West Nile Virus Infection and the CNS

Biological Basis of Psychiatric & Neurological Disorders

NRSC 7614
11 February 2010

Kenneth L. Tyler, M.D. FAAS
Reuler-Lewin Family Professor & Chair, Neurology
Professor of Medicine & Microbiology
University of Colorado School of Medicine
Denver, CO
67M, hairy cell leukemia (‘05) in remission
Rituxan q 3m x 2 yrs (last 8/20/09)
New onset T°, fatigue, altered mental status

T° 102¹, Confused, Ox2, drowsy follows simple commands,
CNs intact, moves all extremities, ? Gen weak, Decr DTRs
“tremulous”, “cogwheeling”

CT-, MR: Few scattered WM lesions, “non-specific”
EEG moderate amount intermixed theta slowing

CSF : 29 wbc (18%P, 56%L, 26%M), 2 rbc, glu 48/94 pro 84
Neg gram, AFB, crypto Ag, fungal stains & cytology

CSF PCR: HSV1/2, VZV, HHV6, HHV8, CMV, EBV, WNV,
Parvo B19, Mycoplasma, Adenovirus, JCV, BKV
CSF Ab: WNV (IgG, IgM), PCR
Serum: WNV (IgG, IgM)
Our Case: WNV Meningoencephalitis

8/28 CSF PCR+ WNV (CSF IgG & IgM negative)
All Other CSF PCRs Negative

Rx: U.S. IVIG (Gammagard, Gamunex)
5 doses: ~1750mg/kg total dose (170g, ~$20,000)

<table>
<thead>
<tr>
<th>Date</th>
<th>WNV-IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/29 Pre</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>9/3 IVIG(15)</td>
<td>0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>9/4</td>
<td>0.24</td>
<td>0.00</td>
</tr>
<tr>
<td>9/5 IVIG(10)</td>
<td>0.87</td>
<td>0.00</td>
</tr>
<tr>
<td>9/7 IVIG (50)</td>
<td>1.14</td>
<td>0.00</td>
</tr>
<tr>
<td>9/10 CSF PCR-</td>
<td>9/11 IVIG (50)</td>
<td>0.47</td>
</tr>
<tr>
<td>CSF 14 wbc</td>
<td>9/12</td>
<td>0.00</td>
</tr>
</tbody>
</table>
WNV Historical Perspective

- 1937: Virus isolated from blood of a woman with Dengue-like illness in West Nile region, Uganda
- 1950’s: WNV noted to be endemic in children in Egypt, Sudan
- 1952-54: 1st cases encephalitis: Cancer Rx trial at MSK in NYC!!
- 1957: Meningoencephalitis in outbreak in Israeli nursing home
- 1950-1990’s: Most epidemics WNF>>CNS (18,000 cases in S. Africa, 1974)
- Worldwide Epidemics:
- First Bird deaths in 1998 in Israel (goslings, white storks)
- Virus appears in U.S./Western Hemisphere in 1999…
<table>
<thead>
<tr>
<th>Year</th>
<th>WNV (CNS)</th>
<th>LAC</th>
<th>SLE</th>
<th>EEE</th>
<th>POW</th>
<th>WEE**</th>
<th>HSV</th>
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<tr>
<td>2000</td>
<td>112</td>
<td>91</td>
<td>28</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2001</td>
<td>167</td>
<td>79</td>
<td>22</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2002</td>
<td>113</td>
<td>24</td>
<td>15</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td>1200</td>
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<tr>
<td>2003</td>
<td>112</td>
<td>21</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2004</td>
<td>73</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2005</td>
<td>59</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2006</td>
<td>52</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2007</td>
<td>55</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>2008</td>
<td>882</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11,406</td>
<td>882</td>
<td>193</td>
<td>79</td>
<td>8</td>
<td>0</td>
<td>10,800</td>
</tr>
</tbody>
</table>

