

# Better ways to make single shot multivalent vaccines for emerging infectious diseases and allergy

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University of  
South Australia



sementis

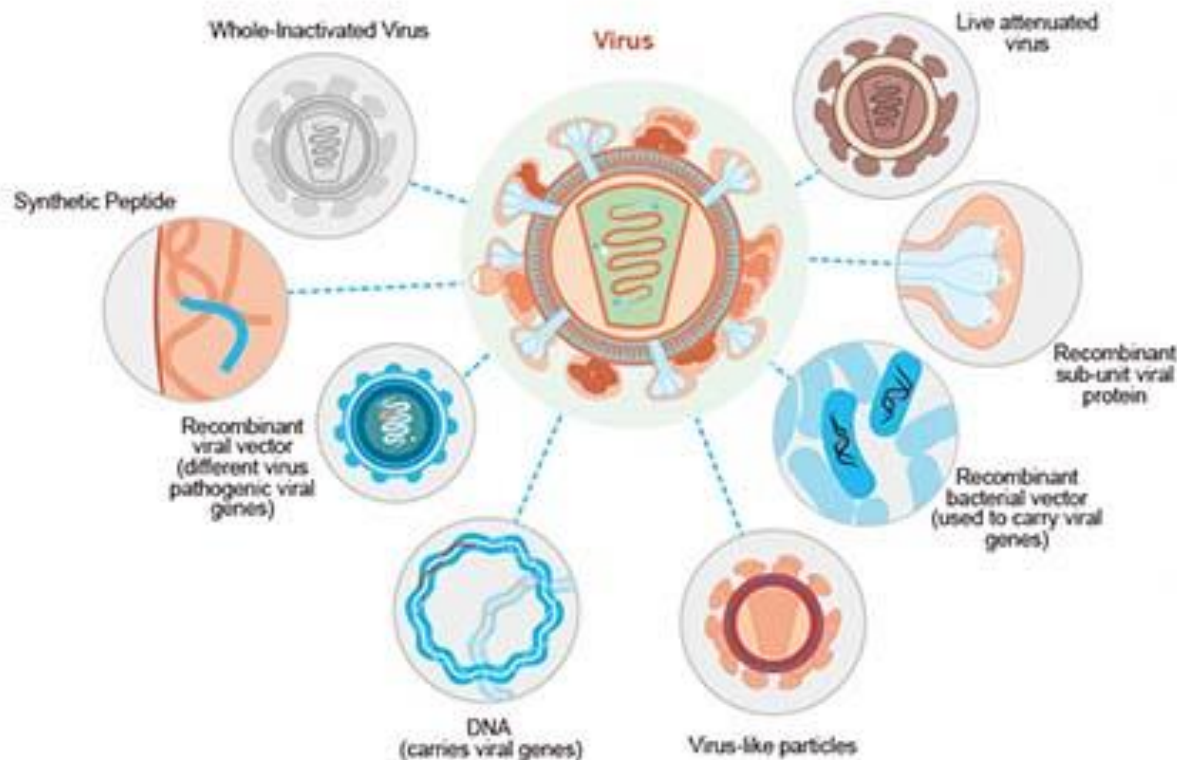


# University of South Australia Cancer Research Institute

SA's new home for cancer research

- Active and passive immunotherapeutics
  - Infectious diseases
  - Allergy
  - Sepsis
  - Cancer
    - Humans
    - Companion animals
    - Tasmanian devils
- Functionalised materials
  - Immune function sensors
  - Medical implants
  - Drug delivery
  - Water contaminant sensing and purification

# Types of Vaccines



## Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever

## Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)

## Subunit (purified antigen)

- Acellular pertussis (aP).
- *Haemophilus influenzae* type B (Hib).
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)

## Toxoid (inactivated toxins)

- Tetanus toxoid (TT).
- Diphtheria toxoid

# Why a Better Way to Make Vaccines?

- Clinical need
  - More effective therapeutic vaccines
    - Chronic viral infections
    - Cancer
    - Allergy
  - Rapid responses to emerging infectious diseases
    - Chikungunya/Zika
    - Ebola/Lassa
    - MERS/SARS CoV
- Economic reasons
  - Expensive
    - Vaccine-specific design and empirical testing regimens
    - Complex biopharmaceutical manufacturing processes
    - Arduous regulatory pathways
- Big Pharma don't like making new vaccines
  - Opportunities for innovative approaches and niche applications



