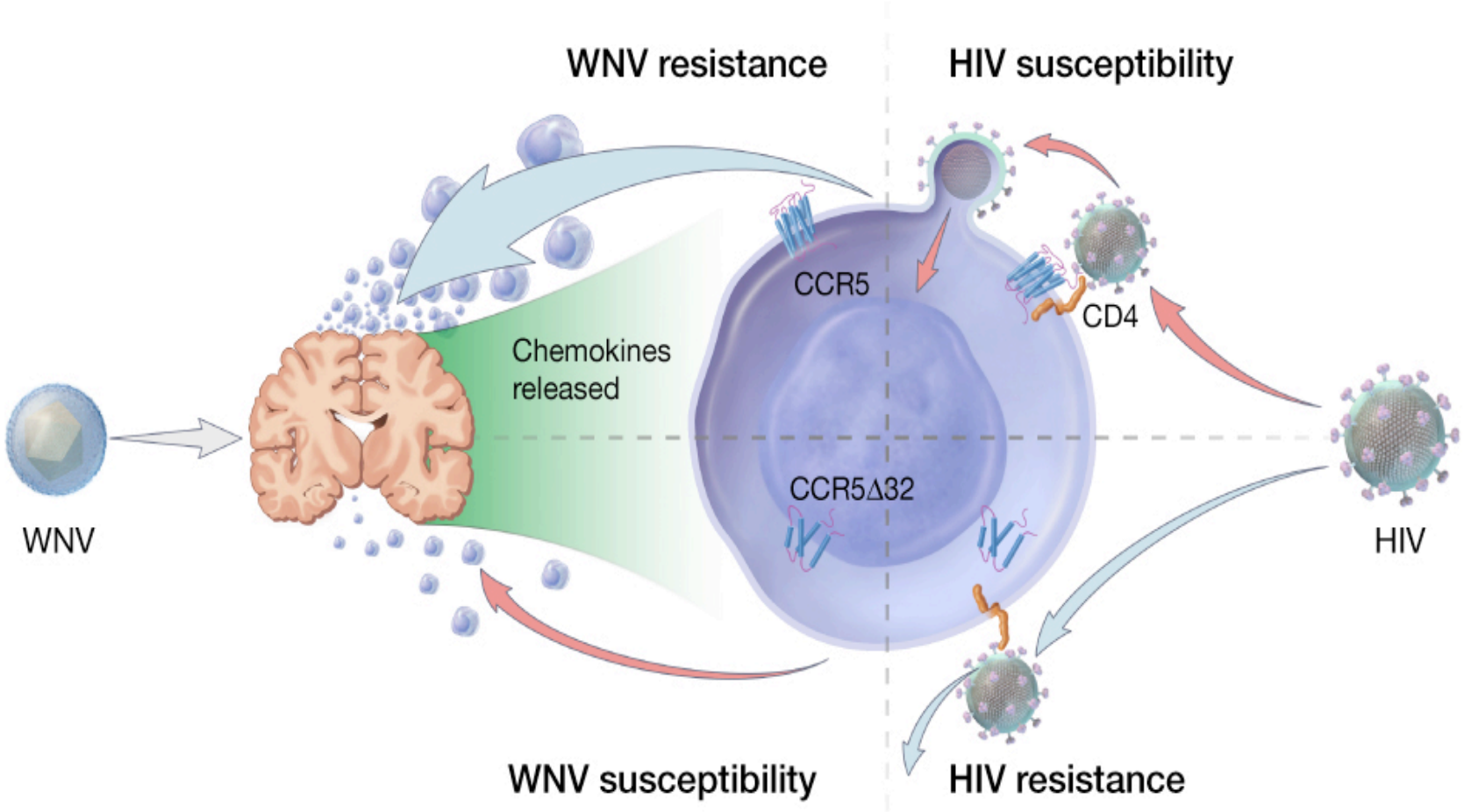
2

CCR5Δ32 homozygotes are HIV resistant but have increased risk of symptomatic WNV disease and death. Homozygous *CCR5Δ32* is the first genetic risk factor identified for WNV disease.

