ARBOVAX®

ADVANCED TECHNOLOGY FOR INSECT-BORNE VIRUS VACCINES

VACCINES AND VACCINATION

VALENCIA, SPAIN

SEPTEMBER 2014

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Arbovirus Structure

- These are unique in that they derive their membrane from phylogenetically different hosts – insects and mammals
- Insect cells differ from mammalian cells in that they have no cholesterol in the membrane – this affects chemical and physical properties
- Surface glycoproteins of the virus are folded into high energy metastable structures – this is seen as important in cellular infection
- Protocols to release these proteins result in collapse to non-native low energy configurations

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Arbovax Unique Approach

- Modify transmembrane domain of target virus
  - Resulting virus incapable of complete replication in mammalian cells – “host-range mutation”
  - Replicates normally in insect cells
  - Retains native conformation of wild type
  - Changes hidden from immune system
  - Immune response same as with wild-type
  - Strong immune response in absence of disease

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Dengue Virus

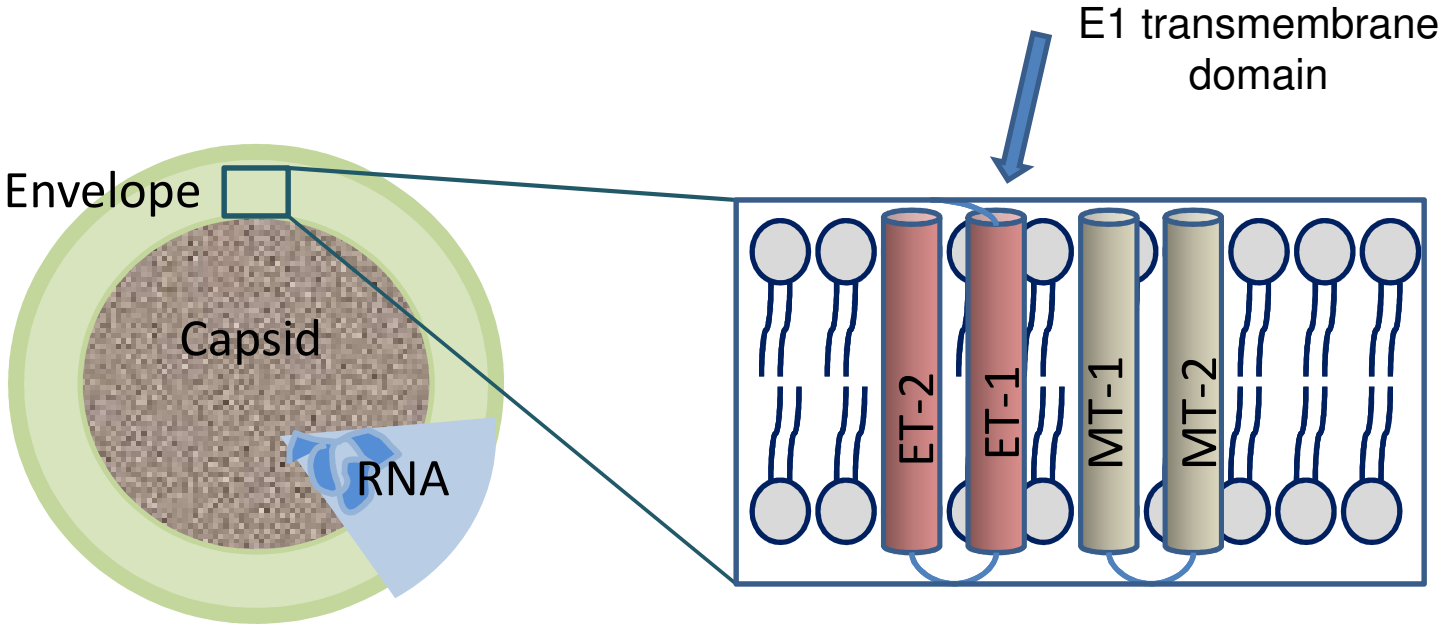


Figure 1: TM domains of envelope proteins transverse the lipid bilayer.