## ChimeriVax Technology

Yellow fever 17D genome cloned as cDNA



Exchange coat protein genes  
of dengue 1,2,3,4 (wild-type)

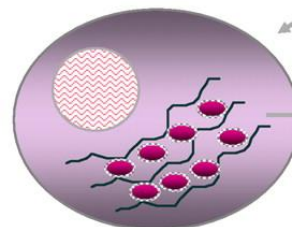


Chimeric cDNA → transcribe to RNA



Transfect mRNA

Envelope is heterologous virus  
containing immunizing antigens



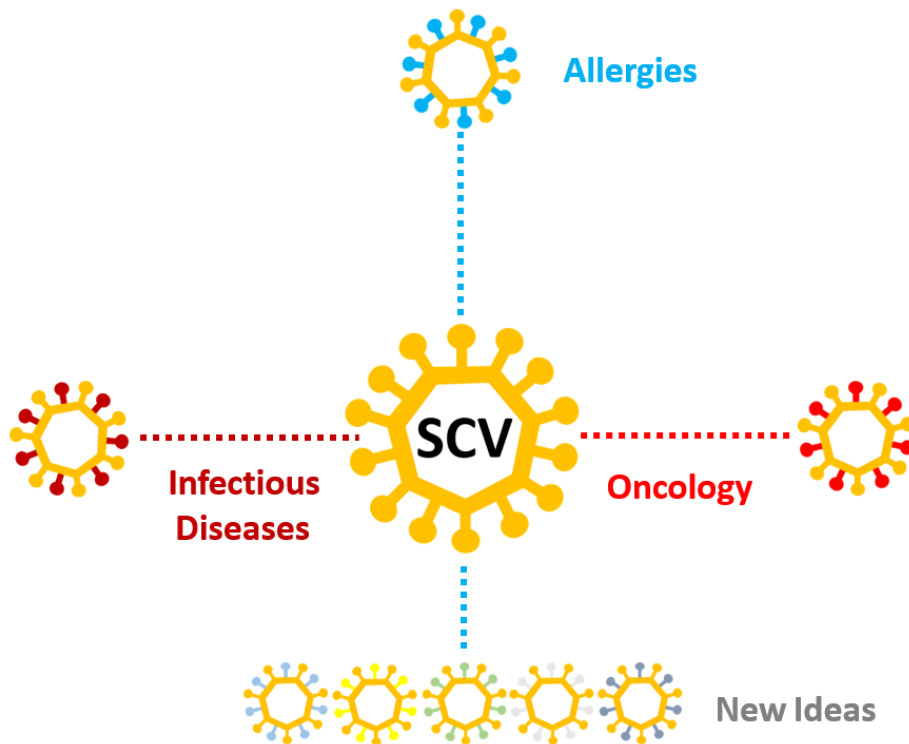
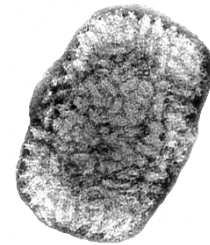
Grow virus  
in cell culture



RNA replicative  
'engine' is YF 17D



# The propriety SCV platform technology developed with Sementis Ltd.



## Vaccine Delivery Vehicle (SCV Vector):

“Genetically crippled smallpox vaccine that can be engineered to make ANTIGENS from disease targets to raise immunity to that disease”