Source: CDC
## WNV U.S. Annual Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>CNS</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>62</td>
<td></td>
<td>7 (11%)</td>
</tr>
<tr>
<td>2000</td>
<td>21</td>
<td></td>
<td>2 (10%)</td>
</tr>
<tr>
<td>2001</td>
<td>66</td>
<td></td>
<td>9 (14%)</td>
</tr>
<tr>
<td>2002</td>
<td>4156</td>
<td>~2900 (70%)</td>
<td>284 (7%)</td>
</tr>
<tr>
<td>2003</td>
<td>9862</td>
<td>2866 (29%)</td>
<td>264 (3%)</td>
</tr>
<tr>
<td>2004</td>
<td>2470</td>
<td>900 (36%)</td>
<td>88 (4%)</td>
</tr>
<tr>
<td>2005</td>
<td>3000</td>
<td>1294 (43%)</td>
<td>119 (4%)</td>
</tr>
<tr>
<td>2006</td>
<td>4269</td>
<td>1459 (34%)</td>
<td>177 (4%)</td>
</tr>
<tr>
<td>2007</td>
<td>3623</td>
<td>1213 (34%)</td>
<td>124 (3%)</td>
</tr>
<tr>
<td>2008</td>
<td>1356</td>
<td>687 (51%)</td>
<td>44 (3%)</td>
</tr>
<tr>
<td>2009</td>
<td>663</td>
<td>335 (51%)</td>
<td>30 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>29,538</td>
<td>~11,646 (39%)</td>
<td>1,141 (4%)</td>
</tr>
</tbody>
</table>

(Likely 1.75 million have been infected, ~150x CNS total)
Cumulative 2008 Data as of 3 am, Apr 09, 2009

These data are provisional and may be revised or adjusted in the future.

Cumulative Human Disease Cases by County - Colorado, 2008

<table>
<thead>
<tr>
<th>County</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams County</td>
<td>6</td>
</tr>
<tr>
<td>Arapahoe County</td>
<td>1</td>
</tr>
<tr>
<td>Boulder County</td>
<td>13</td>
</tr>
<tr>
<td>Delta County</td>
<td>1</td>
</tr>
<tr>
<td>Denver County</td>
<td>3</td>
</tr>
<tr>
<td>Gunnison County</td>
<td>1</td>
</tr>
<tr>
<td>Jefferson County</td>
<td>3</td>
</tr>
<tr>
<td>Kiowa County</td>
<td>1</td>
</tr>
<tr>
<td>Larimer County</td>
<td>13</td>
</tr>
<tr>
<td>Logan County</td>
<td>2</td>
</tr>
<tr>
<td>Morgan County</td>
<td>2</td>
</tr>
<tr>
<td>Otero County</td>
<td>1</td>
</tr>
<tr>
<td>Phillips County</td>
<td>1</td>
</tr>
<tr>
<td>Prowers County</td>
<td>1</td>
</tr>
<tr>
<td>Pueblo County</td>
<td>2</td>
</tr>
<tr>
<td>Weld County</td>
<td>19</td>
</tr>
<tr>
<td>Yuma County</td>
<td>1</td>
</tr>
</tbody>
</table>

Cumulative 2009 Data as of 3 am, Dec 08, 2009

These data are provisional and may be revised or adjusted in the future.

Cumulative Human Disease Cases by Week - Colorado, 2009

n=101, M=F
65% T° 18% Mn, 17% Enc
T° 49.5, Mn 53.5, Enc 67 yrs
Asymptomatic ~ 20%

"West Nile Fever" <1%

CNS disease ~20%

Meningitis
Encephalitis
Acute Flaccid Paralysis

1 CNS disease case = ~150 total infections

~80%
Asymptomatic

WNV Human Infection “Iceberg”
Case Rates by Age and Diagnosis (Chicago 2002, N=220)

Source CDC: William Paul
Table 3. Risk analysis for developing West Nile encephalitis (WNE) for 65 patients with WNE versus 53 patients with West Nile fever.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR from univariate analysis (95% CI)</th>
<th>Adjusted OR from multivariate analysis (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.4 (0.7–3.0)</td>
<td>Not retained in model</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3.4 (0.9–12.9)</td>
<td>7.5 (1.5–37.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.1 (1.1–9.2)</td>
<td>4.1 (1.2–13.6)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.2 (0.7–6.6)</td>
<td>Not retained in model</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5 (0.7–3.2)</td>
<td>Not retained in model</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3.4 (0.4–31.5)</td>
<td>Not retained in model</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>2.7 (1.2–6.5)</td>
<td>...</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>...</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>Undefined&lt;sup&gt;b&lt;/sup&gt;</td>
<td>...</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>2.2 (0.7–7.6)</td>
<td>Not retained in model</td>
</tr>
</tbody>
</table>
ORIGINAL CONTRIBUTION