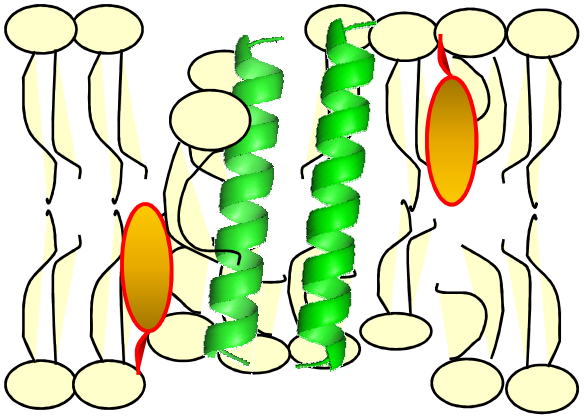
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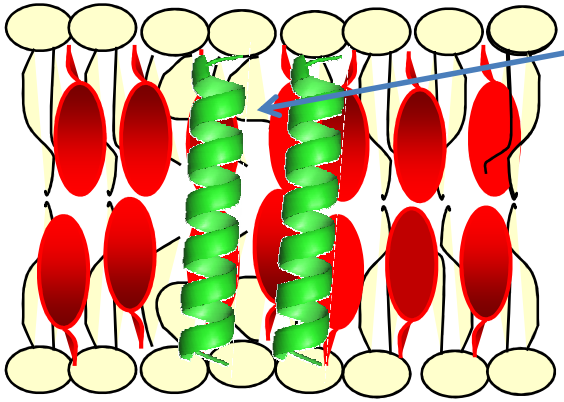
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Insect membrane

WT virus

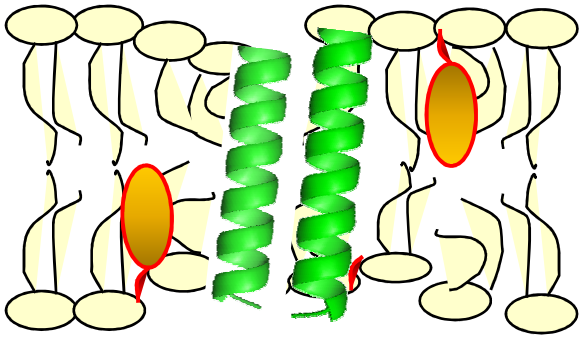
Mammalian membrane

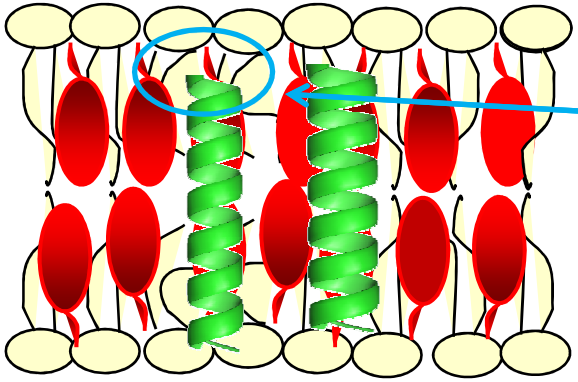




E-1 Transmembrane Domain (TMD)

Deletion mutant





Modified E-1 TMD is unable to span membranes

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Arbovax Technology Advantage

- Maximum immune response (like wild type)
- One dose, tetravalent immunization
- Cost effective manufacture
- Safe: no reversion to wild-type
- 2012 and 2013 PNAS publications strongly support whole virus approach to Dengue vaccine[1,2]

- [1]University of North Carolina School of Medicine. "Achilles heel of dengue virus identified: Target for future vaccines." *ScienceDaily*, 11 Apr. 2012. Web. 13 Apr. 2012.
- [2]Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8+ T cells. www.pnas.org/cgi/doi/10.1073/pnas.1305227110

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Arbovax Technology Advantage