*Totally attenuated vaccine vector system*

## Manufacturing Cell Substrate:

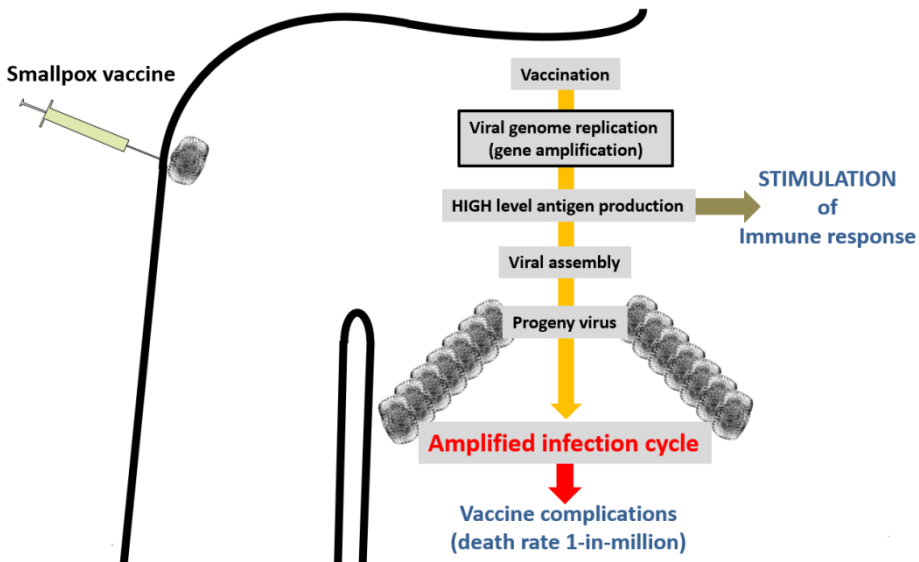
“The **CHO** biotechnology friendly cell substrate engineered to produce the SCV vector”

*A first for the production of vectored vaccines!*

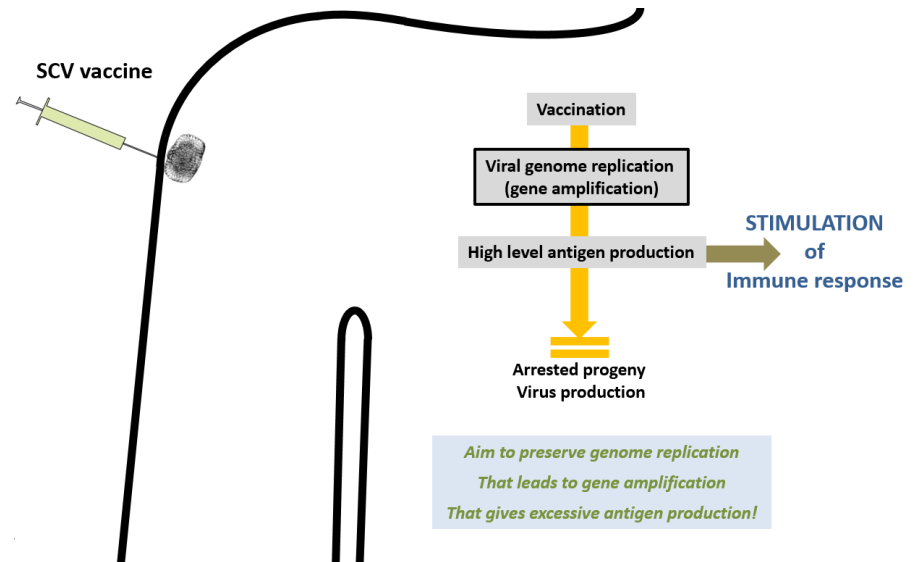
Declared COI: JD Hayball holds shares in Sementis Ltd and sits on the SciAdBrd

# How does the SCV platform work?

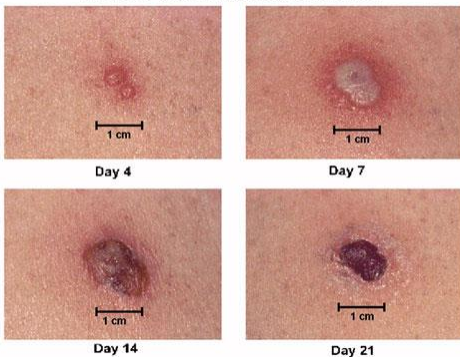
## Smallpox Vaccine (Live replication competent)



## SCV Vaccine (Live NON-replication competent)



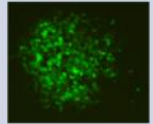

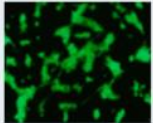
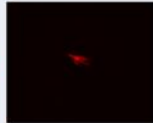
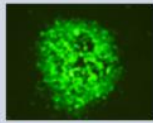

