



**QIMR Berghofer**  
Medical Research Institute

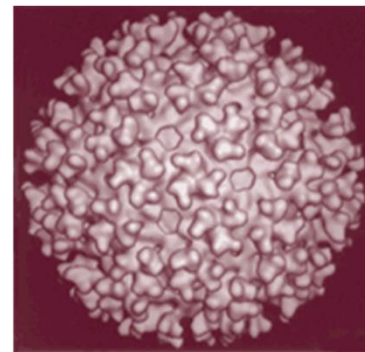
**A new replication-defective, vaccinia-derived, CHO-manufactured, vaccine vector system (SCV) co-expressing chikungunya and Zika virus structural genes is effective in preclinical studies**

Dr Natalie Prow  
ASM 2017



# ALPHAVIRUSES THAT CAUSE ARTHRITIC DISEASE IN HUMANS

- Transmitted by mosquito (arboviruses)
- Single stranded positive sense RNA virus,  
≈12 kb genomes.
- Symptomatic infections nearly always associated  
with weeks to months polyarthrititis/polyarthralgia.



Virus	Occurrence
<b>Chikungunya virus</b>	Large sporadic epidemics every 2-50 years
<b>Ross River virus</b>	Mean of ≈4,000 cases per annum in Australia. Also an epidemic (1979/80) >60,000 cases
<b>Barmah Forest virus</b>	Mean of ≈ 1000 cases per annum in Australia

Suhrbier, A. et al. 2012. Nature Rev. Rheumatol. 8, 420–429.

# CHIKV EPIDEMIC 2005/6, REUNION ISLAND (FRANCE)

>250 deaths – often elderly with comorbidities  
and very young

**High attack rate**

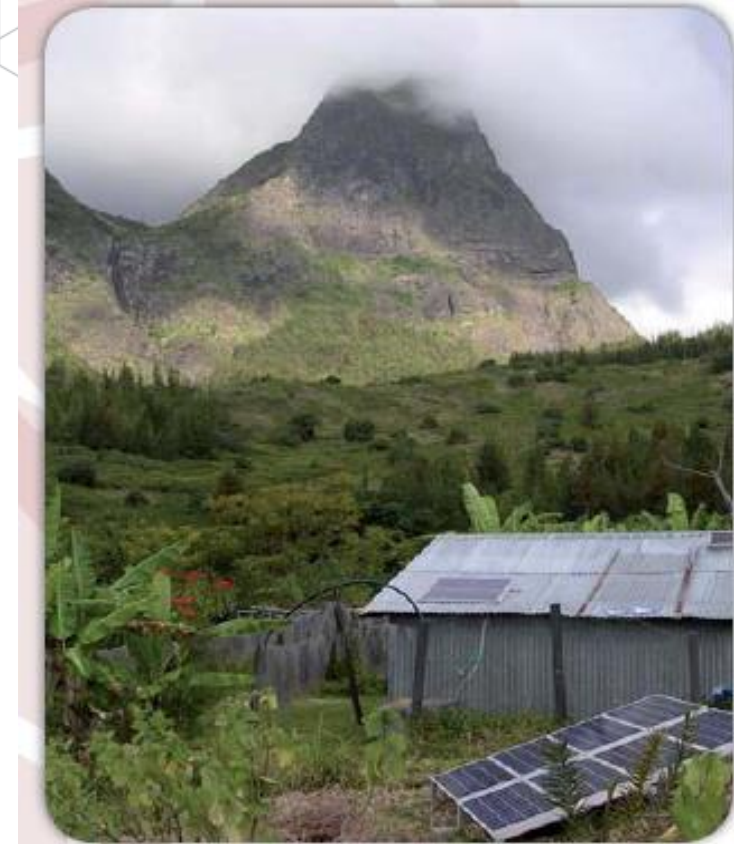
**-266,000 cases** of CHIKV disease were reported  
(38% of the population).

**Rapid rise in case numbers**

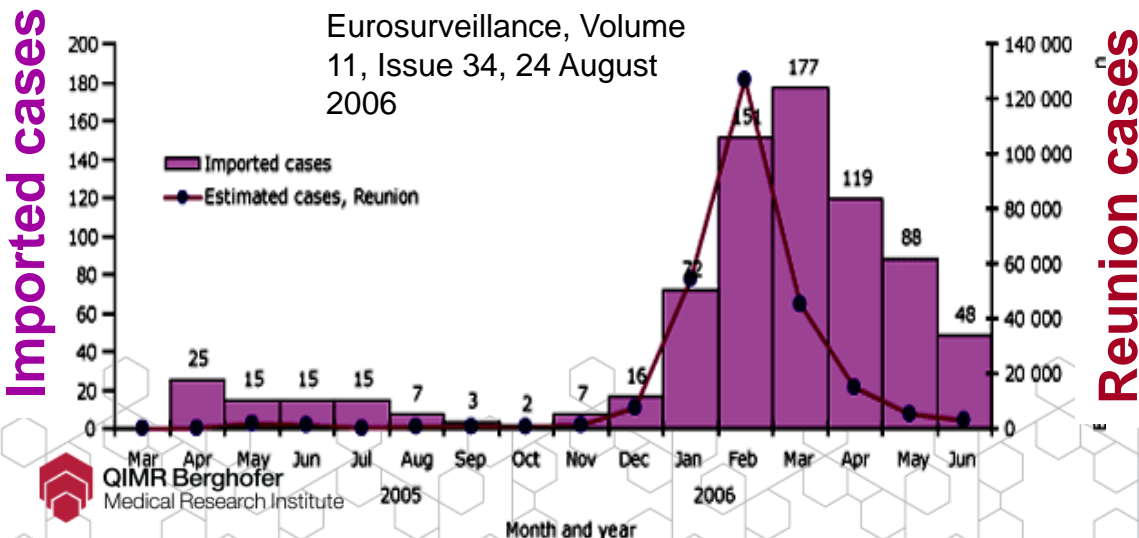
-increased to **130,000/month** in 4 months

**-45,000 cases** during the week of 29 Jan, 2006.

**100's of imported case in France**

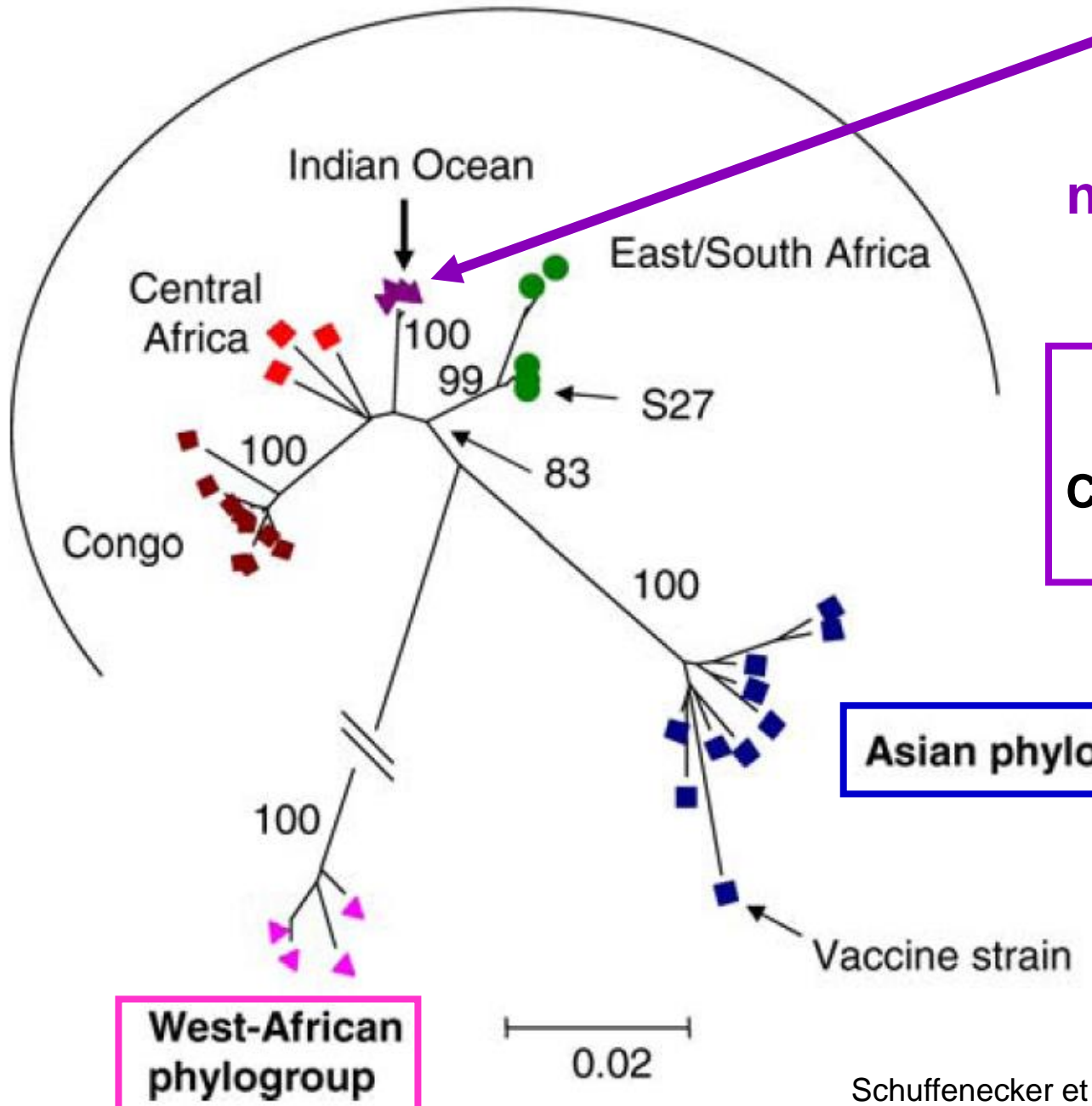


Eurosurveillance, Volume  
11, Issue 34, 24 August  
2006



**East-,Central-, and South-African (ECSA) phylogroup**

**The Indian Ocean/  
Reunion Island  
epidemic was  
associated with a  
new clade of CHIKV**



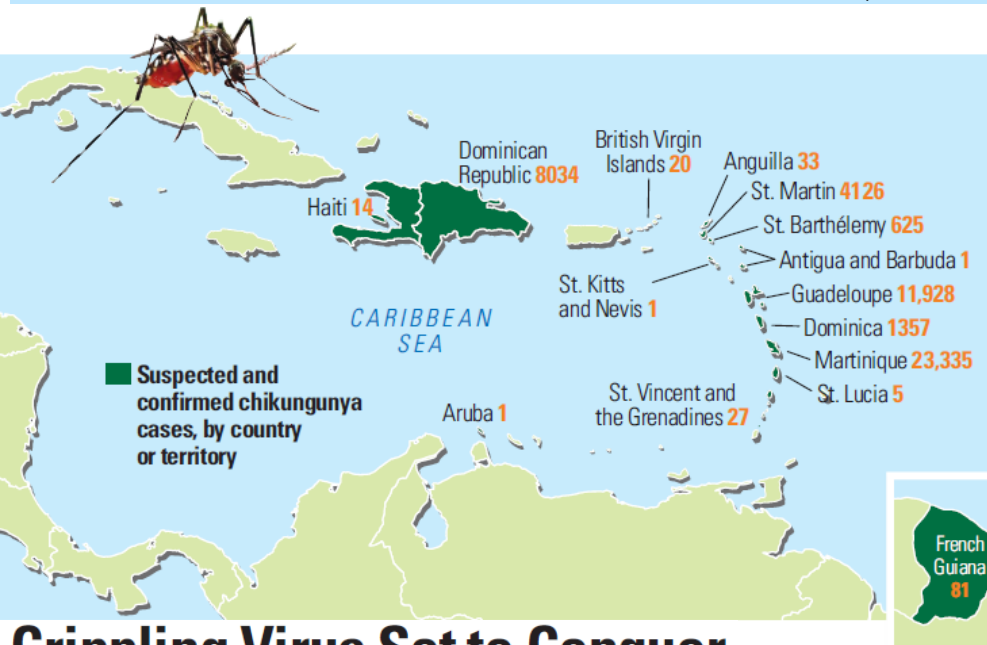
**E1 Mutation (A226V)  
allowed efficient  
CHIKV transmission by  
*Ae. albopictus***