- Technology can be rapidly adapted to other Arboviruses.
- Transmembrane domain alignment within Alpha and Flaviviruses
- Chikungunya vaccine aligned with Sindbis
  - Vaccine candidate identified 1 month
- Successfully tested in mice

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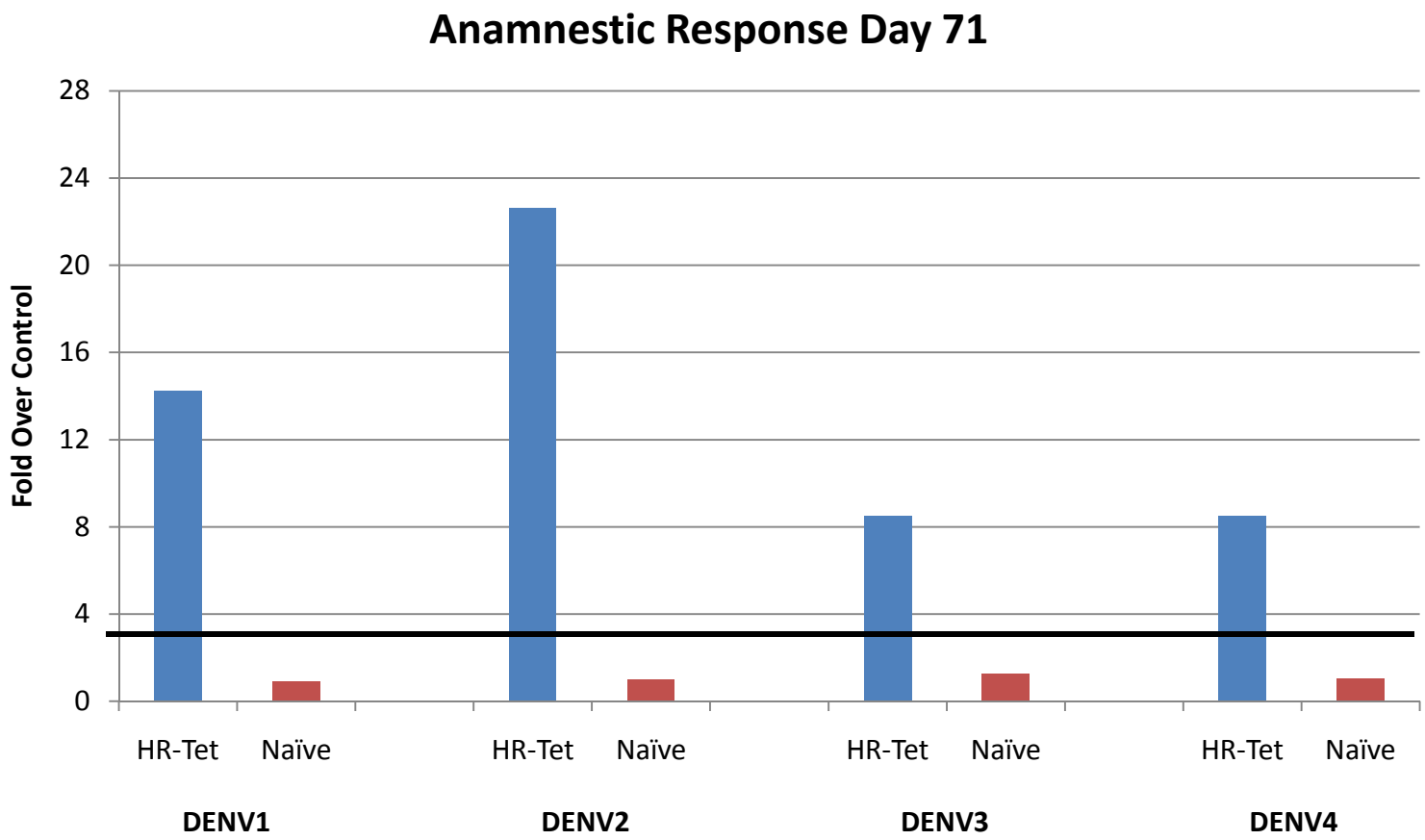
Tetravalent Trial

