# DENGUE VACCINE LANDSCAPE

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# Dengue Vaccines – Feasible

- Type-specific dengue virus (DENV) infection confers protection against disease (?infection) with that serotype
- Can produce vaccine candidates
  - Adequate virus or antigen yield
  - Immunogenic
  - Good safety profiles

# Brief History

- 1945-1960's: Live attenuated vaccines produced in suckling mouse brains
- 1970's – 80's: Live attenuated vaccines produced in cell culture
  - US Army & GSK
  - Mahidol University (Thailand) & sanofi pasteur
- 1990's – today = commercial development
  - sanofi pasteur and GlaxoSmithKline
  - Biotech companies & developing country vaccine manufacturers

# Dengue Vaccines – Challenges

- Interference
  - Live, attenuated vaccines
  - Tetravalent formulation
- Less than ideal assays for anti-DENV
  - measure of protection / correlate of protection
- Evaluation – efficacy and safety
  - Protection against multiple DENV types
  - Differing disease epidemiology
  - Safety - theoretical potential for immune enhanced disease (ADE / DHF)

# Clinical Trials to Evaluate Efficacy of Dengue Vaccines

- Blinded, placebo-controlled clinical trials in age groups with highest disease incidence
- Case identification = community-based surveillance for febrile illness
- Primary end-point for efficacy = dengue fever (DF) from infection by any DENV serotype
- DF = febrile illness ≥2 days + DENV viremia detected by PCR or NS1 antigen

Guidelines for Clinical Evaluation of Dengue Vaccine in Dengue Endemic Areas. Vaccine 2008;26:4113-4119

