Dengue Fever ; symptoms , treatment & vaccine trials

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Symptoms

- Fever ,Headaches & Bradycardia /hypotension
- Aka ache bone-fever- bone/muscle aches
- Clinical presentation-silent infection, dengue fever, Dengue hemorrhagic fever and dengue shock syndrome
- Viral infection-Treatment is supportive
- Asymptomatic-incubation 3-14days
- 80% mild symptoms-uncomplicated fevers
- Clinical course-febrile ,critical and recovery phase

Staging

- Febrile phase-

  >40^0 (104°F)generalized pain,measle like rashes, petechiae,mild bleeding from mucous membranes,biphasic fever.

- Critical phase-

  high resolution fever, fluid accumulation chest &abdominal cavity

(capillary permeability & leakage)- organ dysfunction(Endothelial dysfunction , severe bleeding(coagulation disorder), dengue shock syndrome, dengue hemorrhagic fever

-occurs in< 5% ,secondary infections are at more risk.

- Recovery phase-

Reabsorption of leaked fluid into blood stream

Severe itching,slow heart rate(fluid overload)

Brain fluid overload-reduced consciousness or seizures

presentations

- Silent infection - The person is infected with the virus but shows no symptoms. The vast majority of dengue infections have no symptoms
- Classic dengue fever- Dengue fever lasts for 5-7 days. The infected person has high fever (39 ° to 40 ° C), headache, tiredness, muscle aches and joint pain, malaise, nausea, vomiting, red spots on the skin, abdominal pain (especially in children)
- Dengue Hemorrhagic fever(DHF) –blood coagulation, bleeding of small vessels in internal organs(nosebleeds, gingival, urinary, gastrointestinal or uterine bleeds). Bradycardia(dizziness), collapse and shock
- Dengue shock syndrome- hypotension,restlessness,neurological, cardio respiratory problems, liver failure, gastrointestinal bleeding and pleural effusion

Treatment

- Etiologic agent virus-no specific medicine
- Tx- purely relief of symptoms
- Rest & fluid intake- rehydration
- Antipyretics and pain killers
- Traditional medicine-Brazil cat claw herb(inflammation) & Philippines dengue tawa-tawa herbs & sweet potato tops juice (to increase the platelets counts)

Vaccine Advances

- Epidemiology statistics -international health priority
- Academic labs & pharmaceutical co- several candidates(poor cell culture & no reliable animal model)
- Tetravalent vaccine- poor immunogenicity (interference between the 4 strains)
- No cross protection & fear of immune enhancement by heterotypic DV aantibodies
- Infectious clones technology –stimulated diverse candidates & very promising
- Scientists are reasonably optimistic on getting an effective vaccine licensed by 2012(pre clinical- phase 3)

Live attenuated vaccines

- Initially famous-cell culture Mahidol Thailand)
- Dog Kidney cells, green monkey cells &/ fetal rhesus monkey cell cultures
- Challenge-

  a)-correct balance between insufficient attenuation and over-attenuation

  b) lack of correlation between in vitro markers of attenuation such as small plaque phenotype or thermo sensitivity and in vivo attenuation

  c) the phenomenon of immunological interference between the four DV serotypes
- WRAIR-by serial passage of the 4 Dv strains in dog kidney cells,tested in adults & kids (tetravalent formulations) Lisenced by Gsk currently undergoing phase II trials

Live chimeric virus vaccines

- CDC us employed -homotypic chimeric virus approach
- Engineer DV2 chimeras- inserting the structural protein genes from DV1, DV3 & DV4
- Tested found safe & immunogenic in humans- licensed to Sanofi Pasteur
- Tetravalent chimeric combination-induce a transient and low grade viremia in nonhuman primates (dominant immunogenicity)
- Poor replication & dissemination in mosquitoes(minimal risk of infection& transmission)
- Phase IIb pediatric trial has been launched by Sanofi Pasteur

