Chikungunya Vaccine Research and Development

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CHIK Vaccine Development

Landscape:

Facilitating factors:
• Single CHIKV serotype, no evidence of reinfection or immune enhancement
• Well established correlates of protection for alphaviruses (neutralizing antibodies)
• Ease of genetic manipulation for rational attenuation

Challenges:
• Wild-type rodents are poor models for human disease
• Unpredictable incidence of disease for human efficacy trials and a potentially unstable market
• FDA animal rule has not yet produced a licensed vaccine
The Ideal Chikungunya Vaccine

1. Simple and inexpensive to manufacture
2. Induce rapid and long lasting immunity after a single immunization
3. Stable attenuation with negligible chance of reversion to wild-type virulence
4. Incapable of infecting potential mosquito vectors or producing viremia in reservoir hosts
Chikungunya Vaccine Development

Various platforms:
1. Live-attenuated
2. Inactivated
3. Virus-like particles
4. DNA
5. Measles and VSV-vectored

Bharat Biotech; VLP vaccine

Indian Immunologicals; Walter Reed strain

Takeda and UTMB: Recombinant live attenuated CHIK/IRES

NIAID; VLP vaccine manufactured in CHO cells *Merck option

ArboVax; Recombinant LAIIV

Themis; Measles-based Recombinant

Indian Immunologicals; Inactivated strain 181/clone 25

Yale, Profectus, UTMB: VSV-vectored live-attenuated

Inovio; DNA vaccine

US Army, 181/clone25 live attenuated vaccine (development halted)
A recombinant measles vaccine expressing chikungunya virus-like particles is strongly immunogenic and protects mice from lethal challenge with chikungunya virus

Samantha Brandler, Claude Ruffié, Chantal Combredet, Jean-Baptiste Brault, Valérie Najburg, Marie-Christine Prevost, André Habel, Erich Tauber, Philippe Després, Frédéric Tangy

- Recombinant live-attenuated measles vaccine expressing CHIKV virus-like particles comprising capsid and envelope structural proteins from the La Reunion strain
- A single immunization protects mice from a lethal CHIKV challenge
- Passive transfer of immune sera also confers protection
Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial


- 42 volunteers immunized
- Well tolerated and safe with mild side effects
- Induced neutralizing antibodies in all vaccinated subjects, with 90-92% seroconversion in medium- and high-dose groups after a single dose
- Mean PRNT\textsubscript{50} titers of 48 and 46 after single, medium- and high-doses, respectively
- Mean PRNT\textsubscript{50} titers of 28-416 in medium and high-dose groups after a booster on day 28 or 90
- No indication of interference from pre-existing Measles immunity
Selective expression of viral structural proteins from a plasmid vector generates virus-like particles (VLPs) \textit{in vitro} that resemble replication-competent alphaviruses.

Immunization with VLPs elicits neutralizing antibodies against envelope proteins from several CHIKV strains.

Monkeys immunized with VLPs produce high-titer neutralizing antibodies that protect against viremia.

Passive transfer of these antibodies into immunodeficient mice protected against lethal CHIKV challenge, indicating a humoral mechanism of protection.
Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial


• Three dosage groups: 10 μg (n=5), 20 μg (n=10), and 40 μg (n=10)
• All injections were well tolerated, with no serious adverse events reported.
• Neutralizing antibodies detected in all vaccinees after 2 dose
• Mean 50% neutralization were 2688 in the 10 μg group, 1775 in the 20 μg group, and 7246 in the 40 μg group
• Merck dropped its licensing agreement for this vaccine last year
Recombinant Alphaviruses With Structural Proteins Under EMCV IRES Control

Version 1

Version 2

Gln_{341} > Arg
(cag > cgc)
Replication in Vero Cells

- CHIKV genomic RNA
- CHIKV subgenomic RNA

Graph showing replication kinetics:
- Wild-type CHIKV
- 181/25 vaccine
- CHIKV/IRES vaccine
- CHIKV/IRES vaccine p10
CHIK Vaccine Replication and Tropism in A129 Mice

181/25

CHIKV/IRES

Wt CHIKV
CHIKV/IRES safety in A129 mice: Serial Intracerebral Passages
Correlates of Protection: Role of Anti-CHIK/IRES Antibodies in Protection

A129 mice
Route: ID
Dose: $10^4$ PFU CHIK/IRES

21 days later:
• Transfer pooled serum IP to naïve A129 mice

24h later:
Challenge with $10^2$ PFU WT LaReunion CHIKV

![Graph showing percent survival over days post CHIKV-LR challenge]

- Undiluted serum (circulating NAb: 106)
- 1:5 dilution (circulating NAb: 35)
- 1:10 dilution (circulating NAb: 30)
- 1:20 dilution (circulating NAb: 13)
- 1:40 dilution (circulating NAb: 8)
- Normal mouse serum
CHIK vaccine efficacy study design

**Vaccination**
- CHIKV/IRES (n=4)
- Sham (n=3)
- *M. Fascicularis* (Mauritian origin)
- 5.0 log₁₀ PFU (SQ or ID)

**Telemetry**
1. HR/ECG
2. Respiratory rate
3. Core temperature

**Challenge**
- 5.0 log₁₀ PFU (SQ) CHIKV (*La Reunion*)

**Necropsy: blood/tissue collection**

Timeline:
-14 0 1-3 15-20 30 45 66
Neutralizing antibody responses in cynomolgus macaques after CHIKV/IRES vaccination
Efficacy in Cynomolgus Macaques

Complete protection against fever, hypothermia and viremia
CHIKV/IRES protects A129 mice against Caribbean CHIKV strain challenge
CHIKV/IRES protects cynomolgus macaques against Caribbean CHIKV strain challenge.

Complete protection against viremia.
Summary of Chikungunya Vaccine Development Prospects

- Scientifically, CHIKV is a relatively straightforward vaccine target due to its limited antigenic diversity and lack of evidence for immune enhancement.
- Financial uncertainty and regulatory hurdles may represent the major challenges to CHIKV vaccine development.
- Several CHIKV vaccine candidates including live-attenuated, virus-like-particle and measles vectored versions are poised for Phase I or II clinical trials.
- With adequate funding and a clear regulatory pathway to licensure, a vaccine could be licensed within a few years.
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