Naturally Acquired West Nile Virus Encephalomyelitis in Transplant Recipients

Clinical, Laboratory, Diagnostic, and Neuropathological Features

B. K. Kleinschmidt-DeMasters, MD; Brad A. Marder, MD; Marilyn E. Levi, MD; Stephen P. Laird, MD; J. Trevor McNutt, MD; Edward J. Escott, MD; Gregory T. Everson, MD; Kenneth L. Tyler, MD

Neurology 68:460, 2007

An 85-year-old man with chronic lymphocytic leukemia and altered mental status

Kenneth L. Tyler, MD, FAAN; Allen J. Aksamit, Jr., MD, FAAN; B. Mark Keegan, MD; and Joseph E. Parisi, MD

Clin Transplantation

Impact of rituximab-associated B-cell defects on West Nile virus meningoencephalitis in solid organ transplant recipients


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Delinquent Mortgages, Neglected Swimming Pools, and West Nile Virus, California

William K. Reisen, Richard M. Takahashi, Brian D. Carroll, and Rob Quiring

Adjustable rate mortgages and the downturn in the California housing market caused a 300% increase in notices of delinquency in Bakersfield, Kern County. This led to large numbers of neglected swimming pools, which were associated with a 276% increase in the number of human West Nile virus cases during the summer of 2007.
WNV Risk-Humans

HUMANS:

- SNP rs3213545 in OASL1 ~2x more frequent in humans with severe disease (84% vs. 48%)- Yakub et al. JID 192:741, 2005, -Not Disease Severity, but ?Risk Infection/Growth in Tissues?- Lim et al. PLoS Pathogen, 5(2), Feb., 2009

- CCR5Δ32 homozygosity increases risk of symptomatic disease- Glass et al. JEM 203:35, 2006; Lim et al. JID 197:262, 2008

- Reduced TLR3 expression in Mφ in elderly impairs innate immune response to WNV- Kong et al. JV 82:7613, 2008

- Reduced CD4+ Treg Response — Lanteri et al. JCI 119:3266, 2009
- OAS 1b gene is a mouse WNV susceptibility factor
- OAS and RNase L control inhibit WNV replication in neurons
- No mutations in humans with severe WNV
- SNP rs3213545 in OASL1 ~2x more frequent in humans with severe disease (84% vs. 48%)

Perelygin et al., PNAS 99: 9322, 2002
Mashimo et al., 99:11311, 2002
Yakub et al. JID 192:1741, 2005
Samuel et al. JV 80:7009, 2006
CCR5Δ32 homozygosity and risk of symptomatic WNV infection

Lim et al. JID 197:262–265, 2008
CCR5/CCL5 and inflammatory cell (CD3+) infiltrate in WNV infected mouse brains

Glass et al. JEM 202:1087, 2005
TLR-3

↑ IL-6, IFN, TNF-α

Antiviral effect (peripheral tissues)

Spleen

Blood vessel

Perivascular space

Brain

Diamond & Klein Nat Med 10:1294-5, 2005
Wang et al. Nat Med 10:1366-73, 2005
WNV Meningoencephalitis
Meningitis 25-40%, Encephalitis 55-60%, AFP 5-10%

- T° (70-100%), HA (50-100%), N/V(50-75%), myalgia (30-60%),
- Rash (5-50%), Diarrhea (15-35%), Arthralgia/bp (10-30%), Cough/dyspnea (10-15%)
- Δ Mental Status (50-100%)
- Tremor (postural or kinetic) (30-90%)
- Parkinsonism (rigidity, bradykinesia) (40-75%)
- Weakness (30-60%)
- Ataxia (30%-40%)
- Myoclonus (10-40%)
- CNs (esp. VII) (20%), Visual Δs (20-25%)
- Bulbar Dysfn (Dysarthria, Dysphagia) (20%)
- Sz’s (5%)
CN Involvement

