DEVELOPING SURROGATES AND CORRELATES FOR ZIKA VIRUS VACCINE EVALUATION

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WORLD HEALTH ORGANIZATION ZIKA VIRUS VACCINE WORKSHOP
Traditional Path to Vaccine Licensure

Effectiveness

- 21 CFR 201.57
  - “...all indications [e.g., prevention of disease]...must be supported by substantial evidence of effectiveness.”
  - Effectiveness based on adequate and well-controlled clinical studies using a standardized product

Evidence

- Protection against clinical disease
- Immunologic responses
  - Well-established immunologic marker that predicts protection and can be reliably measured in a validated assay
  - Facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease
Pathway to Accelerated Approval

21 CFR 601.40 and 601.41

- Product evaluated for safety and effectiveness in treating serious or life-threatening disease/condition AND provides meaningful therapeutic benefit over existing treatments
- Approval may be based on adequate, well-controlled clinical trials establishing an effect on a surrogate endpoint that is reasonably likely...to predict clinical benefit...

Requirement for post-marketing surveillance

- Underway at time of approval
- Adequate and well-controlled
- Conducted with due diligence
Surrogate Endpoints for Approval

- A surrogate endpoint that is reasonably likely to predict protection can be identified in clinical studies or through a combination of human and animal data:
  - Animal vaccination / challenge studies
    - *e.g.* threshold neutralizing/binding antibody titers
  - Phase 1/2 human studies
    - *e.g.* neutralization titers specific to vaccine antigen
    - *e.g.* antibody level specific to vaccine antigen
  - For animal rule, there must be a bridging immune marker between animal models and human studies
- Availability of validated assays and assay performance characteristics
  - *e.g.* sensitivity, specificity, precision

Adapted from M. Gruber/ US FDA
ZPIV Immunogenic and Protective in Rhesus Monkeys*


*NHPs vaccinated with 5µg ZPIV SC at Weeks 0 & 4. Challenged at Week 8 with 10^3 PFU ZIKV-BR (n=8 per group).
Purified IgG from ZPIV-Vaccinated Monkeys Protect Balb/C Mice from ZIKV-BR


*MN50 titers in mice measured 1 hour after adoptive Ab transfer. Challenged with 10^2 PFU ZIKV-BR (n=5 per group).
Purified IgG from ZPIV-Vaccinated Monkeys Protect NHPs from ZIKV-BR


[MN50 titers in NHPs measured 1 hour after adoptive Ab transfer. Challenged with $10^3$ PFU ZIKV-BR (n=2 per group).]
Serology and Molecular Assay Standardization

**Serology assay development, evaluation and validation**
- Establish and optimize IgM Antibody Capture (MAC)-ELISA inactivated ZIKV antigen.
- Evaluate clinical samples (serum, plasma) from ZIKV+ of endemic areas, returning travelers.
- Create clinical sample reference panels and validate MAC-ELISA.
- Serology panels from BARDA from PR (acute/convalescent serum PCR +, IgM PRNT +)
- Neutralization assay platforms comparison (next slide)

**Molecular assay development and evaluation**
- Support development of highly sensitive, multiplexed qPCR assay for use in serum and urine in anticipation of attaining EUA status (with Columbia University).
- Compare performance of several qPCR assays using different instrument platforms (ABI, Bio-Rad, BD Max).
- Create qPCR reference standards using heat-inactivated ZIKV diluted into serum.
Standardized Neutralization Assays for Vaccine Evaluation

- Contract to Battelle to develop standardized Zika vaccine assays for research
  - Awarded in September 2016
- Assays include
  - Microneutralization assay, Flow based Reporter Viral Particle (RVP) assay, PRNT. PCR, ELISA
- Assays
  - Transferred into Battelle from USG partners
  - Developed, optimized and or/ qualified within 12-18 months
  - Available for transfer to vaccine developers or can be performed at Battelle
- Consultation with other USG agencies to select specific assays
- Zika serum and panels from BEI, VTEUs and BARDA
- Bilateral comparison of NIAID RVP and WRAIR MN Assays on NHP and human samples
- NIBSC is producing a panel of murine monoclonal antibodies raised against whole inactivated Zika
Additional USG Supported ZIKV Correlates of Protection Research

- Small animal models (both lethal and congenital models)
  - AG129- Justin Julander, Utah State
  - Wt mice +IFNAR blocking mAb- Mike Diamond, WUSTL

- NHPs (viremia models)
  - Dave O’ Connor- U. Wisconsin
  - Southern Research Institute
  - Vaccine Research Center, NIAID

- Natural history studies
  - Nicaragua cohort- Eva Harris, UC Berkeley
  - Zika in infants and pregnancy study- 9 sites in 5 countries
Zika NS1 Protein

- Multifunctional virulence factor
- Essential for viral genome replication
- Infected cells also secrete NS1 as a hexameric lipoprotein particle
- Serum NS1 levels correlate with disease severity
- Sequence & antigenic diversity exists between flaviviruses potentially allowing for better discrimination
Questions