Chikungunya Virus Vaccine Candidate
VALNEVA‘s VLA1553

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Chikungunya virus

- Single stranded RNA virus
- Family *Togaviridae*
- Genus *Alphavirus*
- Antigenically related to other polyarthitis causing alphaviruses e.g. Mayaro-, Semliki Forest-, O’nyong-nyong- and Ross River viruses

Picture: Weaver and Lecuit 2015
Arbovirus outbreaks difficult to predict
Preparedness strategy options needed
Ecological effects on arbovirus-mosquito cycles of transmission
Will AI and quantum-tech bring breakthrough in forecasting? Factors e.g. Bayesian networks - R0

Tabachnik 2016
Chikungunya virus vectors

Aedes aegypti

Aedes albopictus
Transmission cycles of mosquito-born arboviruses
Environmental changes accelerate emergence (mostly caused by humans)
Reservoir- and amplifying-hosts / endemic-, epidemic-, and bridge-vectors

Vasilakis et Weaver 2016
The vector-virus interaction
Mosquitos are more than “transport vehicles”, examples:

Emergence and amplification of new virus strains

- Infection of parental strain in mosquito body
- Transmission of both strains to mammal
- Amplification of new strain in mosquito body
- New strain dominates in mosquito saliva

- Stapleford et al 2014; Lounibos et Kramer 2015; Conway et al 2014

Intrinsic factors affecting the vectorial capacity of a mosquito vector

- Mosquito genetics
- Microbial interactions
- Salivary gland infection barrier
- Salivary gland escape barrier
- Mosquito immunity
- Viral genotype

Saliva-mediated infectivity enhancement

- Mosquito probing into dermal tissue
- Breakdown of the extracellular matrix and modulation of the immune response
- Enhanced dissemination of inoculated virus
- Langerhans cell migration
- Fibroblast

WVC 2019: VLA1553 CHIK vaccine candidate

16-APRIL-2019
Pathogen Mutation with impact

Examples: Viral Envelope E1 Mutation $\rightarrow$ Ae. albopictus Transmission $\uparrow\uparrow\uparrow$ of IOL CHIKV; Ae. aegypti E1:K211E and E2:V264A

- Viral fusion to endosomal membranes
- Increased midgut cell infectivity by 50-100 fold
- Increased viral dissemination to salivary glands
- Increased viral transmission to mice

Tsetsarkin K et al 2007; Berry et al 2019

WVC 2019: VLA1553 CHIK vaccine candidate
Human migration and visiting friends & relatives (VFR) add risk on top of other travellers (business, tourists), military
Chikungunya: vector prevalence and disease outbreaks

Fig 1. World map with countries where autochthonous (locally initiated) chains of CHIKV transmission have been identified. Data from World Health Organization (http://www.who.int/emergencies/diseases/chikungunya/en/) and Pan American Health Organization (https://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931&lang=en). CHIKV, chikungunya virus.

https://doi.org/10.1371/journal.pntd.0006919.g001

Rezza & Weaver 2019
Temperature suitability for transmission now....

Future: PAR↑ by up to 1 Bio (Ryan et al 2019)

**A**

**B**

*Fig 1. Mapping current temperature suitability for transmission.* Maps of current monthly suitability based on mean temperatures using a temperature suitability threshold determined by the posterior probability that scaled $R_0 > 0$ is 97.5% for (a) *Aedes aegypti* and (b) *Ae. albopictus*, and (c) the number of people at risk (in billions) as a function of their months of exposure for *Ae. aegypti* and *Ae. albopictus*. 

WVC 2019: VLA1553 CHIK vaccine candidate

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Often overwhelming speed of outbreaks:
Example: 1 Year of Chickungunya 2014 (1 slide = 1 month)
Distribution of emerging arboviruses
Co-circulation – consequences? E.g. exacerbating the clinical outcome?

Weaver et al 2018
Acute stage, high risk for clinical misdiagnosis

CHIKUNGUNYA FEVER
- Acute polyarthritis
- Tendosynovitis

DENGUE FEVER
- Distal swelling
- Rash

MALARIA
- Jaundice
- Renal failure
- Anemia

LEPTOSPIROSIS
- Bleedings
- Retro-orbital pain
- Transient arterial hypotension

ZIKA
- Myalgia
- Myocarditis

BACTERIAL SEPSIS
- ADRS

Adapted from Simon et al, Schwartz, Infections in travelers, Ed 2009
- Non epidemic area ➔ biological testing for all cases
- During an outbreak ➔ atypical or complicated cases, high-risk patients, unfavourable outcome, end of the outbreak

The Chikungunya Virus Vaccine Project
VLA1553 - Chikungunya vaccine candidate

Attenuation Principle

CHIKV Δ5nsP3 (VLA1553) vaccine is based on ECS African strain of Indian Ocean lineage with cross-protective immunity against Asian isolate which is now rapidly spreading across the Americas.