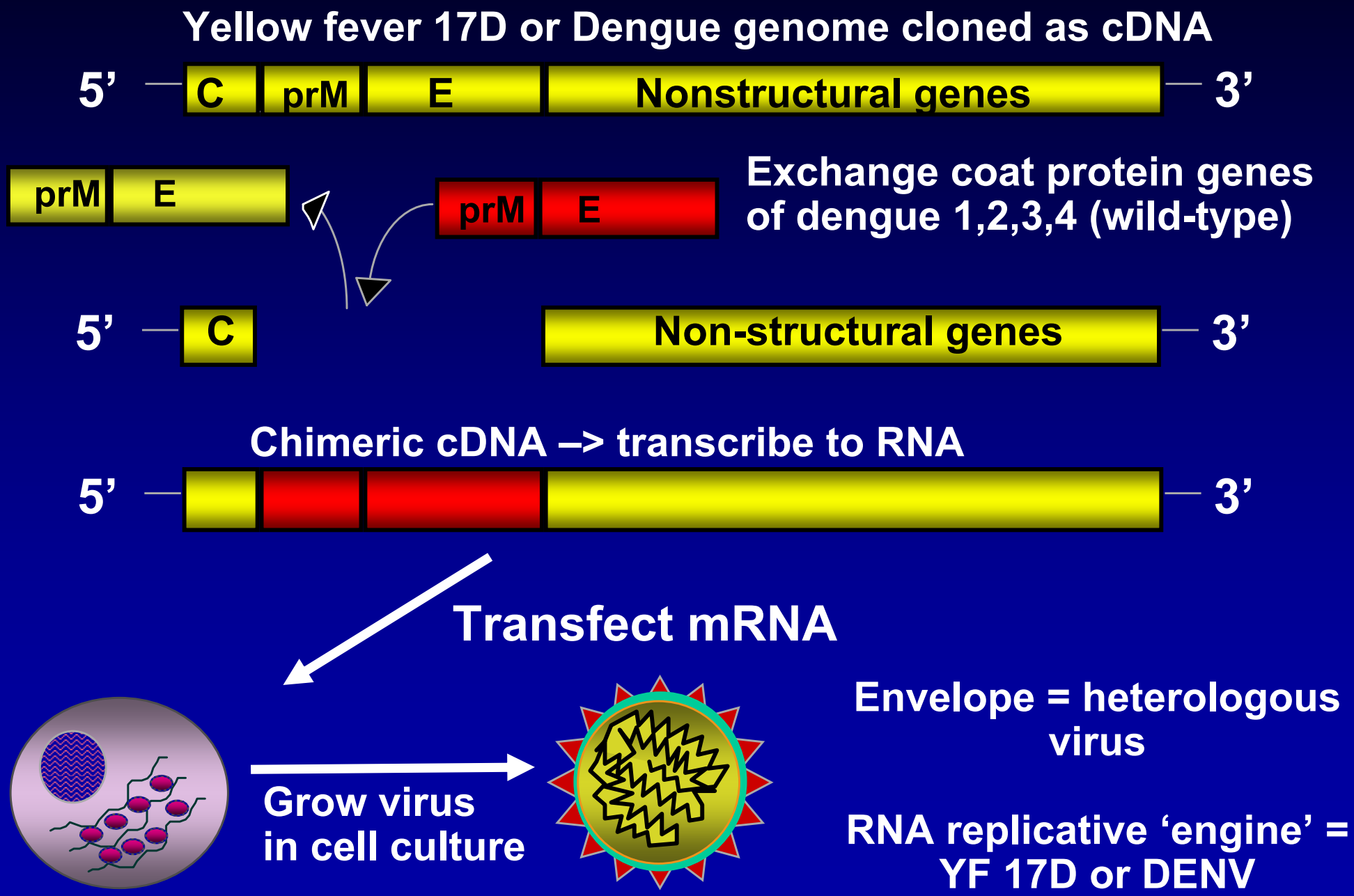
# Types of Dengue Vaccine Candidates

- **Present Generation** (commercial development)
  - Cell culture adapted, live attenuated viruses
  - Infectious clones
    - chimeric viruses
    - attenuation by site directed mutagenesis
  - Recombinant subunits of DENV envelope proteins
- **Next Generation** (in development)
  - Inactivated dengue viruses
  - DNA
  - DNA shuffling
  - Viral vectored subunits
  - Peptide chimeras
  - VLPs

# Dengue Vaccine Candidates (Commercial)

| Developer / Producer | Approach |
|---|---|
| Acambis/ Sanofi Pasteur | 4 chimeras composed of yellow fever 17D virus non-structural genes + respective DENV 1,2,3 and 4 envelope genes |
| WRAIR / GSK | Cell culture passage of clinical isolates |
| CDC/InViragen | DENV-2 attenuated virus + 3 chimeras composed of DENV-2 non-structural genes + respective DENV 1,3, and 4 envelope genes |
| NIAID Laboratory of Infectious Diseases | Genetically engineered, stable mutations in 3' non-coding region of DENV-1, 2, 4 vaccine candidates. DENV-3 candidates = DENV-4/DEN-3 chimeras |
| Hawaii Biotech | Subunit - 80% preM expressed in Drosophila S2 cell lines, +/- NS1, alum adjuvant |

# Chimeric Flavivirus Vaccine Technology



# Safety Considerations
# Live / Chimeric Vaccines

- Reversion to virulence (17D →wt YF)
- Mosquito transmission
- Recombination with other Flaviviruses / viruses
- Potential adverse events from YF chimeras
  - Neurovirulence and neuroinvasivness
  - Viscerotropism - extraneural pathology
- Level of attenuation – potential for dengue
- Theoretical potential for severe dengue in immunologically primed persons

# Status of Dengue Vaccines

| Developer | Producer | Process Development | Evaluation | | |
|---|---|---|---|---|---|
| | | | Phase I | Phase II | Phase IIB-III |
| Acambis | SanofiPasteur | → | → | → | 2009 |
| WRAIR | Glaxo SmithKline | → | → | → | ? |
| | | | → | Mid-2009 Tetravalent | |
| NIH | Biological E | → | ? | | |
| | Butantan | → | 2010 | | |
| | Panacea | → | ? | | |
| CDC | InViragen | → | Q2-2010 | | |
| Hawaii Biotech | Hawaii Biotech | → | Q3-2009 | | |

# Clinical Trial to Determine Efficacy of sanofi pasteur Yellow Fever-Dengue Chimeric Vaccine

- Design: blinded, placebo-controlled clinical trial (Phase IIB)
- Vaccines
  - Dengue - tetravalent, live attenuated 17D YF- DENV chimera
  - Placebo – vaccine diluent
- Administration: 0, 6, 12 months SC
- PI: Arunee Sabchareon, Mahidol University
- Site: Ratchaburi Province, Thailand
- Sample size: 4002 children ages 4-11 years
- End-point: dengue fever (febrile illness + PCR viremia)
- Duration: 27 cases (~ 2 yrs) + 3 year safety follow-up

# Dengue Vaccine Evaluation

# Challenges for Development of Field Sites for Dengue Vaccine Clinical Trials

- Need for **multiple sites** in Asia and the Americas
- Population-based, **febrile illness surveillance** to identify DF cases and determine:
  - Age-specific disease incidence
  - Determine variation in incidence over several seasons (~2-3 yrs)
- **Laboratory capacity** to conduct molecular and sero-diagnostics for acute dengue (DF)
- Development of **infrastructure / capacity** to conduct surveillance, laboratory testing and data management under GCP / GCLP

# Dengue Vaccine Use – Challenges

- Product profile not ideal (live attenuated)
  - More than one dose required in 2nd year of life
  - Administered subcutaneously
- Vaccine delivery
  - catch-up immunization
- Crowded immunization schedule