- CN I:
- CN II: multifocal choroiditis/chorioretinitis, retinal hemorrhage, vitritis, occ. Optic neuritis, occlusive vasculitis
- CN III, IV, VI: Diplopia common, residual ophthalmoplegia rare
- CN V: Jaw weakness
- CN VII: Unilateral/bilateral facial paralysis most common CN abnormality—may occur late
- CN VIII- Dizziness/vertigo common, ? Hearing loss
- CN IX, X- Decreased gag, dysarthria, dysphagia, hoarseness, dysphonia
- CN XI- Weak trapezius, SCM
- CN XII- tongue weakness
A: CT (No contrast)
B: SE T1 [560/17 TR/TE]
C: FSE T2 [3840/99 TR/TE]
D: FLAIR [9999/119 TR/TE]
2389 ms
E: T1 Gadolinium [560/17 TR/TE]

Rosas & Wippold, AJNR
24:1376, 2003
Axial proton density (2667 TR, 13.9 TE, 2 nex)
<table>
<thead>
<tr>
<th></th>
<th>Cells</th>
<th>Glucose</th>
<th>Protein</th>
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<tr>
<td><strong>Meningitis</strong></td>
<td><strong>226 ± 50</strong></td>
<td><strong>65 ± 2</strong></td>
<td><strong>76 ± 3</strong></td>
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<tr>
<td>n=174</td>
<td>128-325</td>
<td>61-69</td>
<td>71-81</td>
</tr>
<tr>
<td></td>
<td>1-7950</td>
<td>39-220</td>
<td>21-207</td>
</tr>
<tr>
<td><strong>Enceph.</strong></td>
<td><strong>227 ± 47</strong></td>
<td><strong>71 ± 3</strong></td>
<td><strong>101 ± 6</strong></td>
</tr>
<tr>
<td>n=76</td>
<td>133-321</td>
<td>65-77</td>
<td>90-112</td>
</tr>
<tr>
<td></td>
<td>1-2600</td>
<td>40-179</td>
<td>32-295</td>
</tr>
</tbody>
</table>

Avg. PMN: 41% (M)-45% (E)
>50% PMNs: 37% (E)-45% (M)

Triphasic Waves and Slowing in West Nile Encephalitis

M Age: 86

Fp₁-F₃
F₃-C₃
C₃-P₃
P₃-O₁
Fp₂-F₄
F₄-C₄
C₄-P₄
P₄-O₂

Comatose

50 µV/10 mm
1 sec

Long Term Sequelae of WNV

- 112 pts 7 yr. q 6m f/u Texas 2002: 50%E, 30%M, 20% WNF
- Persistent symptoms:
  Yr 1 (60%), 2 (46%), 3 (41%), 4 (49%), 5 (42%)
- Fatigue, weakness, depression*, personality Δ, walking difficulty, memory deficits
- Encephalitis>Meningitis>WNF
- Persistent Infection?: IgM, IFNg-IP, Urine PCR?

* New onset in 31%-confirmed by CES-D in 75%
Physical

Time to 95% Recovery:
121d (98-153)
175d (99-334) P.044

Mood

Time to 95% Recovery:
131d (93-193)
139d (63-388) NS

Mental

Time to 95% Recovery:
302d (204-454)
455d (166-1354) NS

Fatigue

Time to 95% Recovery:
112d (87-149)
148d (69-274) NS
Can neurological complications (e.g. parkinsonism, cognitive impairment) develop in pts. as a late sequelae of neurologically asymptomatic acute WNV infection?

Persistent Neurobehavioral Signs and Symptoms Following West Nile Fever

Hall DA, Tyler KL, Frey KL, Kozora E, Arcinieagas DB


54yo M, Crohn’s Disease, Azathioprine Rx
T°, N, V +WNV serum IgM: WNF, recovered
3 wks later’ 4Hz rest tremor, bradykinesia, memory, concentration and mood problems confirmed by Neuro-psych testing, mild ataxia
Persistent, static x 2 yrs
**BRIEF REPORT**

**Persistent Infection with West Nile Virus Years after Initial Infection**

Kristy Murray,¹ Christopher Walker,¹ Emily Herrington,¹ Jessica A. Lewis,² Joseph McCormick,¹ David W. C. Beasley,² Robert B. Tesh,² and Susan Fisher-Hoch¹

¹School of Public Health, University of Texas Health Science Center at Houston, Houston and Brownsville, and ²University of Texas Medical Branch, Galveston

West Nile virus (WNV) RNA was demonstrated in 5 (20%) of 25 urine samples collected from convalescent patients 573–2452 days (1.6–6.7 years) after WNV infection. Four of the 5 amplicons sequenced showed >99% homology to the WNV NY99 strain. These findings show that individuals with chronic symptoms after WNV infection may have persistent renal infection over several years.