**Asian phylogroup**

**Normal vector  
*Ae. aegypti***

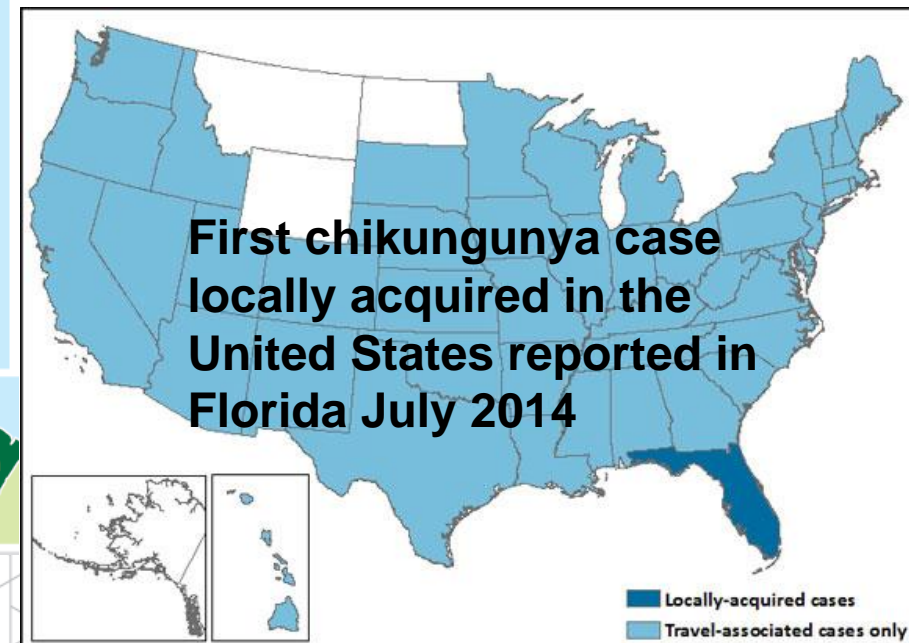


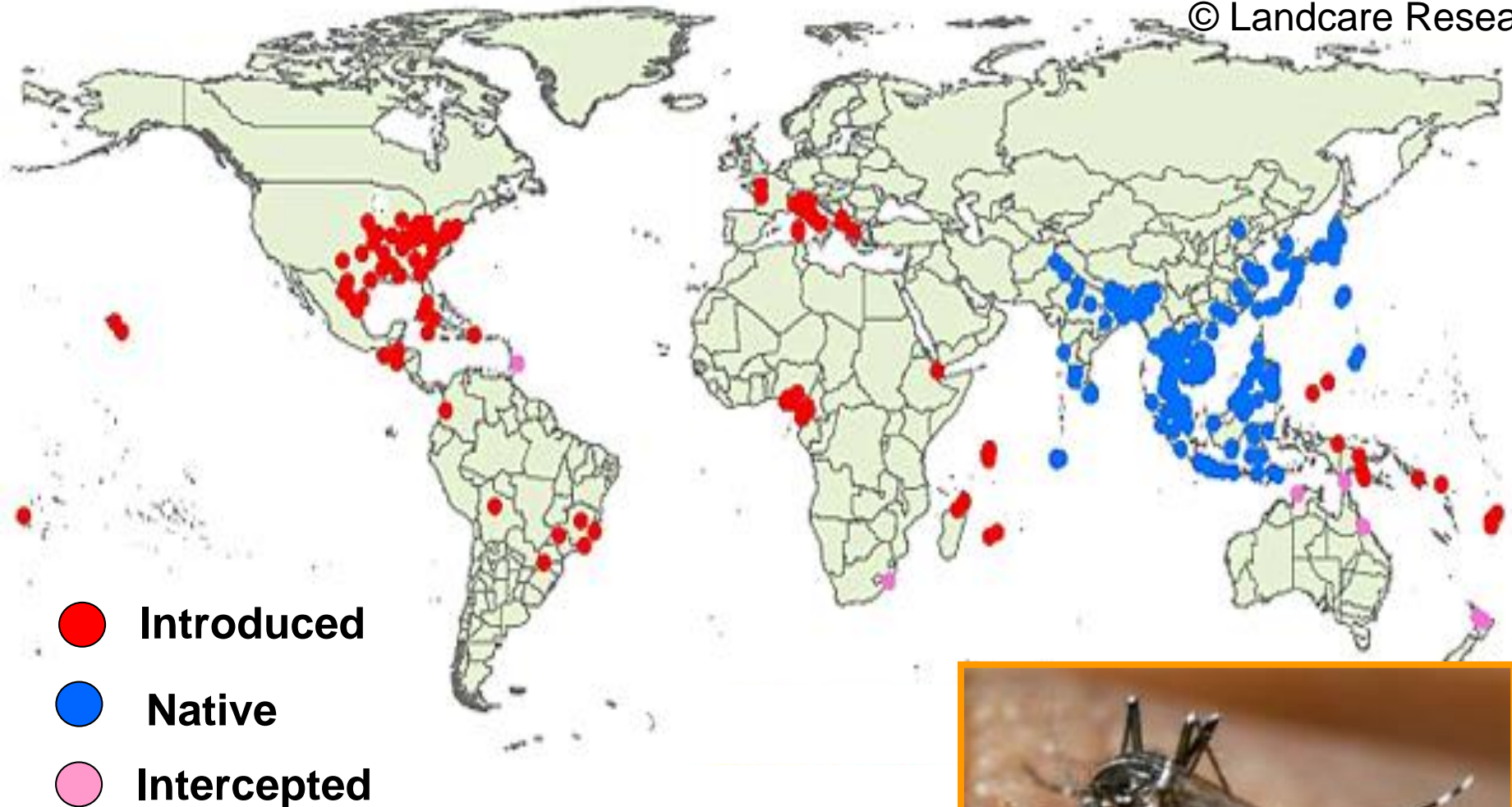
# >1 million CHIKV cases in the Americas 2014



## Crippling Virus Set to Conquer Western Hemisphere

16 MAY 2014 VOL 344 SCIENCE

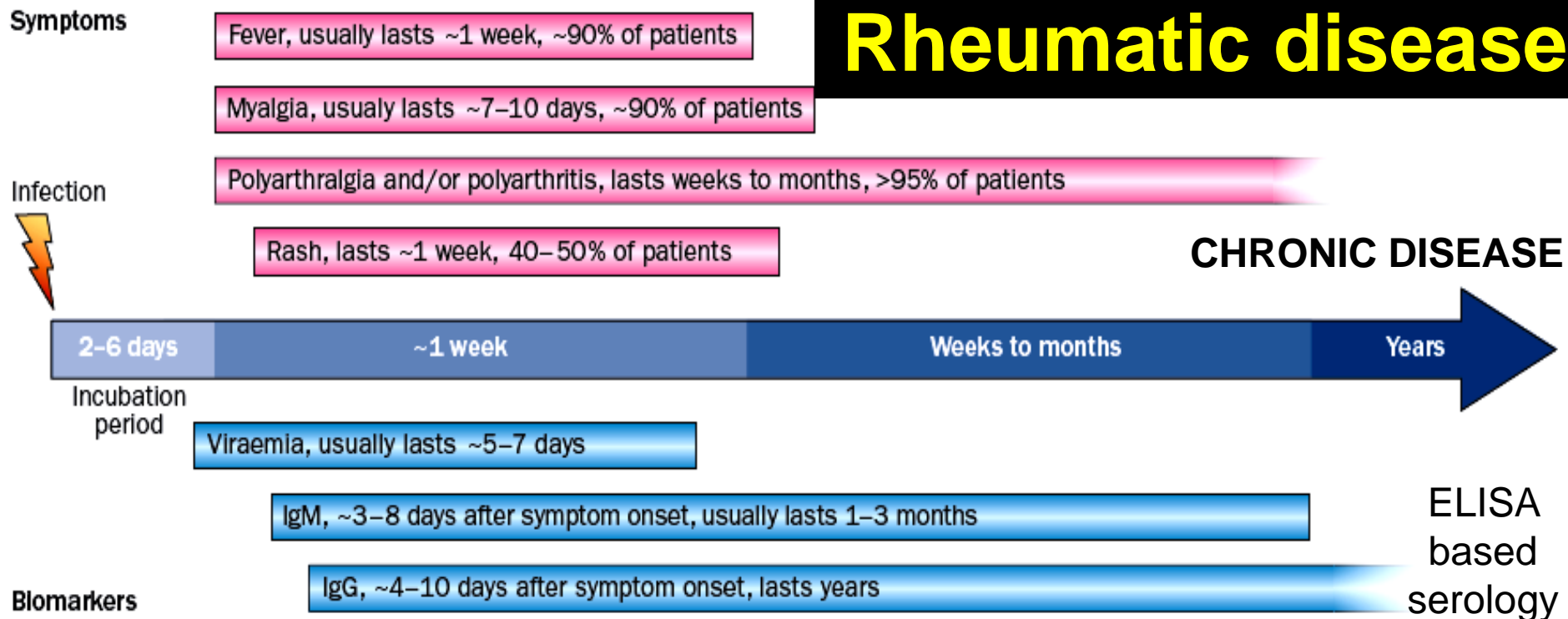




# *Aedes albopictus*; a global invader



# Rheumatic disease



Virus	% asymptomatic	Fever	Rash	Myalgia	Arthralgia arthritis
CHIKV	≈5-18%	90%	40-50%	90%	>95%
RRV	55-75%	20-60%	40-60%	40-80%	80-100% 3-6 months
BFV	?	50%	50-100%	50-80%	70-95%