- **60 aa deletion in gene encoding nsP3**
- No change of deletion detectable after up to 20 passages on Vero cells
- Slightly reduced plaque size as compared to CHIKV clone LR2006-OPY1
- Reduced replication (1.2×10⁷ pfu/mL) as compared to CHIKV clone LR2006-OPY1 (4.4×10⁸ pfu/mL)

Hallengärd et al. 2013
# Chikungunya vaccine candidate Target Product Profile

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Prophylactic active immunization against Chikungunya virus in individuals ≥ 1 year of age</td>
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<tr>
<td></td>
<td>Travel to endemic or outbreak regions (HCPs, military, others)</td>
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<td>Emergency use outbreak response</td>
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<tr>
<td></td>
<td>Routine/endemic use</td>
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<tr>
<td><strong>Dose and Administration</strong></td>
<td>Route of administration: i.m. or s.c.</td>
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<tr>
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<td>Recommended dose: Single dose of $10^5$ (or lower) live-attenuated Chikungunya virus</td>
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<td>Dosage schedule: single dose</td>
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<td>Duration of protection: long lasting immunity, at least 5 years studied</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>Lyophilized; storage at +2 to +8°C</td>
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<td><strong>Co-administration</strong></td>
<td>Co-administration with relevant traveler/military vaccines (e.g. DENV, Yellow Fever, Twinrix, JEV) and routine immunization vaccines</td>
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<tr>
<td><strong>Desired immune response</strong></td>
<td>Neutralizing antibody response (useable as correlate of protection)</td>
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<td><strong>Target Population/Target Groups</strong></td>
<td>Travellers, military personnel, HCPs</td>
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<td>Individuals at risk who live in endemic regions</td>
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<td><strong>Safety</strong></td>
<td>Similar to licensed vaccines for active immunization in adults &amp; children</td>
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<td>Suitable for malnourished populations</td>
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VLA1553 - Chikungunya vaccine candidate
Non-Clinical Studies in Non Human Primates – Immunogenicity/Efficacy

Neutralizing antibodies* against CHIKV in sera of cynomolgus macaques
Single immunization of $1 \times 10^5$ pfu CHIKV $\Delta 5$nsP3 s.c.
Challenge with app. $1 \times 10^4$ pfu wt LR-CHIKV i.v.

- Strong and long-lasting immune response induced after single-shot in NHPs
- No anamnestic response observed after challenge with wt LR-CHIKV
- Cross-neutralizing antibodies against Caribbean CHIKV strain induced
- No viremia at any time point observed in vaccinated NHPs upon challenge with high dose of wt LR-CHIKV (100 AID50)

Source: Roques et al. 2016; * Neutralization titers measured by Luciferase assay.
VLA1553 - Chikungunya vaccine candidate
Non-Clinical Studies in Non Human Primates – Safety

- Viremia 3-4 logs lower than compared to wt LR-CHIKV infection
- Delayed onset of viremia by 1-2 days compared to wt-LR CHIKV infection
- No significant fever (rectal) after vaccination
- No fever (rectal) in vaccinated NHPs after wt LR-CHIKV challenge
- No clinical signs of infection - edema, erythema, joint swelling, hunching, fur ruffling, rash (data not shown)

Mean Viremia + SEM

Log$_{10}$ vRNA copies/mL vs Days post infection

Log$_{10}$ vRNA copies/mL vs Days post infection

Comparison of temperature between Day 0 and Day 2 post infection

**: $P < 0.01$; ***: $P < 0.001$; Kruskal-Wallis followed by Mann & Whitney rank test

Source: Roques et al. 2016
VLA1553 – CHIK vaccine
Summary pre-clinic: Safety and immunogenicity

- Δ5nsP3 has a 60 aa deletion in nsP3 causing the attenuation which is stable and does not revert back when passaged 20 times on Vero cells

- A single shot of Δ5nsP3 CHIKV P0 was highly immunogenic and induced a strong and long lasting neutralizing antibody response

- Δ5nsP3 CHIK vaccine caused no clinical manifestations typically associated with wt CHIKV infections in the NHP model

- Δ5nsP3 CHIK vaccine showed delayed and strongly reduced viremia as compared to wt CHIK infection

- CHIKV Δ5nsP3 is highly immunogenic and sufficiently attenuated to warrant clinical testing
VLA 1553 – 101: Phase 1 Study

Study Design

- Observer-blinded, randomized, multicenter, dose escalation study
- Study Population: 120 healthy volunteers aged 18 to 45 years
- Study Locations: US (2 sites)
- Dosage: $3.2\times10^3$ TCID$_{50}$ (0.1ml), $3.2\times10^4$ TCID$_{50}$ (1ml), $3.2\times10^5$ TCID$_{50}$ (1ml)
- Immunization route: i.m.

