Robust Inactivation of Yellow Fever Virus 17D Vaccine Strain can be achieved by Photochemical Treatment of Platelet Concentrates

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- Yellow Fever Virus (YFV) characteristics, distribution and outbreaks
- Yellow Fever: a threat to the blood supply
- The INTERCEPT™ Blood System
- Pilot YFV inactivation studies
- Inactivation of arboviruses

Disclaimer:
I am an employee of Cerus. Cerus is commercializing the INTERCEPT™ Blood System.
Yellow Fever Virus (YFV)

- **Virology:**
  - *Flavivirus / Flaviviridae*
    - Like Dengue, West Nile, Zika virus

- **Clinical outcomes:**
  - Mild
  - Hemorrhagic fever
  - Neurotropic / Viscerotropie

- **Transmission:**
  - Sylvatic (mosquitoes / monkeys)
    - *Haemagogus sp, Sabethes sp,*
  - Urban (mosquitoes / humans)
    - *Aedes sp (aegypti and albopictus)*
  - Transfusion-transmission
YFV mitigation strategies

- Epidemiology:
  - Sporadic in South America / Africa
    - Sylvatic transmission (~300 cases/year)
  - Travelers returning from endemic areas
  - Angola 2015-16 / Brazil 2016-18

- No effective antivirals / only supportive
  - Plasma exchange
  - Liver transplantation

- Vaccine (difficult to produce - limited world supply)
  - Live attenuated 17D-YFV vaccine strain
  - Effective
  - Adverse events (Neurologic / visceral invasion)
    - Risk for immunocompromised patients
LATAM at risk areas
2016 - 2018 Brazil YFV outbreak

- June 2016 – May 2018:
  - YFV was responsible for
    - 2,034 cases
    - 655 fatalities (32%)
    - Many more unrecognized

- A massive vaccination campaign was undertaken (36.7 million doses delivered)
  - To control the outbreak
First transfusion-transmitted YFV infections in Brazil

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Previous YF vaccine (year)</th>
<th>Blood product received (quantity)</th>
<th>Underlying medical conditions</th>
<th>Symptoms and laboratory abnormalities</th>
<th>YFV IgM</th>
<th>No. of days post-transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>F</td>
<td>No</td>
<td>Irradiated RBC (4 aliquots)</td>
<td>Prematurity, IVH</td>
<td>None</td>
<td>Neg</td>
<td>37</td>
</tr>
<tr>
<td>6 yrs</td>
<td>M</td>
<td>No</td>
<td>Irradiated PC (1 unit)</td>
<td>Wilm´s tumor</td>
<td>None</td>
<td>Pos/160</td>
<td>36</td>
</tr>
<tr>
<td>66 yrs</td>
<td>M</td>
<td>Yes (1964)</td>
<td>PC (1 unit)</td>
<td>Kidney transplant, diabetes</td>
<td>None</td>
<td>Pos/160</td>
<td>33</td>
</tr>
<tr>
<td>58 yrs</td>
<td>M</td>
<td>Yes (1975, 1986)</td>
<td>FFP (2 units)</td>
<td>CRF, tuberculosis, psoriasis</td>
<td>None</td>
<td>Pos/40,960</td>
<td>26</td>
</tr>
<tr>
<td>82 yrs</td>
<td>M</td>
<td>Yes (1959, 1965)</td>
<td>Irradiated PC (1 unit)</td>
<td>B-cell lymphoma</td>
<td>Deceased</td>
<td>NA</td>
<td>-</td>
</tr>
</tbody>
</table>

Data presented by Dr Luiz Amorim, Hemorio at SVTM Swiss congress 2017
Risk of transfusion-transmitted YFV vaccine

- MMWR Jan. 22, 2010 - Evidence of YFV vaccine TTI in the US military
  - 89 military personnel donated blood 4 days after vaccination
    - 6 units were transfused to 5 patients: 1 died, others seroconverted

- Live attenuated virus → viremia after vaccination

- Blood donor deferral period of 2-4 weeks to limit the risk of YFV vaccine TTI
YFV: a threat to the blood supply

- YFV TTI documented for:
  - Wild type strain
  - Live attenuated vaccine strain
- Deferral based on clinical signs:
  - 80% asymptomatic cases
  - Difficult to prevent donation from asymptomatic donors
- Deferral based on risk after vaccine
  - Immunocompromised patients at higher risk for severe outcome

- Deferral policies may increase the risk of platelet shortage in areas impacted by massive vaccination campaign

- Pathogen inactivation could be an alternative strategy to help mitigate the risk of YFV TTI and platelet shortage
INTERCEPT Mechanism of Action Targeting DNA and RNA to Prevent Pathogen Proliferation

1) Amotosalen, a psoralen, penetrates cellular and nuclear membranes and intercalates into helical regions of DNA or RNA.

2) Amotosalen forms covalent crosslinks to nucleic acid base pairs upon exposure to UVA light.