**Disease characterised by acute and chronic symmetrical polyarthritis-polyarthralgia.**

# Adult wild-type CHIKV mouse model of infection and arthritic disease

## 1) Acute viraemia and arthritis

- **Day 1-14 post infection.**

(Recapitulates viraemia, cytokinemia & arthritis)

*Gardner et al., 2010, J Virol 84(16):8021-32*

## 2) Chronic disease and viral persistence

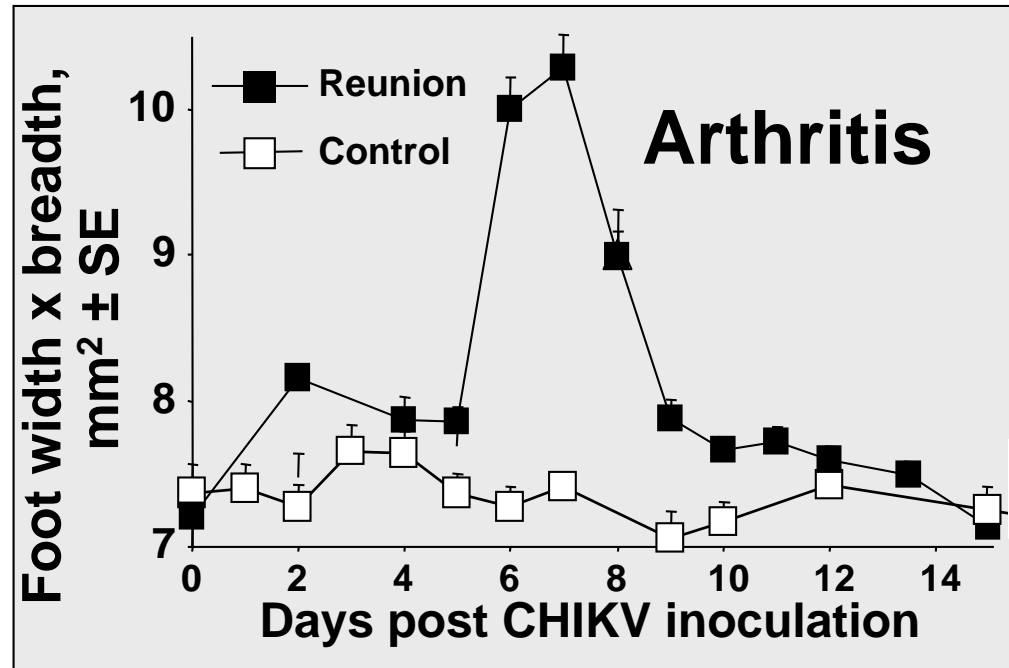
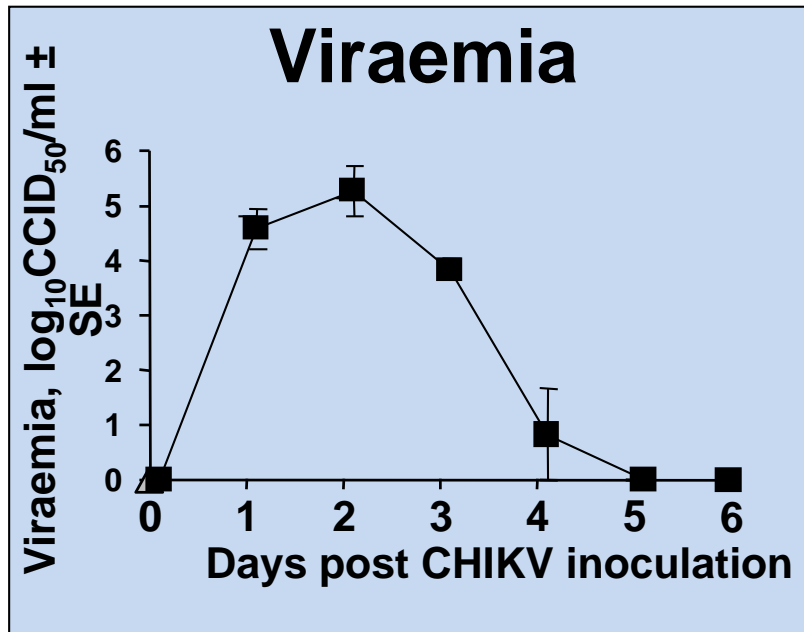
- **Day 30 post infection.**

(Recapitulates viral RNA & protein persistence, cellular infiltrate and cytokine/ISG profile)

*Poo et al., 2014 PLoS Negl Trop Dis. 8(12):e3354*



# Adult wild-type mouse model of chikungunya virus infection (viraemia) and disease (foot swelling/arthritis)

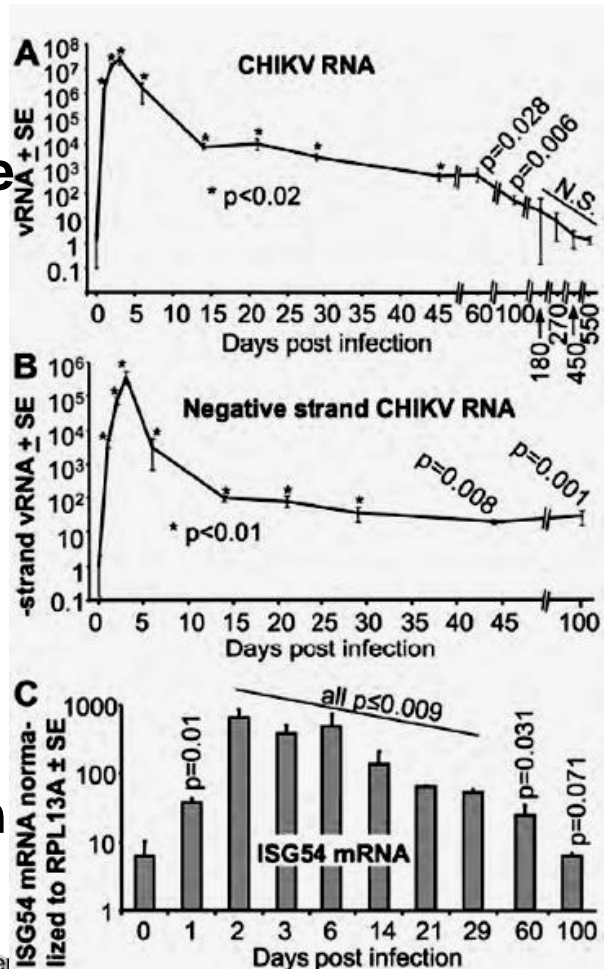


Female C57BL/6 mice > 6 weeks old (Gardner et al. 2010. J Virol 84:8021–32)

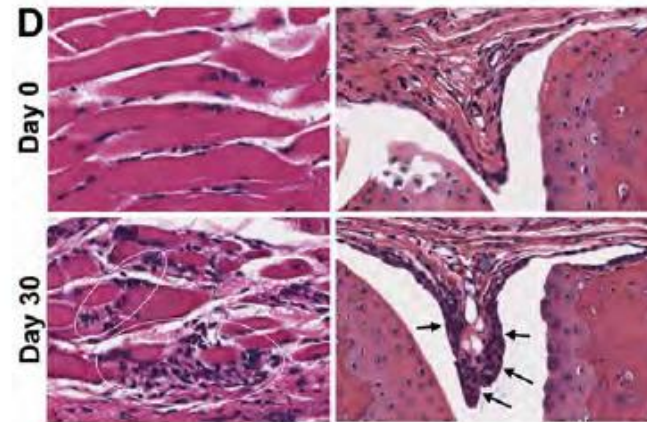
**IRF3/7<sup>-/-</sup> mice die from hemorrhagic shock after CHIKV infection**  
(Rudd et al 2012)

# Mouse model of viral persistence and chronic arthritis disease

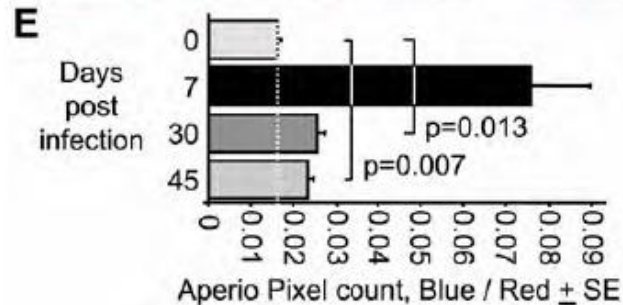
Persistence of CHIKV RNA



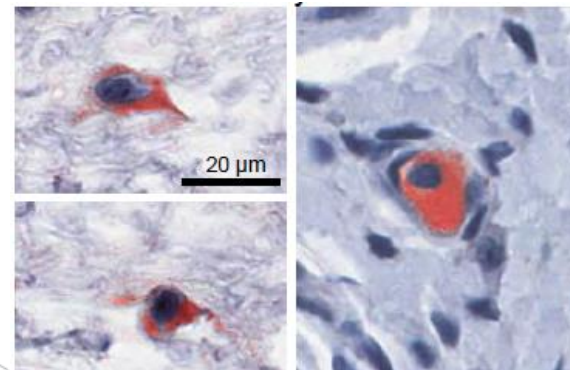
Persistent stimulation of IRGs



Persistent detectable cellular infiltrates (arthritis);