Part A Analysis

Re-vaccination at Month 6/12 with highest dose: Homologous viral challenge
VLA 1553 – 101: Ph1 study Day 28 Results (pooled, blinded)
Excellent immunogenicity after a single shot

### Immunogenicity
- 100% Seroconversion Rate (SCR)\(^2\) at day 28 after single dose\(^1\)
- 96.5% of subjects achieving ≥ 16 fold rise in antibody titers\(^2\)
- High Geometric Mean Titer (GMT) in pooled analysis

### Safety
- No Serious Adverse Events (SAEs) up to day 28\(^1\)
- No Adverse Events of Special Interest (AESIs) up to day 28\(^1\)
- Local tolerability excellent
- Systemic adverse events included short-term fever, headache and fatigue
- Transient cases of reduced levels of neutrophils, lymphocytes or leucocytes w/o accompanying clinical symptoms\(^3\)

**Excellent immunogenicity profile after single vaccination**

**Safety profile acceptable and supporting further development**

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1. Pooled analysis across all study groups since study continues with additional vaccination to potentially obtain a first indication for efficacy; 2 SCR defined as proportion of subjects achieving a CHIKV specific neutralizing antibody titre as NT50 ≥ 20; 3 As for other live-attenuated vaccines
Regulatory pathway to licensure
Approval of Chikungunya vaccine based on immunological correlate

Immune correlate of protection (ICP)

- Good evidence from animals and humans that neut. antibodies provide protection against CHIKV\(^1\).
- Robust IgM/IgG antibody responses following CHIKV infection in humans and animal models.
- Neutralizing antibodies primarily target E1/E2 structural proteins and are protective in passive transfer studies.
- Natural infection is believed to confer live-long immunity\(^2,3\).

- Serological threshold associated with protection after natural infection:
  - Presence of neutr. antibodies against CHIKV of PRNT\(_{80} \geq 10\) was associated with 100% protection from symptomatic CHIKV infection in a prospective human cohort study in the Philippines\(^4\). → potential immune correlate of protection
  - In order to establish a threshold titer for protection after vaccination with VLA1553, Valneva will conduct studies with NHPs using human sera from VLA1553-101.

\(^1\)Gasque P et al 2015; \(^2\)Galatas B et al.2016; \(^3\)Nitatpattana N et al. 2014; \(^4\)Yoon I-K. et al.2015
VLA 1553: Further Development Considerations and Plans

Outline Accelerated Clinical Development *

FDA Fast track granted to VLA1553 development program

Phase 1 expected to provide first unblinded data by mid-2019 (dose-selection)
- Day 28 safety and immunogenicity after single dose
- Viremia data at Days 3, 7 and 14 post-vaccination
- Month 6 safety and immunogenicity data providing information on antibody persistence
- Month 7 re-vaccination safety, immunogenicity and viremia data as early indicator of efficacy

Supporting non-clinical experiments
- Mosquito transmission studies
- NHP study addressing biodistribution
- Passive transfer study in NHPs to develop correlate of protection using human sera from VLA1553-101

Aiming at accelerated approval procedure at FDA

* subject to development progress, regulatory concurrence and company funding
Pivotal Study Considerations

- Large double-blinded, controlled, multicenter safety and immunogenicity study in adults ≥18 yrs.
- N=3,840 subjects of either gender
- Including antibody persistence follow-up for one year

Lot-to-Lot Study Considerations

- To demonstrate lot-to-lot manufacturing consistency in adults aged 18 to 64 yrs.
- N= 165 subjects of either gender
- Randomized to three different manufacturing lots

Pediatric Development Plan

- Pediatric development plan (i.e. PIP and iPSP) for appropriate pediatric age group under development and subject to regulatory discussion

* subject to development progress, regulatory concurrence and company funding
Thank you.
VLA1553-101

CHIKV Microneutralization Assay (µNT)

» Measures virus neutralizing antibody (nAb) titers
» µNT is based on the same principle as PRNT, but allows testing with higher throughput
» The neutralizing titer is defined as reciprocal serum dilution which induces 50% protection from cell death (µNT<sub>50</sub>) compared to the virus control lacking neutralizing antibody
» A µNT<sub>50</sub> titer of ≥ 1:20 is defined as seroconverted
» Titer below the quantitation limit (µNT<sub>50</sub> < 20) are imputed with 10

1. Add heat inactivated sera and perform 2-fold serial dilutions

2. Add equal volume of the vaccine strain CHIKV Δ5nsP3 (virus will be used at a concentration which results in 100% CPE)

3. Transfer 100µL of serum/virus mix onto VERO cells plated in 96 well plates

4. Incubate 1hr at 37°C

4-6 days at 37°C

5. Record cell viability (e.g. Alamar blue staining)

5. The neutralization titer will be defined as reciprocal serum dilution which neutralizes the cytopathic effect.