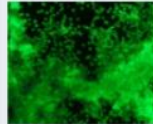

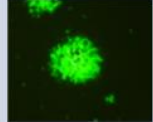

Primary Vaccination Site Reaction



# SCV does not multiply in human and mammalian cells lines

A study was carried to show that SCV does not multiple or propagate in cells derived from key organs of the body after deliberate infection:

	Vaccinia Virus (Parent of SCV)	SCV
Human Bone cell	High Yields of virus (as <i>expected</i> )	No virus production!
Human Lung cells		
Human Kidney cells		
Human Skin cells		
Human Cervical cells		

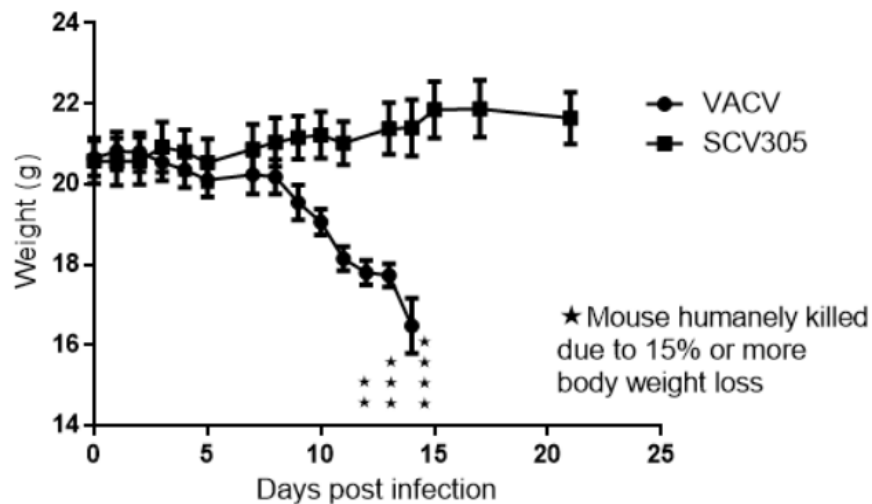
		Vaccinia	SCV
143B	Human Bone Cells		
MRC-5	Human Lung Cells		
HEK-293	Human Kidney Cells		
A431	Human Skin Cells		
HeLa	Human Cervical Cells		



# SCV Technology – Safety

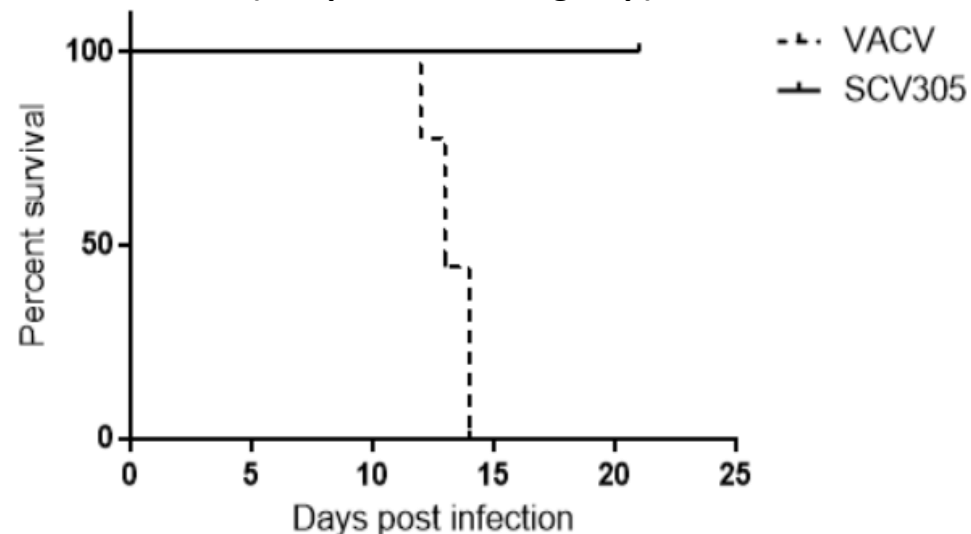
## (biodistribution in immunocompromised mice)

**Average Body Weights  $\pm$  SEM**  
(n=9 per treatment group)



*In the absence of an antiviral immune response SCV was unable to cause productive disease.*