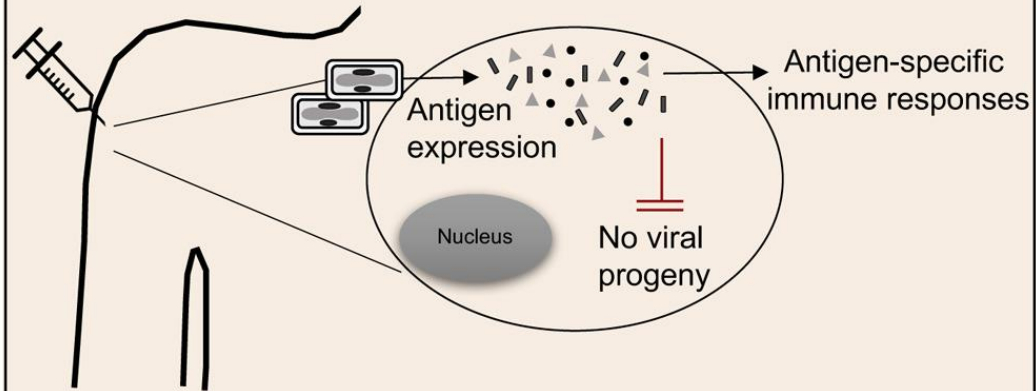


quantifiable using Aperio system

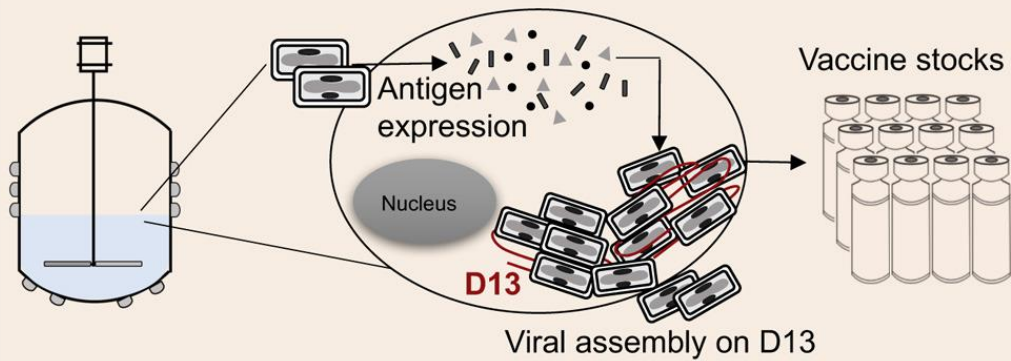


Persistence of capsid antigen (d 30 pi)

