Advanced Clinical Evaluation
Of a Zika Virus Vaccine

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US DoD Zika Mission Mandate

• ZIKV Countermeasures– DoD Priority
  o Global Health Security = National Security
  o Part of a whole of US government response
  o A number of infections have occurred in US armed forces and their dependents
  o Likelihood of autochthonous transmission within the continental US
US Geographic Overlap of Imported Zika Cases with Vector Range

Potential range of *A. albopictus* and *A. aegypti*
Based on Models by Kraemer et al. (2015)

- Lines are the northern extent of the area with an average monthly minimum daily temperature of 18°C or greater.*

State Reporting
Travel-associated Cases of Zika
- No Cases Reported
- 1 Case Reported
- 2 - 9 Cases Reported
- 10 - 49 Cases Reported
- ≥ 50 Cases Reported

Approved for Public Release
## WRAIR ZIKV PIV Development Timelines

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tbody>
<tr>
<td>Mouse Protection</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
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<td>Mouse Protection - Flavi Primed</td>
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<td>NHP Protection</td>
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<th>Clinical</th>
<th>2016</th>
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<tr>
<td>Phase 1 - Flavi Naïve &amp; Primed</td>
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<td>Phase 1 - Dose Ranging</td>
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<td>Phase 1 - Schedule Compression</td>
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<td>Phase 1 - VRC DNA Prime / PIV Boost</td>
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<td>Advanced Testing - Industry Partner</td>
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*PRECLINICAL*

*CLINICAL*
Clinical Phenotypes

- ~4:1 ratio of asymptomatic to symptomatic outcome
- Predominantly mild clinical phenotype

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Clinical Phenotypes

- Adverse neurologic outcomes following infection
  - GBS, ADEM
- Adverse outcomes following infection of the fetus
  - Neurologic
    - Microcephaly, Other neuro impairments (cerebellar, auditory, ocular)
  - Systemic
    - IUFD, growth restriction, placental insufficiency

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study (Lancet 2016; 387: 1531-39)

Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study (www.thelancet.com Published online March 15, 2016)

Goals of Immunization

- **Reduce clinical burden of infection**
  - Microcephaly and other congenital disorders
  - Neurologic disorders
- **Generate herd immunity**
- **Interrupt virus transmission**
  - Mosquito, sexual, maternal
- **Public benefit**
  - Reduce suffering
  - Reduce health care resource utilization
  - Restore societal normalcy
Prior Flavivirus Vaccines

- A safe and efficacious ZIKV vaccine is plausible

- Licensed vaccines spanning multiple constructs
  - Whole virion, live virus
    - Japanese encephalitis (JE), Yellow fever (YF)
  - Chimeric, live virus
    - JE, Dengue (DEN)
  - Whole virion, inactivated
    - JE, Tick Borne encephalitis (TBE)

- Numerous candidates in pre-clinical and clinical development
Vaccine Platforms

- **There may be multiple effective platforms**, thus possibly requiring multiple TPPs to meet different needs
  - Outbreak control, Long term herd immunity, Special populations

- **Non-replicating** (whole inactivated, DNA, recombinant)
  - Proof of concept for safety, efficacy (JE, TBE)
  - Less breadth, durability, production

- **Replicating** (whole virion, chimeric)
  - Proof of concept for safety, efficacy (YF, JE, DEN)
  - More breadth, durability but more reactogenicity and concern for special populations (HIV, pregnancy, pregnancy)
  - Timing concerns with other vaccines
Zika Specific Considerations

- ZIKV strain selection (contemporary, circulating in Americas)
- Early trials: FIH safety, age de-escalation
- Safety intersecting with goal of preventing adverse neurologic and congenital outcomes
- Safety remote from vaccination
- Safety in pregnancy, immunosuppressed
- Safety and immunogenicity in naïve and primed populations
Pre/Early Clinical Development

- **Down-selection of platform and antigen design**
  - Informed by structural studies and prior Flavivirus vaccine research

- **Preclinical assessment**
  - Animal models needed to study pathogenesis and evaluate efficacy

- **Phase 1 safety and immunogenicity**
  - Zika naïve

- **Phase 2 safety/immunogenicity for regimen/dose**

- **Phase 1 or Phase 2**
  - Flavivirus naïve vs primed
  - Endemic and nonendemic regions
Advanced Clinical Development

- **First option** should remain the pursuit of well-designed randomized controlled clinical trials
  - Other adaptive trials may provide some useful information, though with potential limitations

- Irrespective of design, must consider:
  - **Controls**
    - Placebo ideal, especially when assessing incidence of GBS
  - **Endpoints**
    - Infection, disease, GBS, congenital abnormalities
  - **Surveillance**
    - Infection, all disease, severe disease, specific outcomes
  - **Populations**
    - Broad age range, children, women of child bearing age
Efficacy Trial Design