*Received 6 May 2009; accepted 21 August 2009; electronically published 4 December 2009*
Acute Flaccid Paralysis

- Asymmetric Flaccid Weakness
- Acute Onset and Rapid Progression
  - 88% reach nadir <24 hrs (<6h-3d)
- 1 Limb (18%), 2 Limb (22%), 3/4 (60%)
- Decreased/Absent Reflexes
- Preserved Sensation (>90%), but 60% have pain
- CNs (70%): Dysphagia (65%), VIIth (50%), Dysarthria (30%), EOM (20%), VC paralysis (10%)
- ± Respiratory Failure (40%)

See Sejvar et al. EID 11:1021-7, 2005
Acute Flaccid Paralysis

- CSF pleocytosis & elevated protein
- MRI: T2 abn in Anterior horns spinal cord
- EMG/NCV:
  Decreased CMAPs
  Preserved SNAPs
  ~Normal CVs
  Motor > Sensory & Axonal > Demyelinating
  Denervation: Fibs, PSWCs, Decr MU recruitment
WNV Poliomyelitis

Spinal Cord Whole Mount (LFB-PAS)  Anterior horn (H&E)
7.5X Original Magnification   200X Original Magnification

DeMasters et al., Arch Neurol 61:1210-20, 2004
AFP Prognosis

- Respiratory impairment: 50% Mortality
- Persistent weakness frequent
- Survivors show some improvement but variable (One case: QP+R to normal)
- Less weakness acutely - more strength improvement
- More during first 0-4 mos vs. 4-12 mos
- GBS-Like (13%): Complete recovery
- Facial palsy: Complete recovery (1 yr)

Sejvar EID 12:514, 2006
Unusual Manifestations

- Acute or subacute opsoclonus myoclonus syndrome
- Predominant brainstem/cerebellar encephalitis
- ? ADEM
- ? Stroke/vasculitis (children?)
- ?Chronic/persistent encephalitis (immunoCx?)
- ? Relapsing neurological syndromes
- ? Parkinsonism without overt acute WNND
“We’re pretty sure it’s the West Nile virus.”
IgM 80+% IgM+ by d 8 Persists up to d 500??

IgG Peaks at ~4 wks Persists lifelong

JEV, SLEV, YFV, Dengue heterologous Abs
WNV Prevention

- Reduce Standing Water
  - Clean Roof Gutters
  - Remove Old Tires
  - Aerate/Add Fish to Ornamental Pools
  - Clean & Chlorinate Swimming Pools
  - Remove/Add Drain Holes to Containers
- Minimize Outdoor Time @ Dawn/Dusk/
- Wear Long Sleeves & Long Pants
- Use DEET (> 10%) Bug Repellant
- Permethrin coated clothing
- Use Outdoor Fluorescent >Incandescent Lights
Omr-IgG-am™

5% IV, Human Immunoglobulin Solution

CASG 210 (NCT00068055) Phase I/II completed
Development of a humanized monoclonal antibody with therapeutic potential against West Nile virus

Theodore Oliphant1, Michael Engle2, Grant E Nybakken3, Chris Doane2, Syd Johnson4, Ling Huang4, Sergey Gorlatov4, Erin Mehlhop3, Anantha Marri2, Kyung Min Chung2, Gregory D Ebel5, Laura D Kramer5, Daved H Fremont3 & Michael S Diamond1,2,3

Neutralization of West Nile virus (WNV) in vivo correlates with the development of an antibody response against the viral envelope (E) protein. Using random mutagenesis and yeast surface display, we defined individual contact residues of 14 newly generated monoclonal antibodies against domain III of the WNV E protein. Monoclonal antibodies that strongly neutralized WNV localized to a surface patch on the lateral face of domain III. Convalescent antibodies from individuals who had recovered from WNV infection also detected this epitope. One monoclonal antibody, E16, neutralized 10 different strains in vitro, and showed therapeutic efficacy in mice, even when administered as a single dose 5 d after infection. A humanized version of E16 was generated that retained antigen specificity, avidity and neutralizing activity. In postexposure therapeutic trials in mice, a single dose of humanized E16 protected mice against WNV-induced mortality, and may therefore be a viable treatment option against WNV infection in humans.