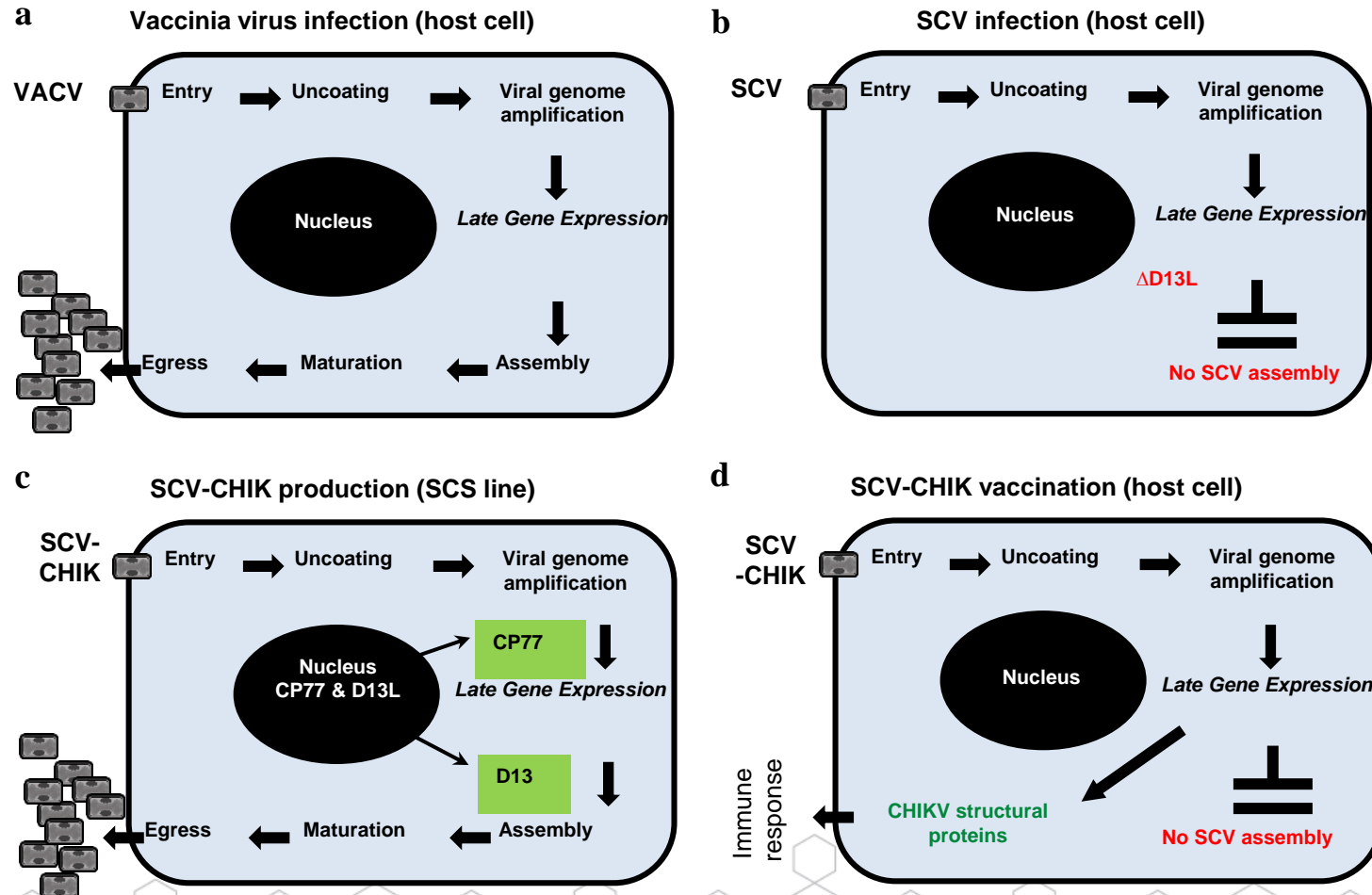
## Vaccination



## Manufacture

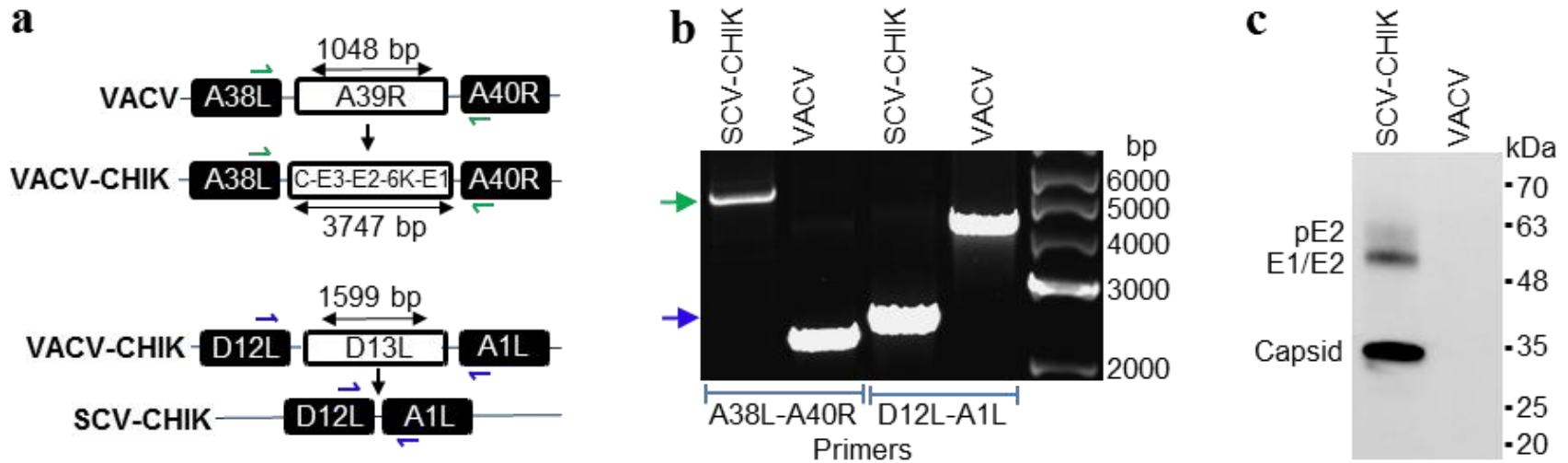


# Rationale for the Sementis Copenhagen Vector (SCV) vaccine platform technology

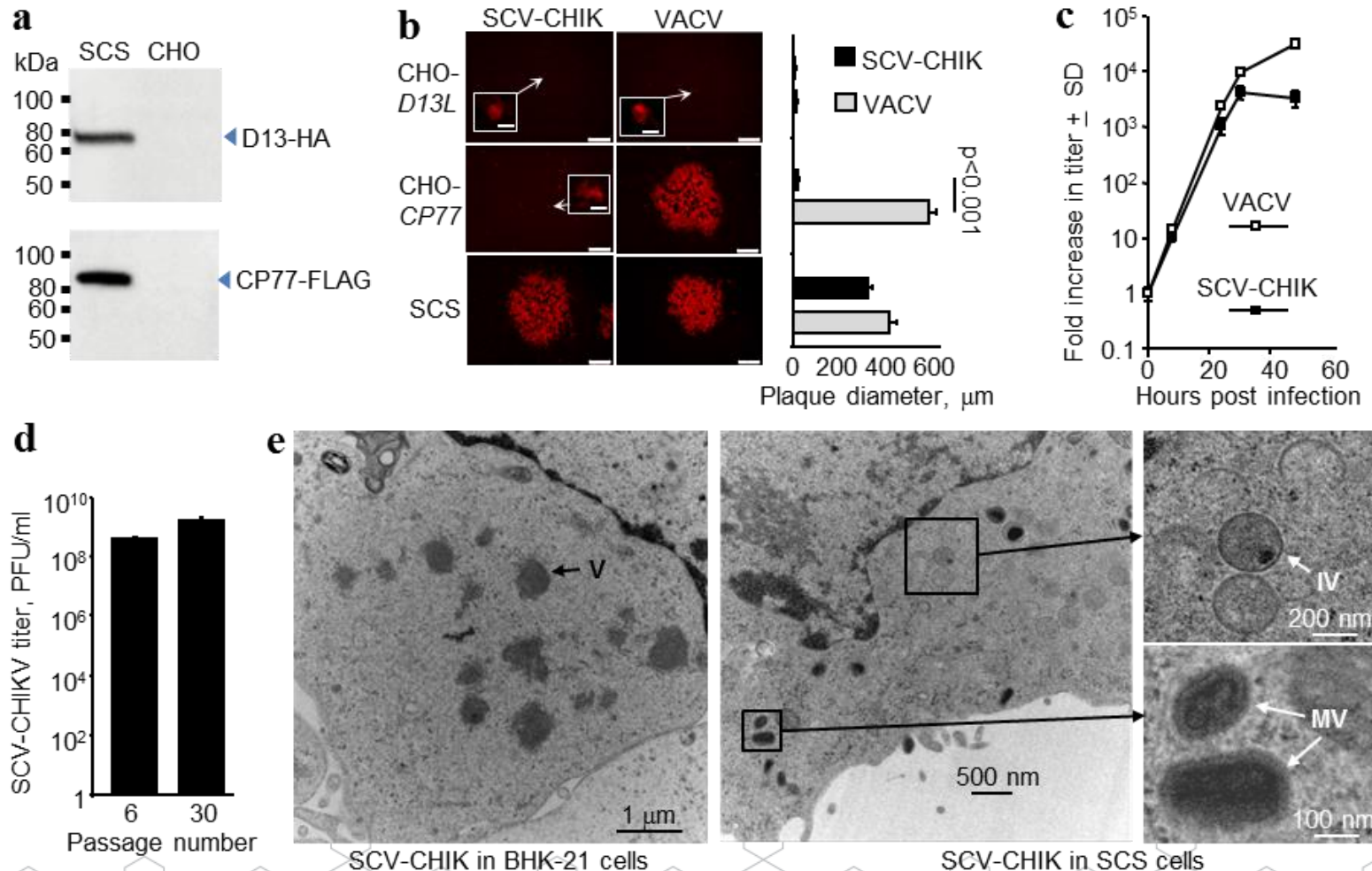




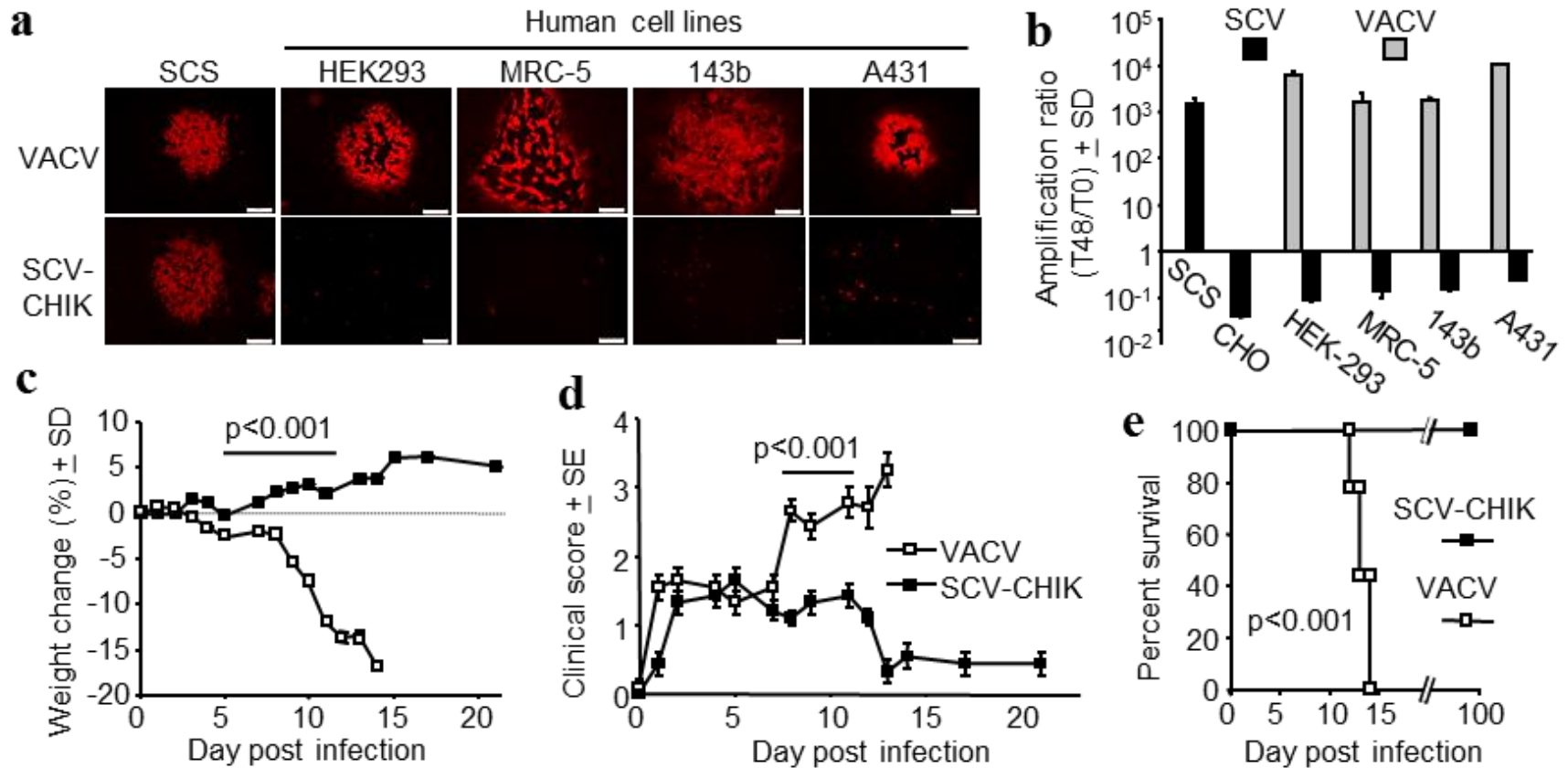
# Construction and *in vitro* characterisation of the SCV-CHIK vaccine



# Production and morphology of SCV-CHIK in SCS cells

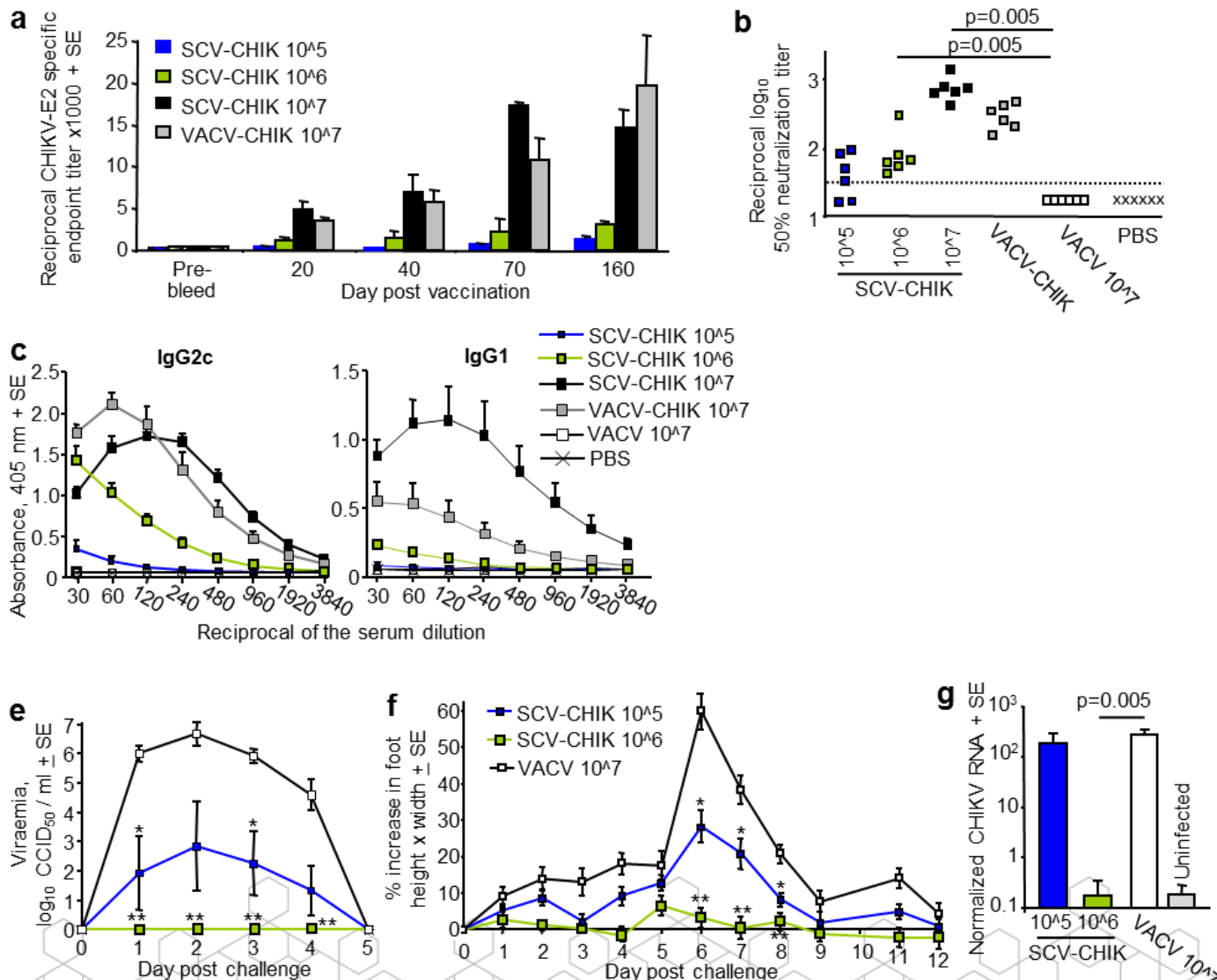


# SCV-CHIK replication defect in human cell lines and attenuated pathology



SCID mice vaccinated

# A single shot SCV-CHIK induces antibodies and protects against CHIKV infection and disease





# Conclusions

- **Innovative vaccinia virus-derived vaccine platform (SCV)**
- **Multiplication deficient by targeted deletion of the essential viral assembly gene, D13L**
- **SCV cell substrate line developed for SCV vaccine production in CHO cells**
- **Benefit - scale up capacity for manufacturing**
- **Single shot vaccination of SCV-CHIK provided protection against CHIKV challenge, preventing both viraemia and arthritis**