- Endemic zones (>5% incidence of infection)
  - 20% clinically symptomatic (mild)
- Double-blind, placebo-controlled
- Multiple endpoints to consider
  - Clinical – Symptomatic disease in adults/children, GBS, congenital complications
  - Virologic – Serum & urine PCR in symptomatic & asymptomatic
  - Immunologic – Seroconversion in symptomatic & asymptomatic
- Powered on incidence of confirmed disease
  - Neurologic complications constitute secondary, exploratory endpoints
Clinical & Laboratory Endpoints

• Symptomatic disease with confirmed laboratory diagnosis
  • Serum PCR, Urine PCR, Seroconversion
    • Timing of diagnosis
    • Underestimation of true incidence
    • If interested in reduction in viral load, then have to look at asymptomatic cases
      • Potentially with frequent urine PCR
      • Depending on the assay, serologic cross-reactivity may not be a major problem
  • Symptomatic disease may include any clinical manifestation
    • May include subset analyses for specific complications
Efficacy Trials in settings of low attack rates

- Prior dengue vaccine RCTs implemented in dengue endemic regions
  - SE Asia and Latin America
  - Any disease, any severity, any serotype
  - 2.5% - 4.5% average clinical attack rate

- Conducting a ZIKV vaccine trial in settings with a clinical attack rate of 20% is feasible

- Because of mild illness, will require a sophisticated active surveillance system
  - Hospital, clinic, community based
Correlates of Protection

- Correlates of protection may be needed if efficacy trials with standard clinical endpoints become infeasible.
- Most likely to comprise a threshold titer of neutralizing antibodies, per previous Flavivirus vaccines

- Yellow Fever Vaccine
  - Protective titer $\geq 1:10$
  - Effective against 7 viral genotypes

- JE and TBE Vaccines
  - Protective titer $\geq 1:10$
  - High efficacy rates

- Dengue and WNV vaccines
  - E protein induced neutralizing antibody
Immunologic Assays

- Microneutralization assay, based on qualified dengue assay.
  - ELISA based readout
  - Moderately high throughput
  - Zika feasibility established
  - Require human Zika anti-serum to further characterize
  - Cross-reactivity to dengue appears minimal

- Flow based neutralization assay
  - High-throughput
  - Zika feasibility established
  - Currently utilizing for serosurvey
  - Will harmonize with MN assay
  - Cross reactivity to dengue appears minimal
Viral Assays

- **RT-PCR**
  - Optimized for high sensitivity
  - Only tested on ZIKV spiked samples
  - Currently establishing quantitative standards

- **Sequencing**
  - Primer directed next NGS for high-throughput and deep variant analysis.
  - Optimization and fine tuning
  - Biological viral load
  - Established methods for Vero & mosquito cell lines
Detection of Zika Virus - Urine

- Detection of virus in 6 patients in blood, urine by RT-PCR
Detection of Zika Virus - Blood

Table 1
ZIKV RT-PCR results for patients with both samples collected.

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<thead>
<tr>
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<th>Positive</th>
<th>Negative</th>
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<tr>
<td>Saliva</td>
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<tr>
<td>Positive</td>
<td>52 (28.6%)</td>
<td>16 (8.8%)</td>
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<tr>
<td>Negative</td>
<td>35 (19.2%)</td>
<td>79 (43.4%)</td>
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<tr>
<td>Blood</td>
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<tr>
<td>Positive</td>
<td></td>
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<tr>
<td>Negative</td>
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Fig. 1. Proportion of positive samples (Y axis in %) according to the number of days after symptoms onset (X axis) for the 182 patients with saliva, blood or both samples tested by ZIKV RT-PCR.
Supporting Activities

- Solidify a diligent **active surveillance system** for Zika viral infection – symptomatic, asymptomatic

- **Cohort studies** to
  - Determine persistence of virus across multiple biologic compartments
  - Longitudinally characterize convalescent immune response in Zika infected survivors.

- Bridge human cohort studies to animal studies to identify potential humoral and/or cellular **correlate of protection**.

- **Standardize assays** to measure ZIKV viral load and specific immune responses in Flavivirus naïve and primed individuals
Vaccine Development Challenges

- Immunopathology incompletely understood
- No known correlate/surrogate of protection
- Incomplete understanding of potential immunologic interactions with a prior flavivirus exposure
- Relatively mild clinical disease with notable and unique exceptions such as GBS and congenital disorders
- No well characterized animal model of disease
Summary Points

- Much of what is known about ZIKV comes from experiments conducted in the 1950-1960s
  - Research on other Flaviviruses can be informative
    - Past and current flavivirus vaccine development efforts have demonstrated a ZIKV vaccine is plausible

- Multiple vaccine platforms may be effective for different endpoints and populations
Summary Points

- RCTs remain the gold standard
  - Modified designs can serve as alternatives to design limitations

- Epidemiologic studies of incidence, clinical attack rates, viral kinetics and correlates of protection after infection are needed to inform design and endpoints of trials

- Active surveillance systems will be key to capturing clinical endpoints, both mild and severe
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