Desafios para o desenvolvimento de uma vacina para o Zika vírus

Challenges for the development of a vaccine for Zika virus

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Flavivirus Vaccines

• Most neutralizing antibodies are induced against E protein, and all approved and most developing flavivirus vaccines contain E antigens
Flavivirus Infections in Humans

- **Mosquitoes-transmitted viruses:**
  - Yellow Fever,
  - Dengue Fever,
  - Japanese encephalitis,
  - West Nile viruses,
  - St. Louis encephalitis
  - Zika virus

- **Flaviviruses transmitted by ticks:**
  - Tick-borne Encephalitis (TBE),
  - Kyasanur Forest Disease (KFD)
  - Alkhurma disease,
  - Omsk hemorrhagic fever
Worldwide distribution of flaviviruses

Adapted from T. Ishikawa et al. / Vaccine 32 (2014) 1326–1337
Flaviviruses Vaccines

Adapted from T. Ishikawa et al. / Vaccine 32 (2014) 1326–1337
Flavivirus Vaccines

- Flavivirus vaccines against YFV, JEV TBEV and DENV infections have been developed using different platforms.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine type</th>
<th>Strain</th>
<th>Substrate</th>
<th>Adjuvant</th>
<th>Immunization schedule</th>
<th>Manufacturer(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>YFV</td>
<td>Live attenuated vaccine</td>
<td>17DD and 17D-204</td>
<td>SPF embryonated chicken eggs</td>
<td>no</td>
<td>One dose, 10 years</td>
<td>Brazil (Bio-Manguinhos/Fiocruz), France (Sanofi Pasteur); Senegal (The Institute Pasteur in Dakar); Russia (Chumakov Institute of Poliomyelitis and Viral Encephalitis)</td>
<td>Licensed in 1937</td>
</tr>
<tr>
<td>YFV</td>
<td>Inactivated (β-propiolactone) vaccine</td>
<td>17D-204</td>
<td>Vero cell (bioreactors)</td>
<td>Alum</td>
<td>Two doses, 4wks apart</td>
<td>Xcellerex/GE HealthCare (US)</td>
<td>Phase 1</td>
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<tr>
<td>JEV</td>
<td>Inactivated (formalin) vaccine</td>
<td>Nakayama Beijing-1 (P1)</td>
<td>Mouse brain</td>
<td>no</td>
<td>Two doses, 4wks apart</td>
<td>Green Cross (South Korea), Central Research Institute (India), Adimmune corp (Taiwan), Government Pharmaceutical Organization (Thailand), Vabiotech (Vietnam)</td>
<td>Licensed in 1930</td>
</tr>
<tr>
<td>JEV</td>
<td>Inactivated (formalin) vaccine</td>
<td>Beijing-1 (P3)</td>
<td>Primary hamster kidney cell (PHK)</td>
<td>no</td>
<td>Two doses, 1wk apart</td>
<td>Beijing, Shanghai, Wuhan and Changchun Institute of Biological Products (China)</td>
<td>Licensed in 1968</td>
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<tr>
<td>JEV</td>
<td>Live attenuated vaccine</td>
<td>SA14-14-2</td>
<td>Primary hamster kidney cell (PHK)</td>
<td>no</td>
<td>One dose Booster 7 yrs</td>
<td>Chengdu Institute of Biological Product (China)</td>
<td>Licensed since 1988</td>
</tr>
<tr>
<td>JEV</td>
<td>Inactivated (formalin) vaccine</td>
<td>SA14-14-2</td>
<td>Vero cell</td>
<td>Alum</td>
<td>Two doses, 4wks apart</td>
<td>Valneva SE (France) Biological E (India)</td>
<td>Licensed since 2009 WHO prequalified</td>
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<tr>
<td>JEV</td>
<td>Inactivated (formalin) vaccine</td>
<td>Beijing-1</td>
<td>Vero cell</td>
<td>Alum</td>
<td>Two doses, 4wks apart</td>
<td>Biken (Japan)</td>
<td>Licensed in Japan since 2009</td>
</tr>
<tr>
<td>JEV</td>
<td>Live-attenuated chimeric vaccine</td>
<td>SA14-14-2 prM/E genes replaced YFV-17D genes</td>
<td>Vero cell</td>
<td>no</td>
<td>Single dose Booster dose have not yet been determined</td>
<td>Sanofi Pasteur (France)</td>
<td>Licensed in Australia and Thailand since 2010</td>
</tr>
<tr>
<td>TBE</td>
<td>Inactivated (formalin) vaccine</td>
<td>Neudorf (TBEV-Eu)</td>
<td>Primary chicken embryo cell (PCEC)</td>
<td>Alum</td>
<td>Three doses</td>
<td>Baxter AG, Austria</td>
<td>Licensed since 1976</td>
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<tr>
<td>TBE</td>
<td>Inactivated (formalin) vaccine</td>
<td>Sofjin (TBEV-Fe)</td>
<td>Primary chicken embryo cell (PCEC)</td>
<td>Alum</td>
<td>Three doses</td>
<td>Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russia</td>
<td>Licensed since 1982</td>
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<tr>
<td>TBE</td>
<td>Inactivated (formalin) vaccine</td>
<td>German K23 (TBEV-Eu)</td>
<td>Primary chicken embryo cell (PCEC)</td>
<td>Alum</td>
<td>Three doses</td>
<td>Novartis, Switzerland</td>
<td>Licensed since 1991</td>
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<tr>
<td>TBE</td>
<td>Inactivated (formalin) vaccine</td>
<td>205 (TBEV-Fe)</td>
<td>Primary chicken embryo cell (PCEC)</td>
<td>Alum</td>
<td>Three doses</td>
<td>Microgen, Russia</td>
<td>Licensed since 2001</td>
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<tr>
<td>DENV</td>
<td>Live-attenuated chimeric vaccine</td>
<td>DENV 1, 2, 3 and 4 prM/E genes replaced YFV-17D genes</td>
<td>Vero cell</td>
<td>no</td>
<td>Three doses six months apart</td>
<td>Sanofi Pasteur</td>
<td>Licensed since 2015</td>
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<tr>
<td>Developer</td>
<td>Preclinical development</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Licensure</td>
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<tr>
<td>GSK and WR AIR/r</td>
<td>TDENV/PIV: purified inactivated vaccine developed using formalin inactivated</td>
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<td>Bio-Manguinhos</td>
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<td>Merck</td>
<td>V180: recombinant subunit vaccine developed using wildtype premembrane and truncated envelope protein via expression in the Drosophila S2 cell expression system</td>
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<td>NIAID</td>
<td>TV003/TV005: live attenuated vaccine using wild type strains with genetic mutations</td>
<td>TV003: live attenuated vaccine developed using wild type strains with genetic mutations</td>
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<tr>
<td>Butantan Institute</td>
<td>TV005: live attenuated vaccine developed using wild type strains with genetic mutations</td>
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<tr>
<td>Panacea Biotech</td>
<td>DIME100: DNA vaccine developed using premembrane and envelope proteins of DEN1 expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012.</td>
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<td>NMRC</td>
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<tr>
<td>Sanofi Pasteur</td>
<td>DENVax: live attenuated vaccine developed using wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene</td>
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<td>Takeda</td>
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*Table last updated January 4, 2016