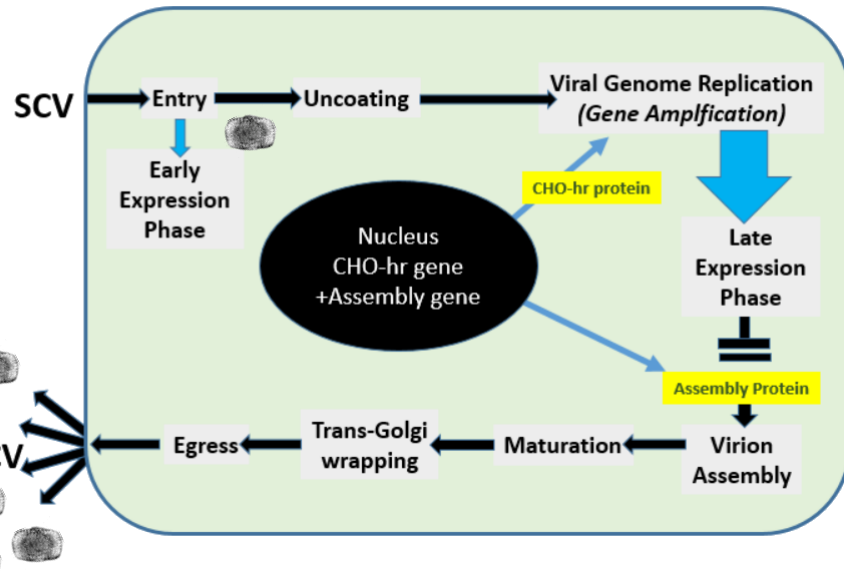
**Survival Plot**  
(n=9 per treatment group)



*In the absence of an antiviral immune response SCV is not pathogenic.*

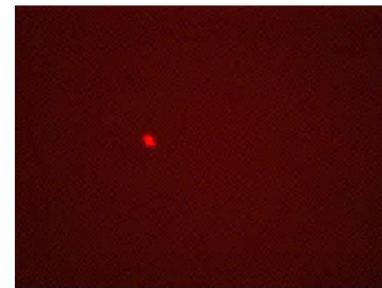
# SCV cell substrate for manufacturing

## SCV Production CHO Cell Line

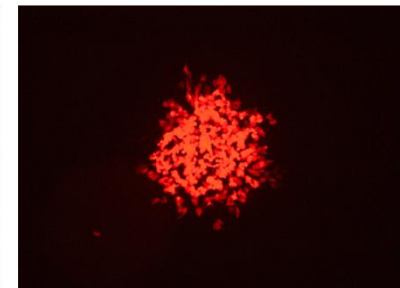


## Infection with SCV

(Totally attenuated SCV expressing Red Fluorescent Protein)