# Zika virus history

**1947** – 1<sup>st</sup> isolation from rhesus monkeys in Zika Forest, Uganda (MR766 prototype)

**1952** – 1<sup>st</sup> recorded human infection, Nigeria

**2013-14** – French Polynesian outbreak

>25,000 people infected

**1948** – 1<sup>st</sup> isolation from *Aedes africanus* mosquito

**2007** – 1<sup>st</sup> major human outbreak, Yap Islands, Micronesia

185 people infected

**2015 (ongoing)** – Latin American outbreak

1.6 million people infected in Americas

# Why the panic?

## COUNTRIES WITH CONFIRMED **ZIKA** CASES



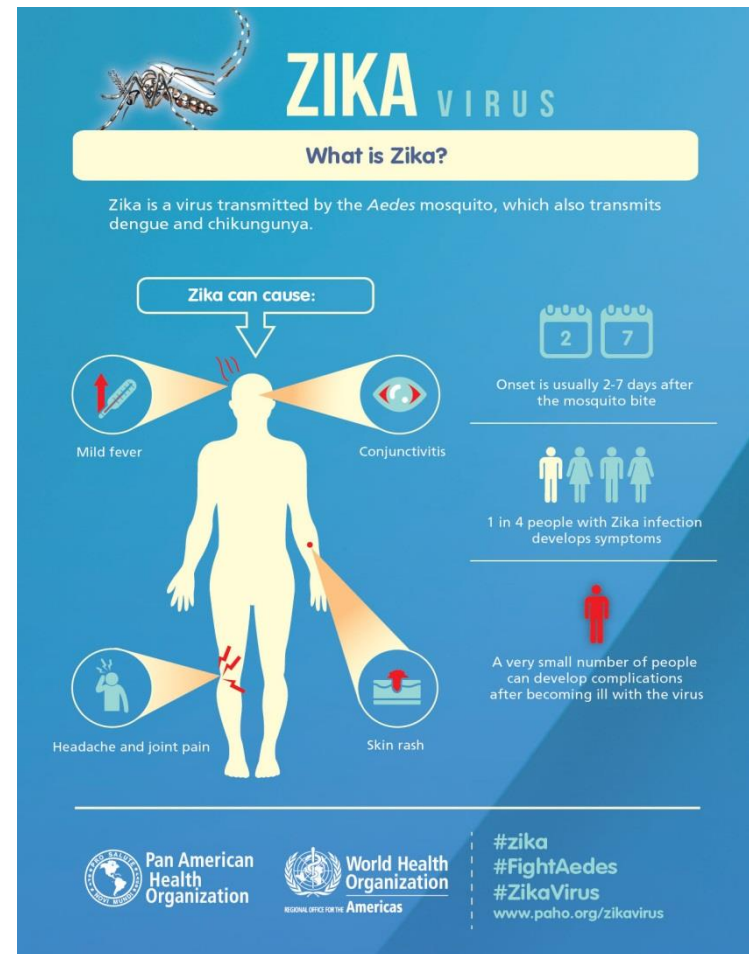
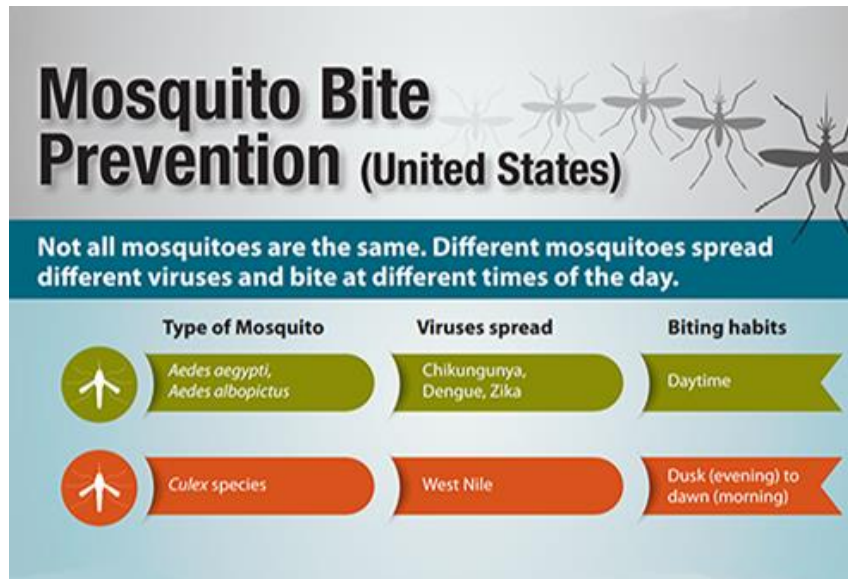
UGANDA  
NIGERIA  
TANZANIA  
EGYPT  
CENTRAL AFRICAN  
REPUBLIC  
SIERRA LEONE  
GABON  
INDIA  
MALAYSIA  
PHILIPPINES  
THAILAND  
VIETNAM  
INDONESIA

MICRONESIA  
POLYNESIA  
EASTER ISLAND  
THE COOK ISLANDS  
NEW CALEDONIA  
BRAZIL  
CHILE  
COLOMBIA  
EL SALVADOR  
GUATEMALA  
MEXICO  
PARAGUAY  
VENEZUELA

SURINAME  
CAPE VERDE  
FIJI  
FRENCH GUIANA  
HONDURAS  
MARTINIQUE  
PUERTO RICO  
PANAMA  
SAMOA  
VANUATU  
USA  
NETHERLANDS  
GERMANY

- Could be as many as 500,000 to 1 million Zika infections in Brazil
- Only 1 in 5 develop clinical symptoms
- 4,231 suspected microcephaly cases are still being investigated (March 9, 2016)
- Zika virus is spreading rapidly
- Confirmed non-vector modes of transmission
- No vaccines or approved therapies
- Little is known about the virus, transmission etc

# Zika virus – transmission cycle



Transmission via

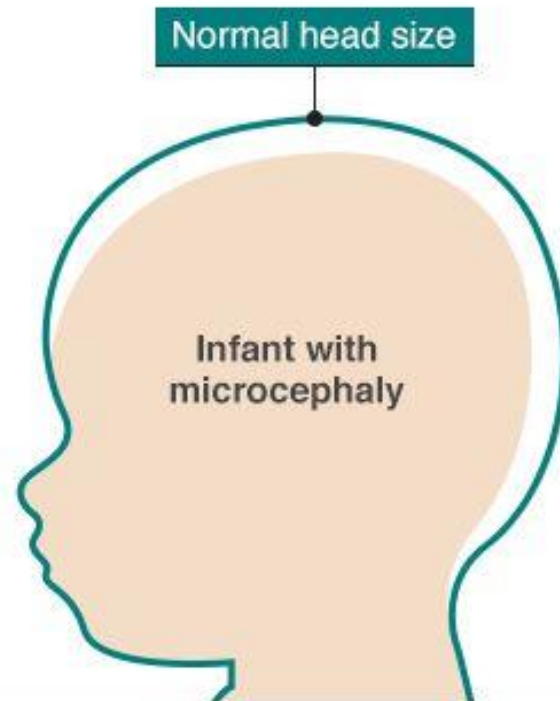
1. Mosquito
2. Mother to baby *in utero*
3. Sexual transmission
4. Blood transfusion



# Neurological birth defects

## Microcephaly

- Symptoms include below-average head size
- Often caused by failure of brain to grow at normal rate
- Head circumference measuring **less than 31.5-32cm** at birth
- Affects **25,000 children** in US each year