Virus	Animal	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9	Day 11
WT-Tet*	1253	DV2	DV1,2,4	DV1,2,3	DV3,4	DV3	DV4	DV2,4	---
	1272	DV2,4	DV1,2,4	DV2,3	DV3,4	DV3	DV4	DV2,4	DV4
	1407	DV2,4	DV1,2	DV2,3	DV3,4	DV3	DV4	DV2,4	DV2,4
	1427	DV1,2,4	DV1,2,4	DV2,3	DV3,4	DV3	DV4	DV2,4	DV2,4
TetV	1095	DV1,2	DV1,2,3,4	DV1,2,3,4	DV2,4	DV3	DV2,3,4	DV2,4	DV2,4
	1114	DV1,2,4	DV1,2,3,4	DV2	DV2,3,4	DV3	DV2,3,4	DV2,4	DV2,4
	1225	DV1,2,4	DV1,2,3,4	DV1,2,3,4	DV2,3,4	DV2,3	DV2,3,4	DV2,4	DV2,4
	1463	DV1,2	DV1,2,3,4	DV1,2,3,4	DV2,3,4	DV2,3	DV2,3,4	DV2,4	DV2,4

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Strong Immune Response



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Tetravalent Trial

Groups	Serotype	Sero-Conversion	
		Pre-Challenge*	Post-Challenge
HR-DV-Tet Vaccine	DV1	100% (16/16)	100% (4/4)
	DV2	100% (16/16)	100% (4/4)
	DV3	100% (16/16)	100% (4/4)
	DV4	100% (16/16)	100% (4/4)
Naïve	DV1	NA	75% (3/4)
	DV2	NA	75% (3/4)
	DV3	NA	100% (4/4)
	DV4	NA	100% (4/4)

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Tetravalent Trial

- Sero-conversion of 75% is the benchmark for LAV sero-conversion
- Animal sero-conversion rates are very high compared to other LAVs
- DV2 has 100% of pre challenge and high PRNT sero-conversion titers which were not seen with any chimeric LAV
- Animals inoculated with HR DV tetravalent vaccine respond rapidly with increased IgG following challenge.

To date no other LAV platform has performed this favorably with or without a vaccination boost.

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Additional Target: Chikungunya Virus

- Causes flu-like symptoms and painful arthritis-like joint swelling that may persist for years
- Emerging threat in Asia, India, South America and Caribbean
- CDC reporting over 600 cases in North America, as of Aug 2014
- Transmitted by A. Albopictus (tiger mosquito) found in over 30 U.S. states
- No commercially available vaccine for the prevention of this disease

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Chikungunya Preclinical Development

- Mice are an excellent model for trials
  - Display all human symptoms
- Began with five host range mutants injected into mice (N=225)
- Monitored injection site, foot and ankle swelling
- Efficacy measured by:
  - Virus titer
  - Presence of virus neutralizing antibodies
- **Determined that one mutant (TM17-2) is a good vaccine candidate**

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Assay of Infection after Challenge

	Naïve	MR44	TM17-1	TM17-2
Virus in serum	+	+	+	-
Virus in ankle	+	-	-	-
Virus in quad	+	+	+	-
NAb	+	-	-	+
Inflammation	+	-	-	-

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Chikungunya Study Conclusions

- TM17-2 is an excellent candidate to move forward:
  - No swelling at the site of infection
  - Viremia less than wild-type
  - No virus became established in the joints or muscles
  - Good neutralizing Ab response (immunogenic)
  - No challenge virus replicated (protection)
  - No virus in serum, ankle or quad
  - Five fold increase in NAb after challenge
  - Pre-IND discussion with FDA completed early 2014
  - Candidate is ready to move forward to phase 1 human trial

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Current Status

- Paper published in Journal of Virology 2014
- US FDA review of Dengue and Chikungunya pre-IND submission cleared move forward to human phase 1 trial
- 30 subjects, 6 month phase 1 trials expected late 2015
- Phase 2 trials to follow

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THANK YOU

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