CHO

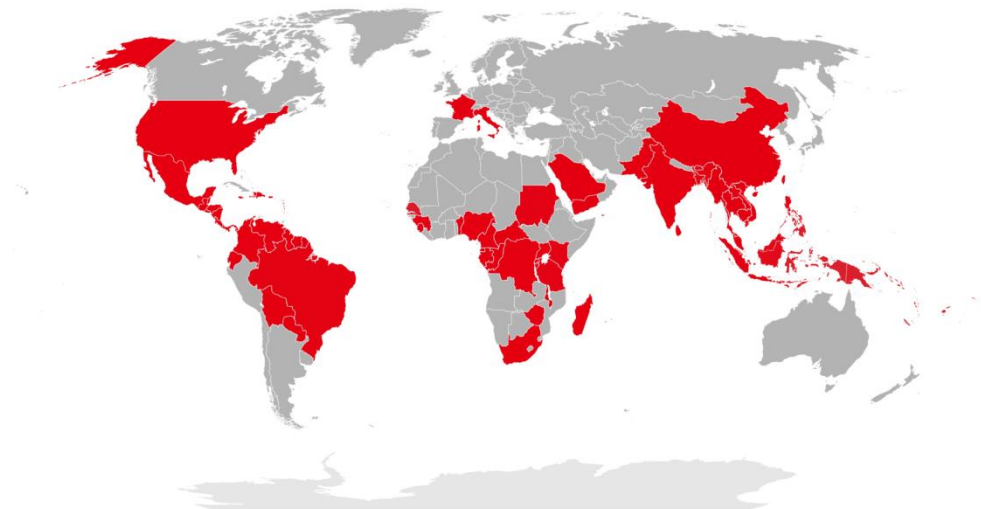
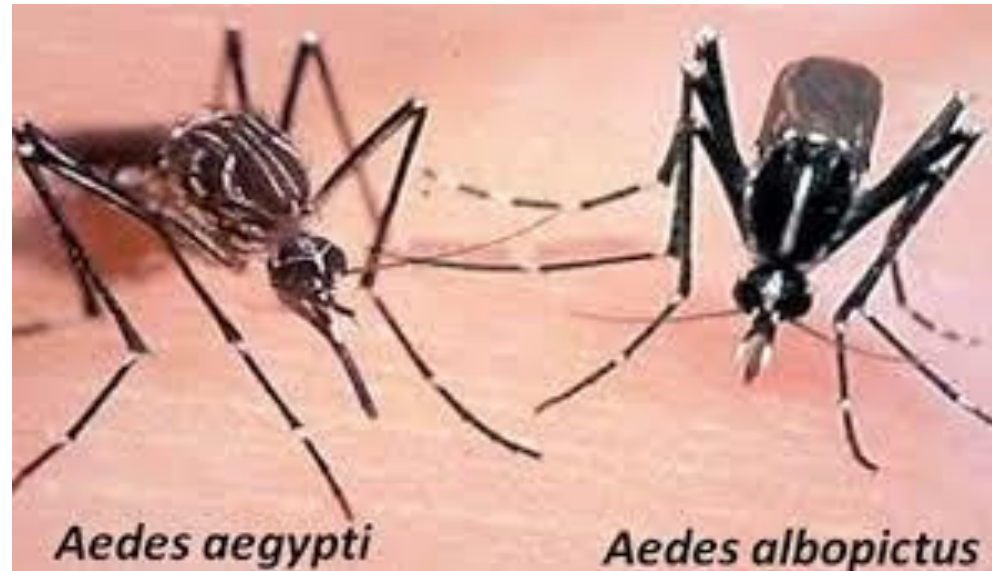
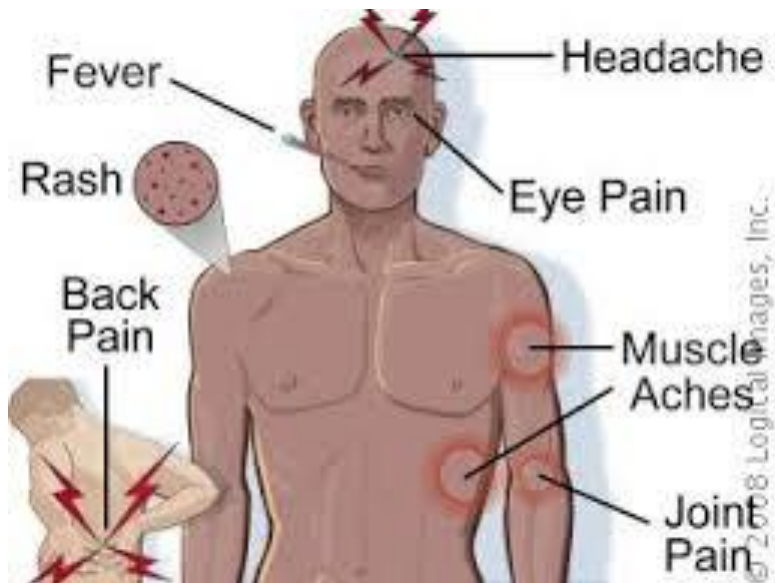
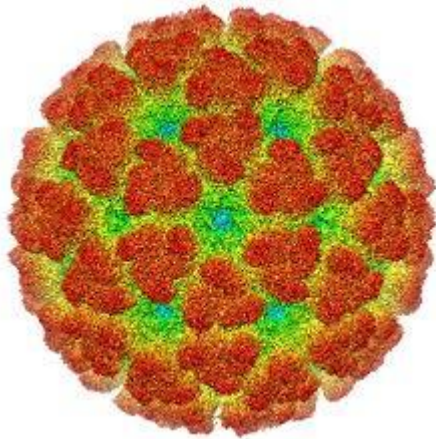