1 GlaxoSmithKline and Walter Reed Army Institute Research.
2 National Institute of Allergy and Infectious Diseases, US NIH: National Institutes of Health. NIAID licensed its strains to several developing country manufacturers on a non-exclusive basis.
3 Both Butantan Institute and Panacea Biotech use NIAID vaccine formulation.
4 US Navy Medical Research and Development.
5 Dengvaxia has been approved by Mexico, the Philippines and Brazil for 9 to 45 year olds living in dengue endemic areas.
Vaccine development activities

Pre-licensure
- Medical need & disease burden
- Scientific feasibility
- Basic vaccine research
- Candidate vaccine
- Pre-clinical
- Manufacturing process development
- Product characterization

Post-licensure
- Phase IV studies to broaden indication or to assess specific populations
- Pharmacovigilance
- Phase IV studies on safety/effectiveness
- Risk management plan
- Registration

Hardt et al., Vaccines 2013, 1(3), 204-224;
Candidate selection
Antigen delivery platform definition
Upstream process definition
Downstream process definition
Seed lots preparation
Pilot scale up
Formulation (adjuvants, stabilizers, preservatives)
Industrial scale up (consistency lots production)
Final product

Quality Control
Antigen Characterization
• Yields
• Identity
• Purity
• Stability

QC Cell Substrate and Virus seed
• Adventitious agents
• Tumorigenicity
• Karyotype
• Genetic stability
• Sterility
• Identity
• Cell viability

QC Tests Intermediate Product
• Appearance
• Sterility
• Bioburden
• Endotoxin
• DNA
• HCP
• Potency
• Identity
• Integrity
• Purity

QC Tests Final Product
• Appearance
• pH
• Osmolality
• Endotoxin
• Identity
• Potency
• Sterility
• Adjuvant concentration
Pre-Clinical and Clinical Phases

Pre-licensure

- Animal models
  - Disease models
  - Challenge models
    - LD50
    - Viremia
    - RNAemia
  - Immunogenicity
- Animal studies - Proof of Concept
  - Protection
  - Dose ranging
  - Immunity
    - Humoral
    - Cell mediated
    - Memory
  - Safety
  - Correlates of protection
- Animal QC
  - Toxicology
  - Potency
  - Safety
- Phase 1 Clinical Trial
  - Safety
  - Immuno-genicity
  - Dose ranging
- Phase 2 Clinical Trial
  - Safety
  - Immuno-genicity
- Phase 3 Clinical Trial
  - Efficacy
  - Immuno-genicity
- Phase 4 Clinical Trial
  - Pharmacovigilance

Post-licensure
Use insect repellents!
Thank you!
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