Source: ADAM, WHO

BBC

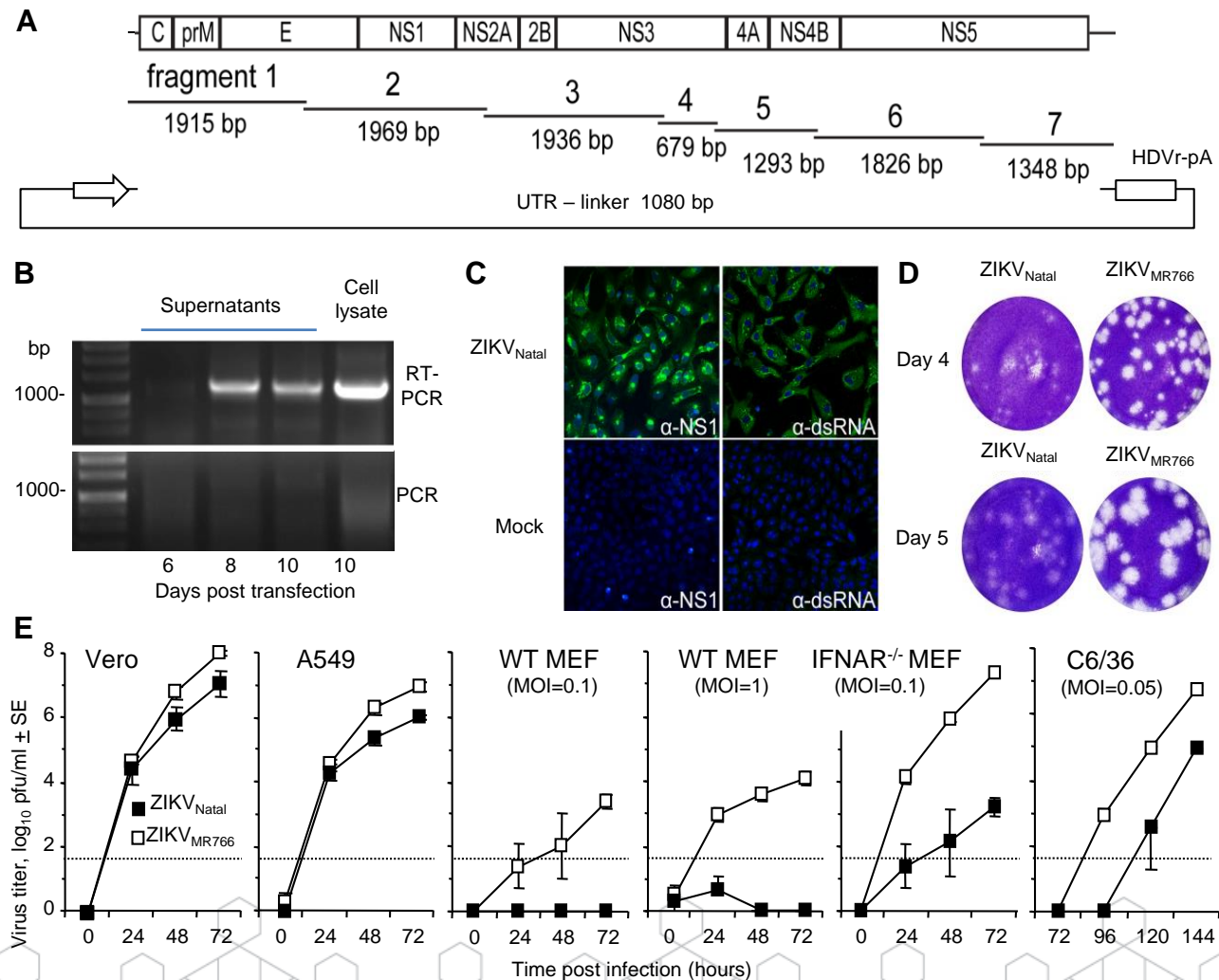




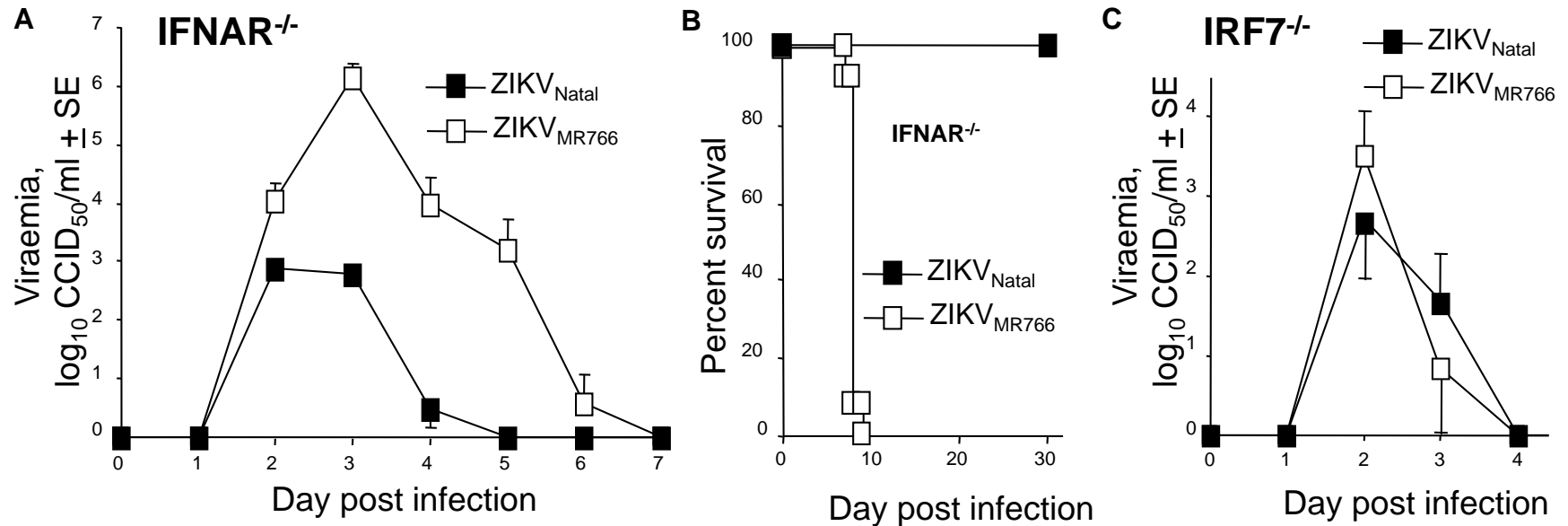
# Development of a single vectored SCV-CHIK/ZIKA vaccine

## Need for preclinical mouse models

# De novo generation of infectious Zika<sub>Natal</sub> by CPER

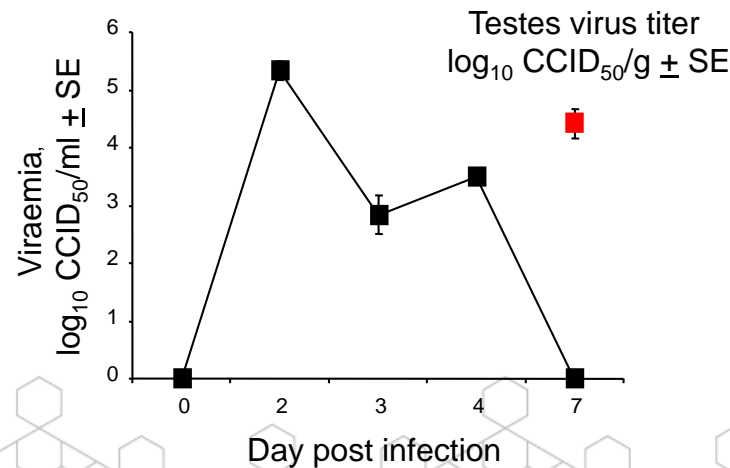
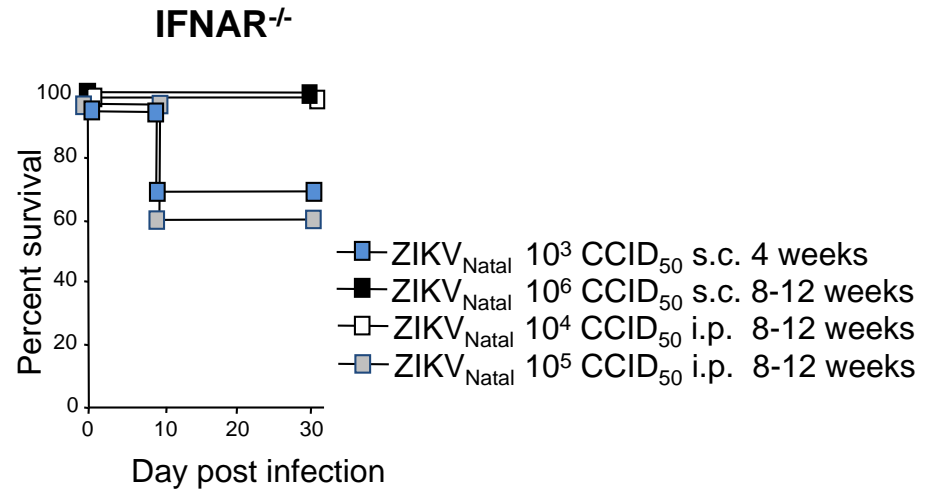
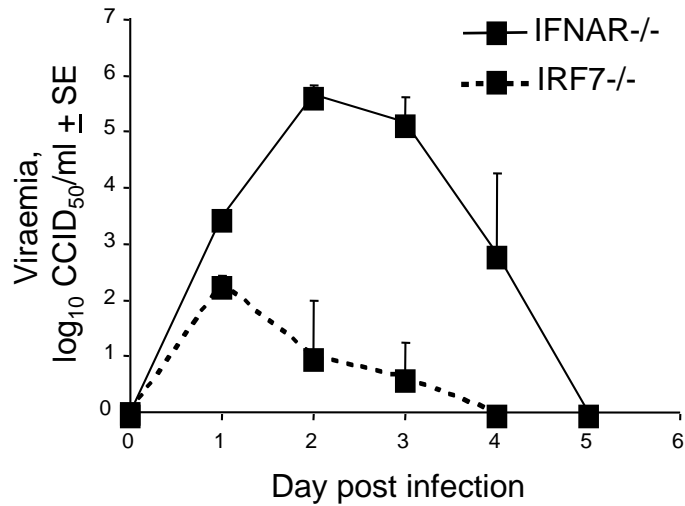