SCV Rescue cell line

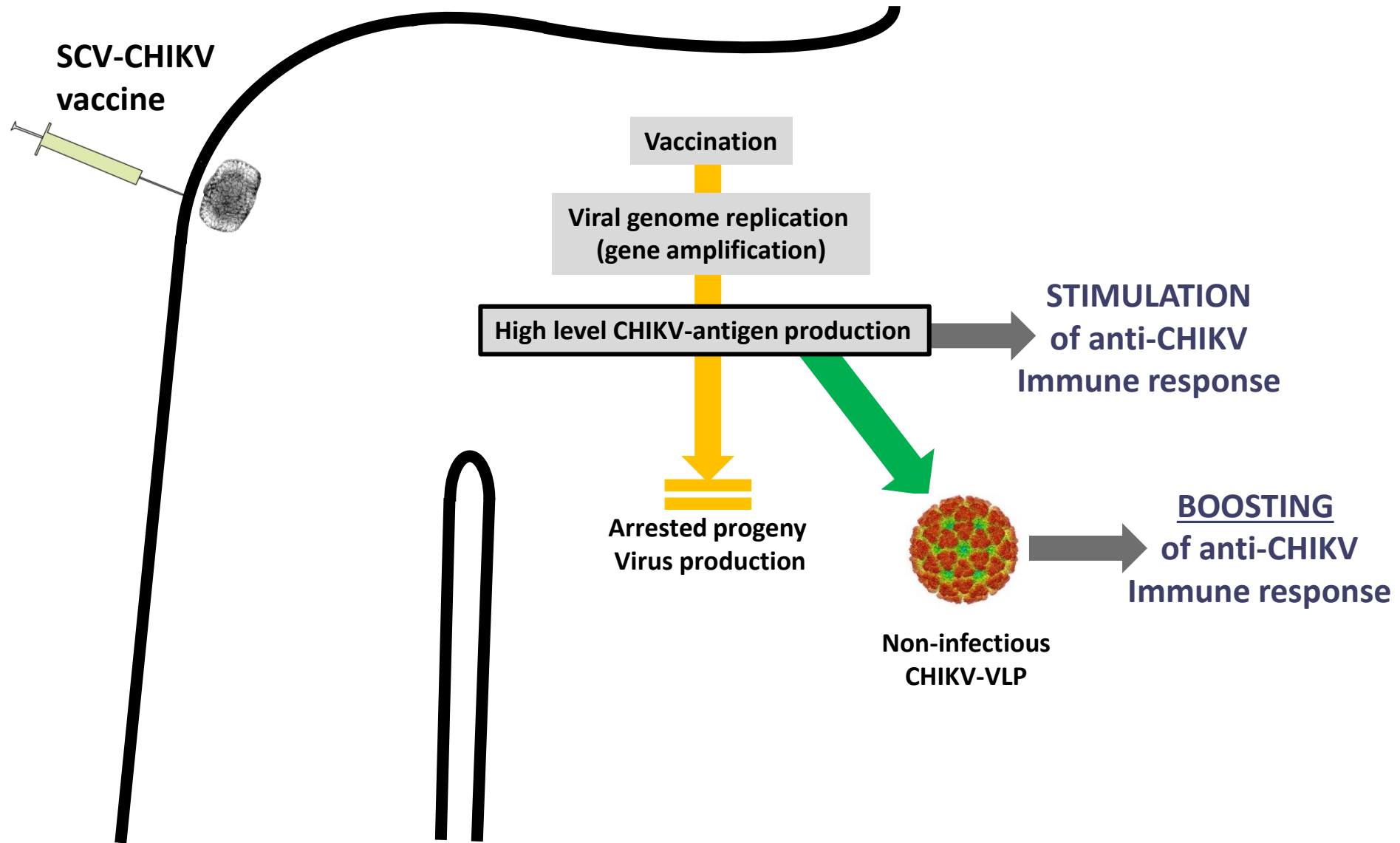
Sementis' SCV-cell substrate for manufacturing was derived from GMP produced CHO-S cell line :

