Merck Dengue Vaccine Program

First Regional Dengue Symposium
Rio de Janiero
03-Nov-2015

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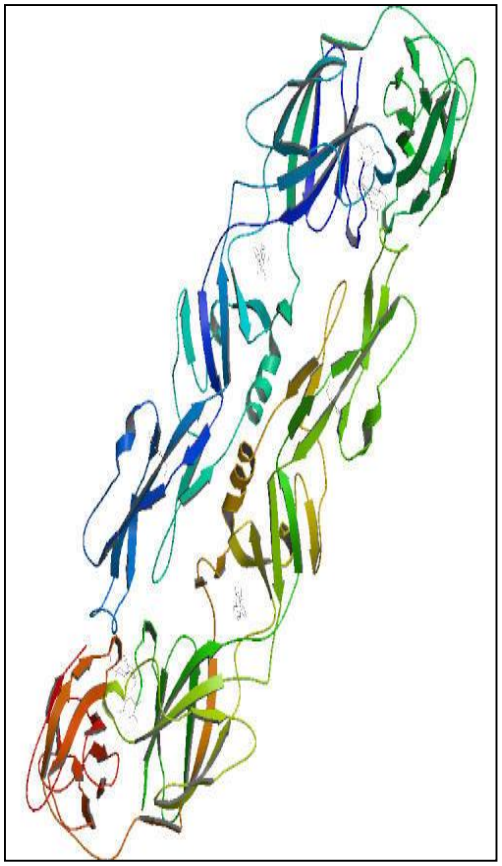
Merck's Dengue Program V180:

V180 Key Characteristics

- Recombinant, truncated envelope glycoprotein (DEN-80E) expressed for all 4 dengue virus types in Drosophila S2 insect-cell culture
  - Native-like conformation; good yields
- Envelope protein is key target for virus-neutralizing antibody; includes T-cell epitopes
- As a soluble subunit vaccine, V180 will likely require adjuvant in flavivirus-naïve populations (may not be needed in flavivirus-experienced)



Crystal structure of Merck DEN2-80E protein:
S. Harrison, Harvard University

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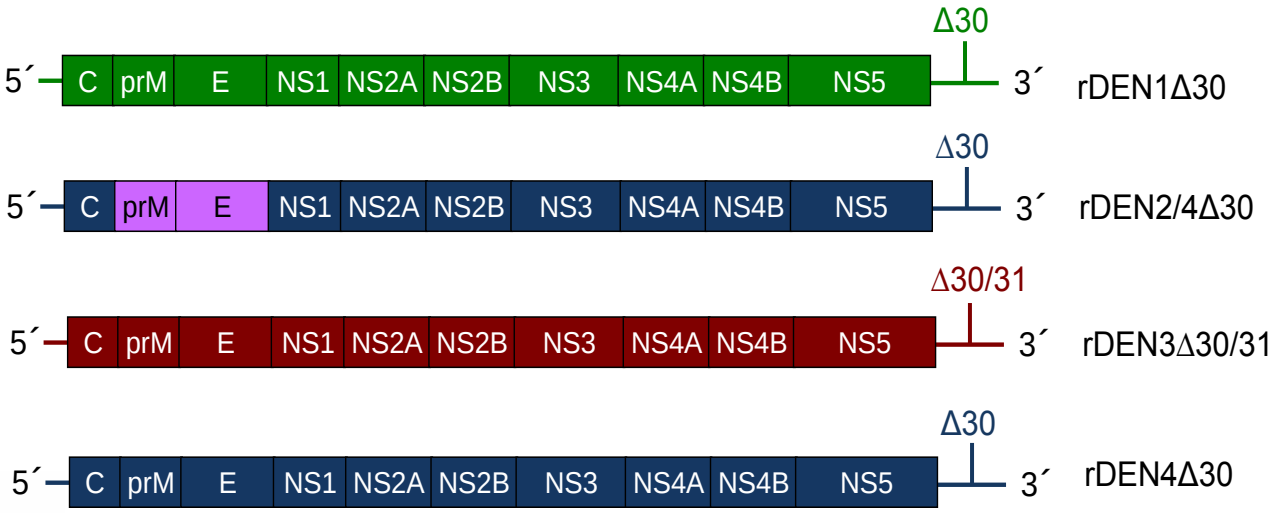
Merck's Dengue Program V181:

V181 Key Characteristics

- NIH live attenuated viruses for all 4 DENV types (LATV); molecularly defined attenuating mutations
- Tested as monovalent /tetravalent formulations in >1000 volunteers in US Phase I studies
- Phase II studies ongoing in Brazil (Instituto Butantan) and in Thailand (NIH sponsored)
- Merck in-licensed the vaccine in October 2014



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V180 P001 First-In-Human Trial: Study Design

- **Overall objective:** To evaluate V180 for safety and immunogenicity
- **Design**: Randomized, blinded, placebo-controlled, dose-escalation
  - Enrolled in 3 cohorts by escalating antigen dose (low, medium, high)
- **Population**: Flavivirus-naïve, healthy young adults 18 to 49 years old in Australia
- **Sample size:** Total N=98
- **Formulations:** V180 with/without adjuvant; placebo
- **Dosing schedule:** 3 injections at 1-month intervals
- **Primary safety and immunogenicity assessments:** At 28 days Postdose 3 (PD3)
- **Long-term safety and immunogenicity follow up:** Through 1 year PD3
- **Current status:** Trial completed

V180 P001 Study Results

- All formulations were generally well tolerated. There were no SAEs and the external Data Monitoring Committee allowed the study to continue according to protocol.
- Formulations containing ISCOMATRIX™ adjuvant were highly immunogenic inducing seroconversion ($FRNT_{50}$ titer ≥ 10) in 85.7-100% of subjects depending on the serotype. GMTs ranged from 73-1344 depending on the formulation and serotype.
- Non-adjuvanted formulations or a formulation adjuvanted with Alhydrogel™ showed evidence of immunogenicity but were less consistent in inducing seroconversion (0 - 62.5%) and resulted in lower GMTs (<10 – 20) depending on the formulation and serotype.
- Titers declined over time for all formulations postdose 3 but generally plateaued above baseline for formulations containing ISCOMATRIX™ adjuvant

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V180 and V181 Next Steps:

- Clinical trial evaluating ability of recombinant V180 to boost immune responses in subjects who have previously received V181 ongoing in collaboration with NIH (NCT 02450838)
  - Randomized, placebo-controlled trial
  - N=20 subjects
  - V180 with and without Alhydrogel™ adjuvant
  - Being conducted at Johns Hopkins University and the University of Vermont
- Manufacturing of V181 ongoing to support Merck-sponsored clinical trials of the live attenuated virus vaccine
- Next steps in development being defined