# ZIKV<sub>Natal</sub> infection of IFNAR<sup>-/-</sup> and IRF7<sup>-/-</sup> mice

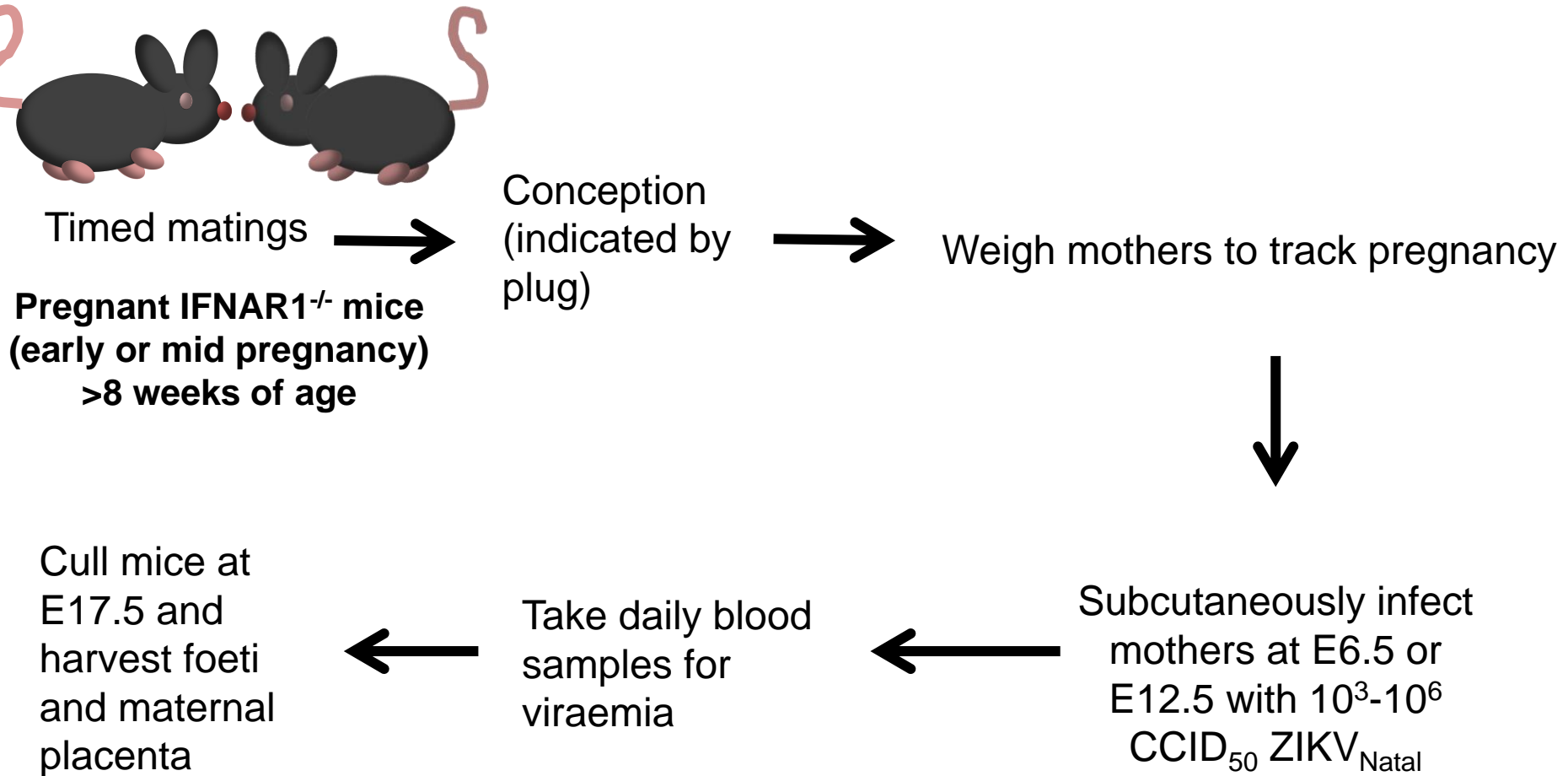




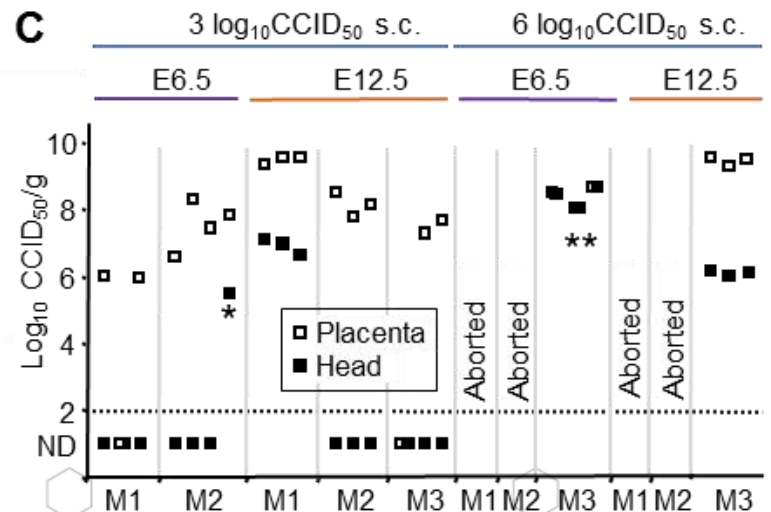
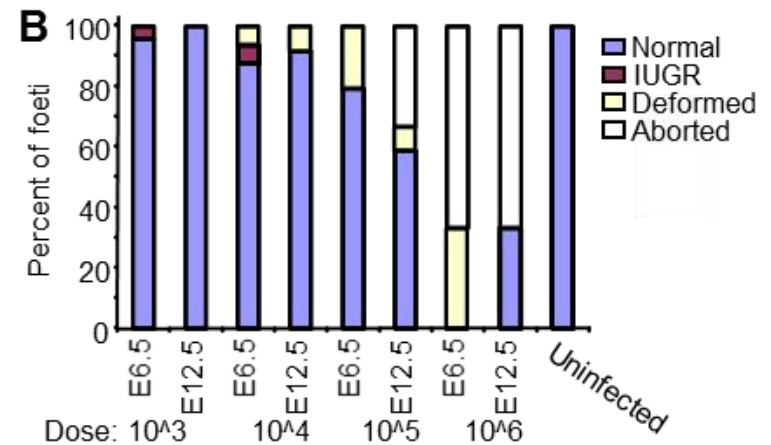
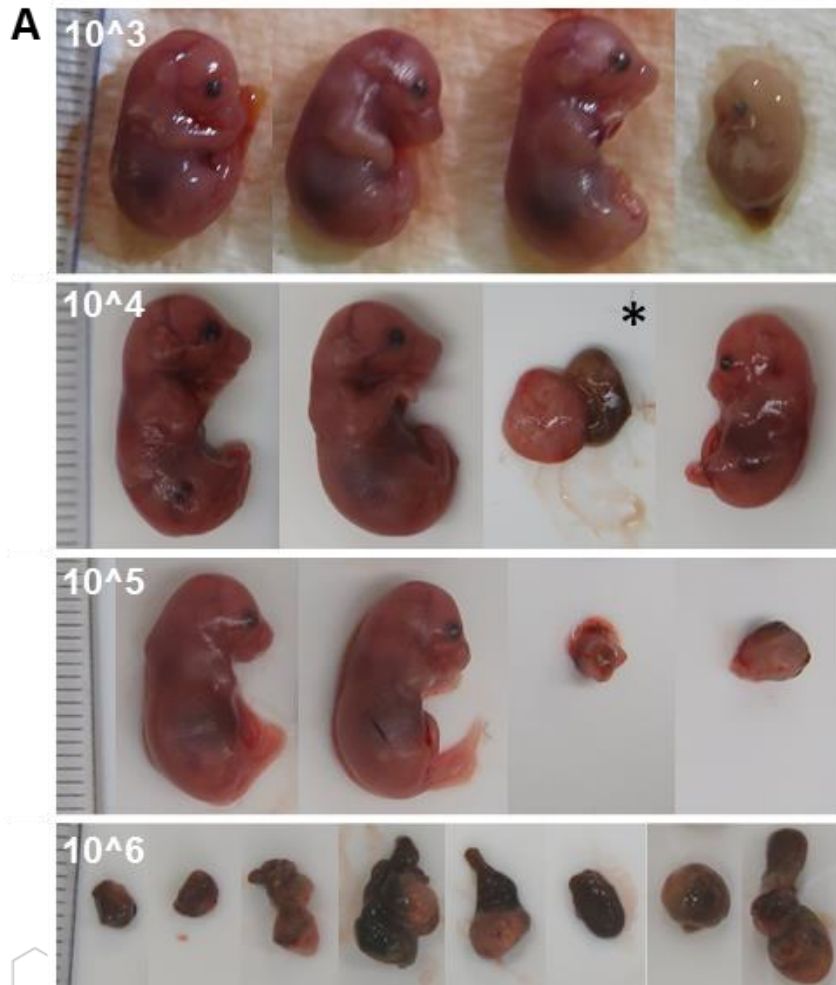
# Characterisation of ZIKA<sub>Natal</sub> *in vivo*



# Pregnancy model steps: a brief overview



# Pregnancy outcomes of ZIKV<sub>Natal</sub>-infected dams



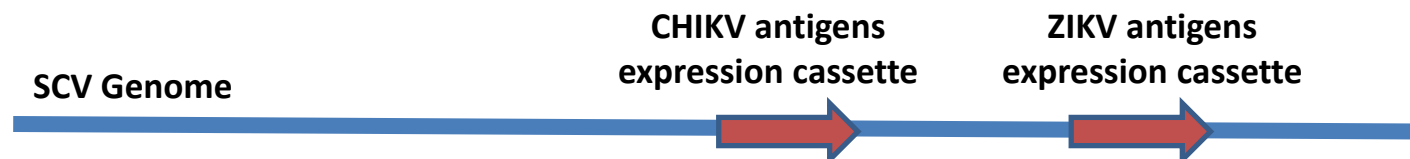
# SCV-CHIKV+ZIKV Vaccine Design

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Sementis' single vectored dual chikungunya and Zika virus vaccine: SCV1002

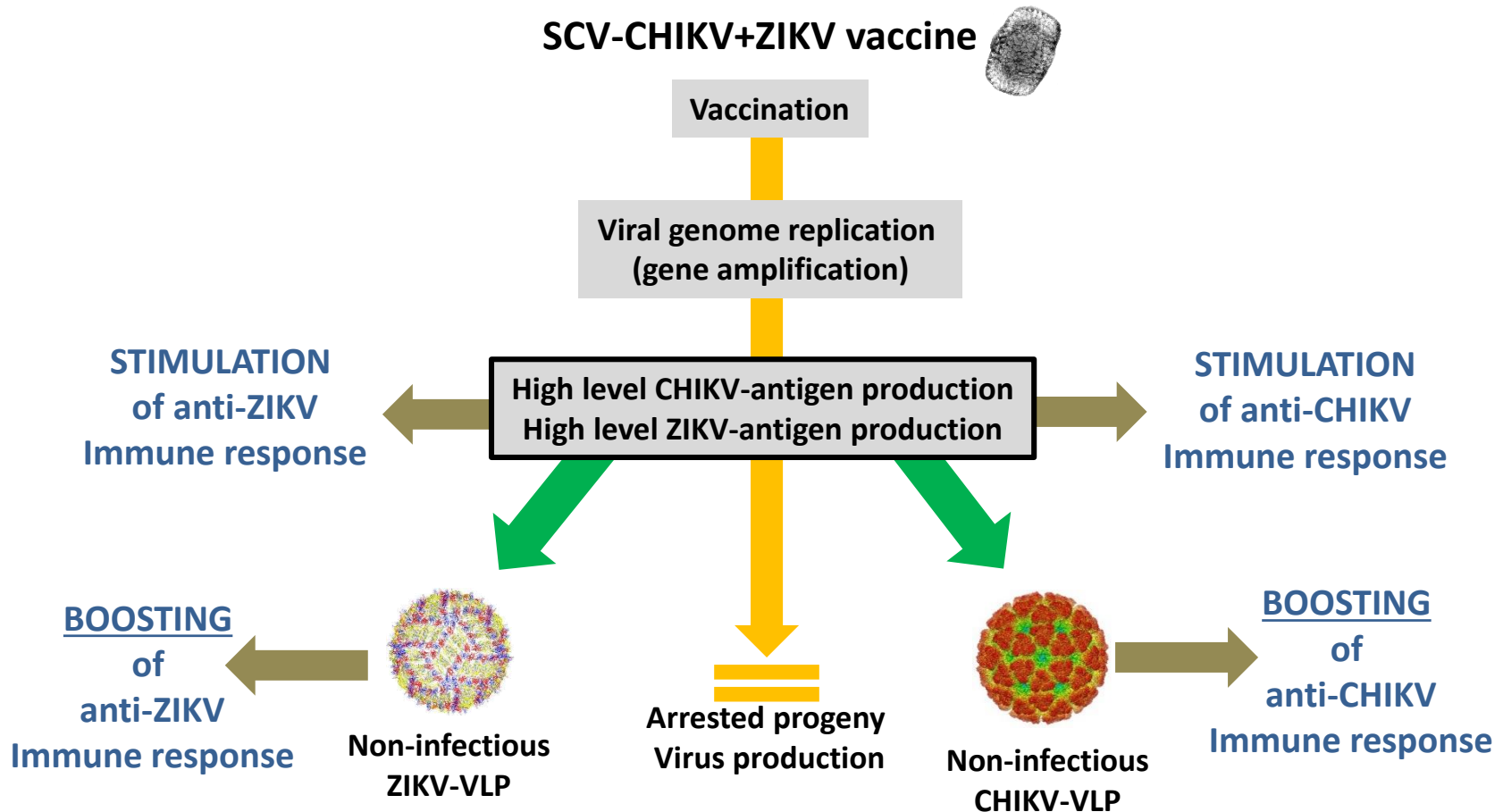
## Vaccine design:

- Contains ZIKV PrME polyprotein structural protein expression cassette. The structural protein coding sequences are a representative of the Brazilian strain ZikaSPH2015 (Genbank: KU321639).
- Contains CHIKV 26S polyprotein structural protein expression cassette. The structural protein coding sequences are representative of the Reunion strain 06\_21 (Genbank: AM258992).
- Expression of the structural proteins upon vaccination will also lead to VLP formations for ZIKV and CHIKV.





# How SCV-CHIKV+ZIKV (SCV1002) Vaccine Works



# Preclinical testing of SCV1002 still ongoing!

- ***De novo* generation of a clinically relevant isolate, unequivocally associated with congenital Zika syndrome using a circular polymerase extension reaction protocol**
- **Established fetal brain infection model in IFNAR-/-**
  - Inc intrauterine growth restriction
- **No clinical symptoms in dams**
- **Established male testis infection model**
- **Testing a single vectored SCV-CHIK/ZIKA in CHIKV and Zika adult mouse models**
- **Ongoing testing in fetal brain and testis infection models**



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Eldi P, Cooper TH, Liu L, **Prow NA**, Diener KR, Howley PM, Suhrbier A, Hayball JD. Production of a chikungunya vaccine using a CHO cell and attenuated viral-based platform technology. *Mol Therapy*. Accepted 18<sup>th</sup> June, 2017

Setoh YX\*, **Prow NA\***, Peng N, Hugo LE, Devine G, Hazlewood JE, Suhrbier A, Khromykh AA. De Novo generation and characterization of new Zika virus isolate using sequence data from a microcephaly case. *mSphere* 2(3). pii: e00190-17 \*contributed equally



**Funding**