Live recombinant,DNA & sub unit vaccines

- Naval Medical Research Center
- Dv genes inserted to Ad 5 vector-recominants expressing the 4 Dv serotypes
- Tested on mice-shown to induce neutralizing antibodies on the 4 Dv serotypes
- Tested on macaques- induced significant protection against challenge with all four DV serotypes
- DNA-based vaccine approach-Biojector device (immunization) Evaluation of phase 1 ongoing
- Hawaii Biotech Inc- BALB/c mice elicited long-lasting neutralizing antibodies against all 4 serotypes

Flavivirus proteins

- Virions contain only three virus-coded proteins called structural proteins -Capsid (C)

  -Preme,mbrane (prM) (internal proteins)

  -Envelope (E) glycoprotein (viral attachment & mediate protectective immune responses)

(Located the amino terminus and incorporated into mature, infectious virions)

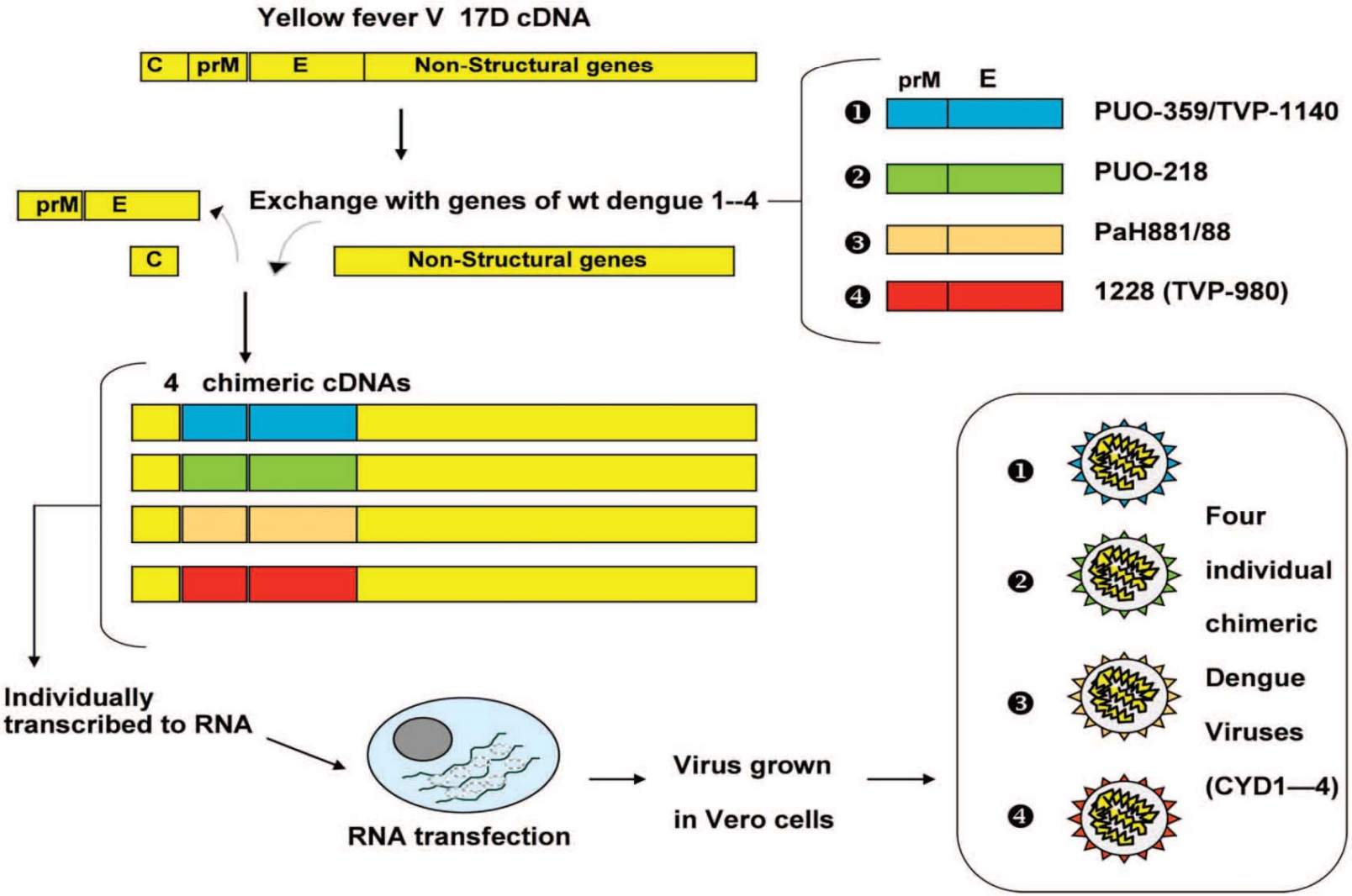
- several non structural proteins located at the carboxyl terminus are involved in the intracellular replication of the virus

- NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5 (important role of mediating immunity)
- NS1 important vaccine component- expressed on the surface of infected cells making them targets for immune cytolysis(secretion is an important event in human host infections
- shown to be involved in the early steps of viral replication

Development of Sanofi Pasteur tetravalent

- Composed of 4 four recombinant chimeric live attenuated vaccines - on a yellow fever vaccine 17D (YFV 17D) backbone (ChimeriVax)
- Each expressing the prM and envelope genes of one of the four dengue virus serotypes
- studies have demonstrated that the TV dengue vaccine is genetically & phenotypically stable,non-hepatotropic, less neurovirulent than YFV 17D
- Both invitro & invivo - showed that the TV dengue vaccine induced controlled stimulation in human dendritic cells &significant immune responses in monkeys
- Candidate vaccine is immunogenic and safe in humans –currently being evaluated in large scale efficacy studies
- The Live attenuated & chimeric nature-necessitates extensive preclinical and clinical characterization
- Status as GMOs- compliance with additional specific regulations

Construction of the four chimeric vaccines.



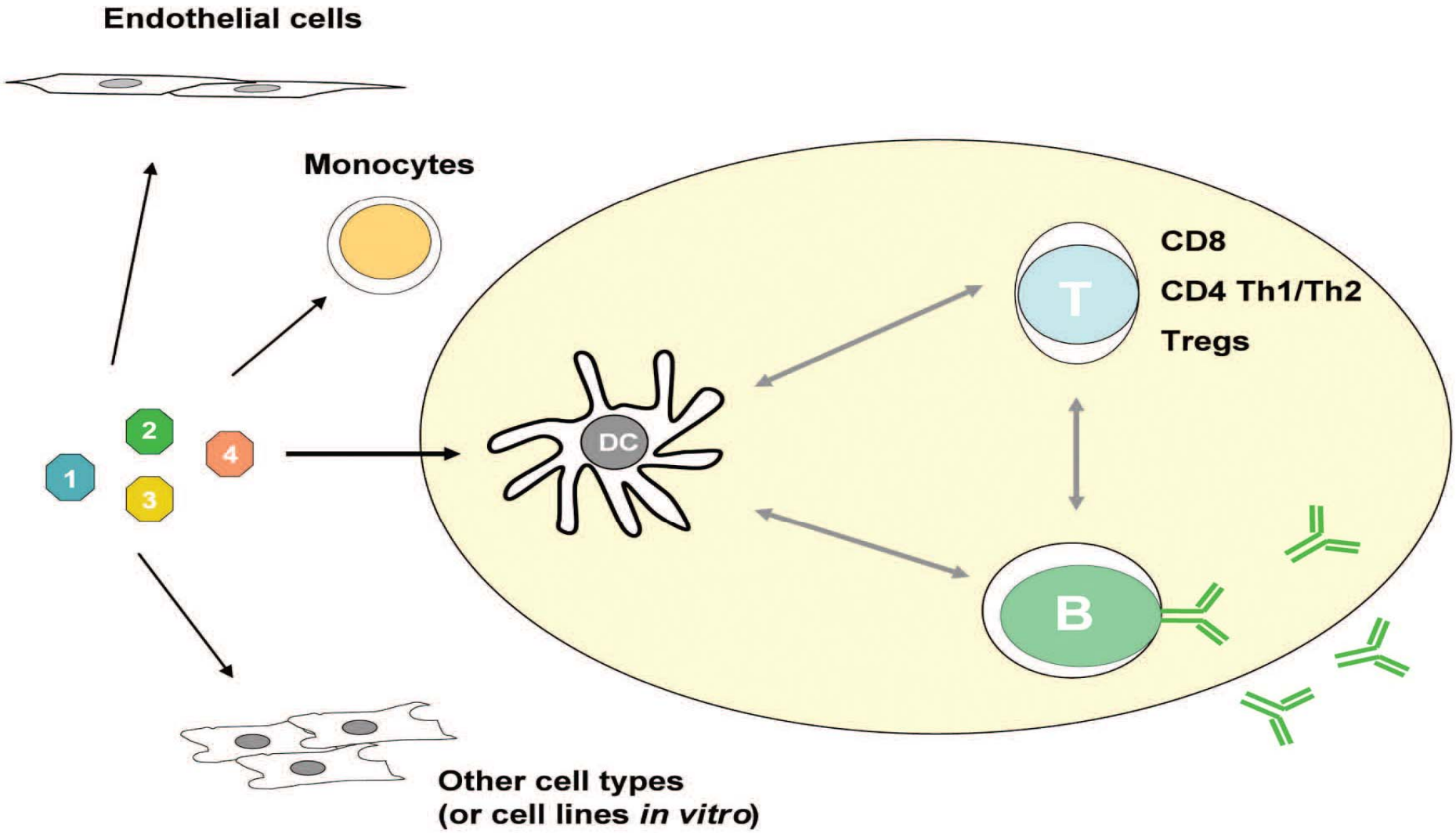
Human Vaccines 6:9, 696-705; September 2010;

Pre clinical assays evaluation

Tools and models	End points
Vaccine produced on primary cells, Vero cells, C6/36...	Genotype, Phenotype Structure (conformation maturation,glycosylation..)
Vero cells, C6/36, DCs, Primary and Transformed cells	Infectivity, Yields, Tropism Potential interferences
PBMCs, DCs, Monocytes Endothelial cells	Phenotype modification Cytokines induction