A Therapeutic Antibody against West Nile Virus Neutralizes Infection by Blocking Fusion within Endosomes

Bruce S. Thompson1, Bastiaan Moesker2, Jolanda M. Smit2, Jan Wilschut2, Michael S. Diamond1,3,4,*, Daved H. Fremont1*

1 Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, United States of America, 2 Department of Medical Microbiology-Molecular Virology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 3 Medicine, Washington University School of Medicine, St. Louis, Missouri, United States of America, 4 Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri, United States of America

Abstract

Defining the precise cellular mechanisms of neutralization by potently inhibitory antibodies is important for understanding how the immune system successfully limits viral infections. We recently described a potently inhibitory monoclonal antibody (MAb E16) against the envelope (E) protein of West Nile virus (WNV) that neutralizes infection even after virus has spread to the central nervous system. Herein, we define its mechanism of inhibition. E16 blocks infection primarily at a post-attachment step as antibody-opsonized WNV enters permissive cells but cannot escape from endocytic compartments. These cellular experiments suggest that E16 blocks the acid-catalyzed fusion step that is required for nucleocapsid entry into the cytoplasm. Indeed, E16 directly inhibits fusion of WNV with liposomes. Additionally, low-pH exposure of E16–WNV complexes in the absence of target membranes did not fully inactivate infectious virus, further suggesting that E16 prevents a structural transition required for fusion. Thus, a strongly neutralizing anti–WNV MAb with therapeutic potential is potently inhibitory because it blocks viral fusion and thereby promotes clearance by delivering virus to the lysosome for destruction.
WNV Envelope Glycoprotein
3A resolution

Domain II (yellow)  Domain I (red)  Domain III (blue)

(Nybakken et al JV 80:11467, Dec. 2006)
Dr. Tyler has consulted for Macrogenics Inc. which is designing human clinical trials utilizing this Mab.
IFN-α n3 (alferon*) Protocol

Rahal JJ: http://www.nyhq.org/posting/rahal.html

3 million U (0.6ml) IV x1 then SQ @ 12 hrs on d1
3 million U SQ days 2-7 (total 8 doses)

1°: NIH Stroke Scale at admission, 1, 2, 3 wks
EEG, Neuroimaging “or LP” obtained & repeated as
“indicated clinically”
Daily CBC, QOD hepatic/renal fn during Rx
Ventilatory Status, Alimentation, Seizures
2°: LOS, Deficits at 4,8 wks p-discharge, Mortality

(* FDA approved human leukocyte derived IFN-α
preparation, Hemispherx Biopharma)
EQUINE VACCINES Licensed:
(1) Formalin-inactivated (Interceptor, Fort Dodge Animal Health, $20/dose)
(2) Recombinant canarypox-WNV (PrM/E) (Recombitek, Merial, $15/dose)
(3) Chimeric YF17D-WNV (Prm/E) (PreveNile, Intervet [Acambis License], $20/dose)

HUMAN VACCINES in Clinical Trials
(1) Phase I: ChimeriVax-WNV (Acambis) Randomized, Dbl-Blind, 60 healthy volunteers: Safety, tolerability, immunogenicity: 96-100% develop high titer Abs @28d.
    Phase II, 97% immunogenic at 28d in healthy 18-40yo, 41 + in progress (NCT00746798)
(2) Phase I: WN/DEN4-3’delta30 chimeric vaccine-safety, immunogenicity
(3) Phase I: Single plasmid DNA Vaccine encoding prM + E of NY99: subviral particles
    15 healthy volunteers 18-50, 3 doses (d0, 28, 56)
    Safe, well tolerated (mild injection site reactions), good PRNT (93%), ELISA (80%)
    T-cell immune responses ELISpot, Cytokine Staining (ICS) (E protein: ICS 93%, ELISpot 53%)
Individual neutralizing Ab responses to WN virus

Monath et al. PNAS 103, 6694-6699, 2006