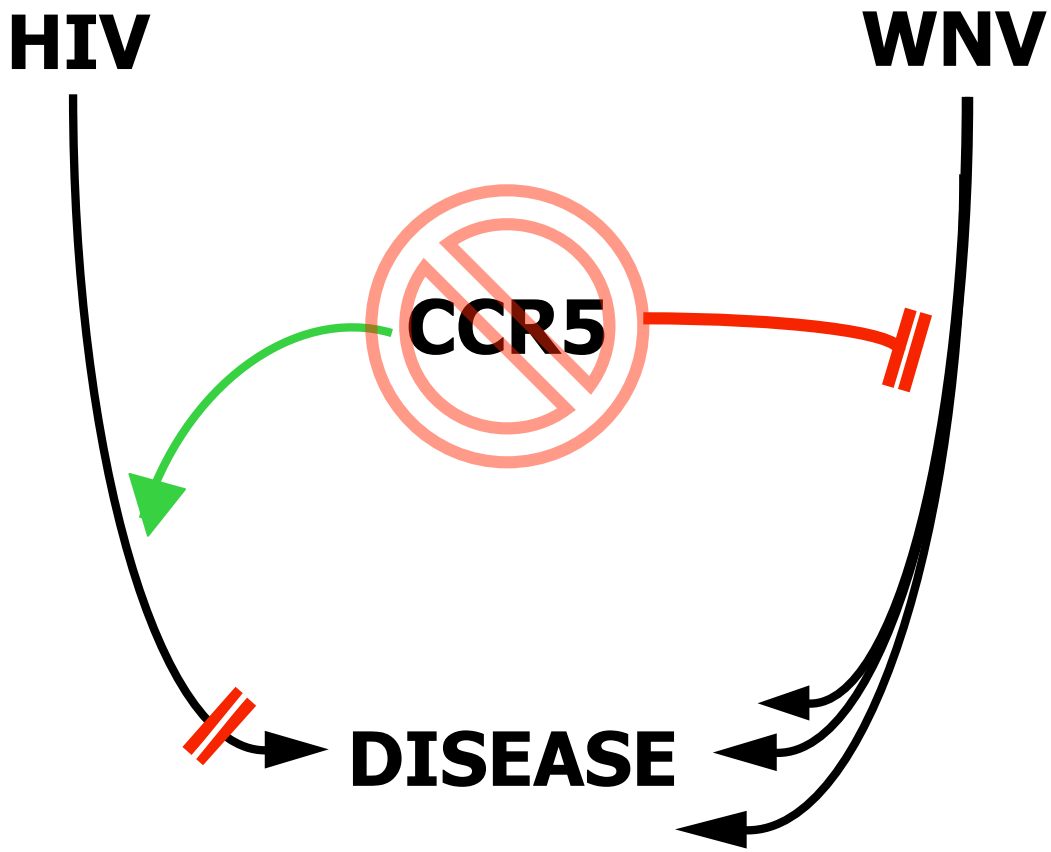
3

CCR5 blocking agents may increase risk of WNV disease.

Viral Usage of CCR5



Therapeutic intervention



Impact on CCR5-targeted drug development

1. Genetic removal of CCR5 is a risk factor for WNV symptomatic disease. Whether pharmacological blockade of CCR5 will result in increased risk for symptomatic WNV disease is unknown and should be tested prospectively.

2. CCR5 inhibitors that block HIV entry without disruption of endogenous chemokine binding/function should be explored.

3. The need for novel anti-retroviral targets for HIV is immense. Drugs targeting CCR5 and other invariant cellular structures should be pursued with high priority.

Variables to consider

1. Level of CCR5 blockade. What level of CCR5 is needed for WNV resistance? Intermediate levels of CCR5 might be adequate to confer WNV resistance since CCR5Δ32 heterozygosity is not associated with increase risk of symptomatic disease.

2. Distribution of CCR5 blockade. Systemic CCR5 blockade that aims for complete CCR5 coverage may increase risk of symptomatic WNV disease, whereas microbicides that target local levels of CCR5 are unlikely to enhance disease.

3. Level of WNV activity. Seasonal WNV epidemic activity and mosquito exposure of treated individuals are factors that may influence WNV susceptibility. Individuals on CCR5-targeted drugs should be aware of these risks and take cautionary measure to avoid mosquito bites (chemical repellants and protective barriers).

CCR5: no longer "good-for-nothing"

Acknowledgements

National Institutes of Health

Philip M. Murphy

William G. Glass

David H. McDermott

Rushina Cholera

Ji-Liang Gao

Colorado Department of Public Health and Environment

John Pape

Arizona Bureau of Epidemiology and Disease Control Services

Ronald Cheshire

Sudkamon Lekhong

Shuk Fong Yu

William Frank