3) DNA and RNA replication is blocked. Pathogens and leukocytes cannot replicate and are ‘inactivated.’
The INTERCEPT Blood System for Platelets

- Using a sterile connecting device (SCD), the platelet container is connected to the INTERCEPT kit.
- Amotosalen (1) is added by gravity flow and the platelet mixture is illuminated with UVA light (2).
- Residual amotosalen and its photoproducts in the platelet mixture are reduced to low levels using a compound adsorption device (CAD) (3) before the platelets are transferred to the storage containers.
Pilot study objectives

- Evaluate the ability to inactivate 17D-YFV using amotosalen (S-59) and UVA light for pathogen inactivation treatment of platelet components (PC)

- Use infectivity assays with Vero76 cells
YFV vaccine inactivation – Experimental design

Pre-Inactivation samples
Infectious titer by plaque assay on Vero 76 cells

Infectivity by plaque assay expressed in plaque forming units (PFU/mL)

Post-inactivation samples
Residual infectious titers by plaque assay (Vero cells)
# YFV vaccine inactivation - Results

<table>
<thead>
<tr>
<th></th>
<th>PC in 35% plasma / 65% PAS (n=4*)</th>
<th>PC in 100% plasma (n=1*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-PI Treatment</strong> (Log(_{10}) PFU/mL)</td>
<td>4.65 ± 0.6</td>
<td>5.19</td>
</tr>
<tr>
<td><strong>Post-PI Treatment</strong> (Log(_{10}) PFU/mL)</td>
<td>&lt;-0.70 ± 0.0</td>
<td>&lt;-0.7</td>
</tr>
<tr>
<td><strong>Log reduction</strong> (Log(_{10}) PFU/mL)</td>
<td>&gt;4.65 ± 0.6</td>
<td>&gt;5.19</td>
</tr>
<tr>
<td><strong>Log reduction</strong> (Log(_{10}))</td>
<td>&gt;5.34 ± 0.6</td>
<td>&gt;5.89</td>
</tr>
</tbody>
</table>

* n=4 more replicates in PAS and 100% plasma are planned for regulatory submission
### Inactivation of Arboviruses with the INTERCEPT Blood Systems to the Limit of Detection

<table>
<thead>
<tr>
<th>Arbovirus</th>
<th>Log$_{10}$ Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
</tr>
<tr>
<td>WNV</td>
<td>≥6.8$^4$</td>
</tr>
<tr>
<td>DENV</td>
<td>&gt;5.6$^1$</td>
</tr>
<tr>
<td>CHIKV</td>
<td>≥7.6$^7$</td>
</tr>
<tr>
<td>ZIKV**</td>
<td>&gt;6.6$^2$</td>
</tr>
<tr>
<td>°YFV (strain 17D)**</td>
<td>NA</td>
</tr>
<tr>
<td>°MAYV**</td>
<td>NA</td>
</tr>
<tr>
<td>°RRV**</td>
<td>NA</td>
</tr>
</tbody>
</table>


* INTERCEPT Blood System for RBC is in development and not approved for commercial use.
**Data for pathogen inactivation of Zika, Yellow Fever, Mayaro, or Ross River Viruses by INTERCEPT Blood System have not been submitted to TUV or FDA for review.
# Arbovirus Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dengue¹</th>
<th>Chikungunya²</th>
<th>Zika³,⁴</th>
<th>West Nile⁵</th>
<th>Yellow Fever⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus family</td>
<td>Flaviviridae</td>
<td>Togaviridae</td>
<td>Flaviviridae</td>
<td>Flaviviridae</td>
<td>Flaviviridae</td>
</tr>
<tr>
<td>Virus genus</td>
<td>Flavivirus</td>
<td>Alphavirus</td>
<td>Flavivirus</td>
<td>Flavivirus</td>
<td>Flavivirus</td>
</tr>
<tr>
<td>Serotypes</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Illness outcome</td>
<td>Severe dengue – plasma leakage</td>
<td>Rarely severe, Arthralgias</td>
<td>Rarely severe, Guillain-Barré Microcephaly</td>
<td>Neuroinvasive disease, Meningitis, Encephalitis, Polyomyelitis</td>
<td>Rarely severe, but ~15% of patients progress to serious form; hemorrhagic fever, multisystem organ failure</td>
</tr>
</tbody>
</table>

Conclusions

- S-59/UVA-mediated PRT is efficient at inactivating the 17D-YFV vaccine strain in PC independently of resuspension medium
  - Similar to results obtained with other Flaviviruses, including West Nile, Dengue and Zika virus

- Because of high rates of asymptomatic infections, donor deferral is an inefficient mitigation strategy for most arboviruses

- Blood recipients are often immunocompromised
  - At risk for the development of severe clinical outcomes

- Pathogen reduction is a potential mitigation strategy to prevent TTI’s and maintain PC availability in areas
  - affected by large YFV outbreaks
  - with widespread vaccination campaigns