FcγR positive cells Primary monocytes, cell lines, DCs	Protective / enhancing activity of antibodies
Mosquito vectors *Aedes aegypti, Aedes albopictus*	Replication and transmission
Animal models Monkeys Normal mice SCID-hu mice KO mice, AG129 ...	Immunogenicity, Innate and adaptive immunity Viremia, safety Genetic stability Interferences

Human Vaccines 6:9, 696-705; September 2010; © 2010 Landes Bioscienc

Immune responses-Dengue vaccine



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Clinical development/challenges

- the need to induce an adequate and balanced immune response to all four serotypes(geographical bal)
- the need for two or three vaccination -1 yr
- absence of correlate and threshold protection -need to demonstrate clinical efficacy
- the need to demonstrate long term safety and immunogenicity
- risks of sensitization to severe dengue infection (DHF) after vaccination and of acute viscerotropic disease(AVD) and neurotropic disease (AND)
- need to comply with GMO regulations & with Good Clinical Practice guidelines

Future challenges/conclusion

- Understand immunology and non clinical research

-high-throughput serotype specific neutralization assays

-reliable and simple assays to examine antibody binding affinity and kinetics

-understanding interference mechanisms between dengue viruses

-non-clinical safety models need to be further explored

❖ preclinical and clinical results support the favorable immunogenicity and short-term safety

- An extensive clinical development program for dengue TV is underway
- Both humoral and cellular responses are induced in humans against all four serotypes
- Long-term follow-up will address the duration of immunity and theoretical long-term safety issues