- Sourced as a GMP produced batch of CHO-S from Life Technologies (also known as ThermoFisher Scientific), Cat # A1136401, royalty free, one off licence fee per field, ie, infectious diseases, immunotherapeutics
- Suspension cell line – suitable bioreactor production
- Cultured in serum-free chemically defined medium, eg, CD-CHO medium from Life Technologies, Cat # 10743029

# The Test Case: Chikungunya virus vaccine



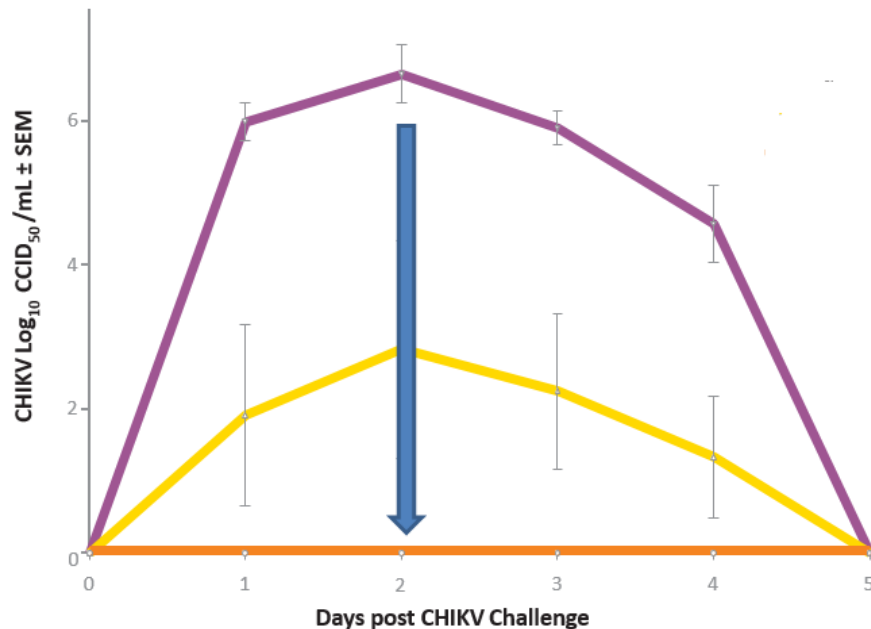
# How our SCV-CHIKV vaccine works



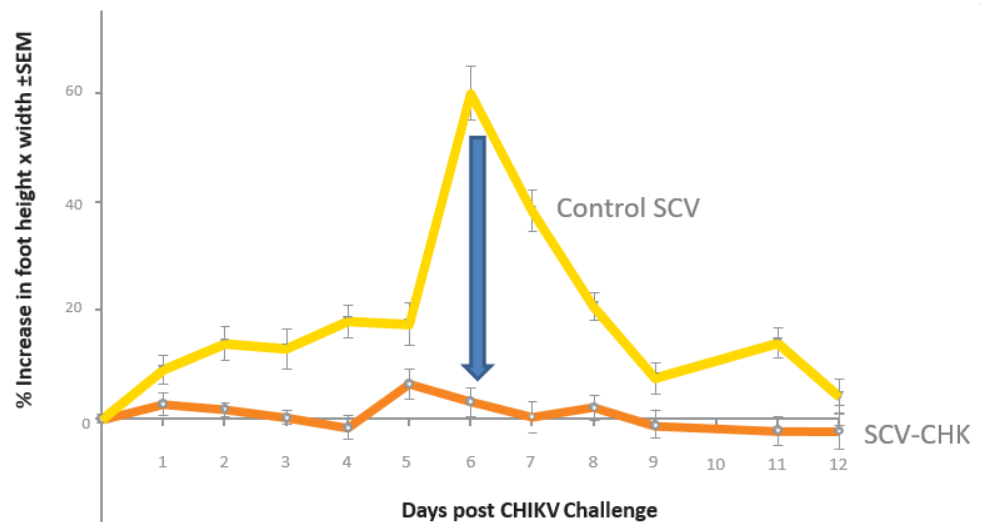
# A single shot of SCV-CHIKV protects mice against viraemia and virus induced arthritis

Immunisation with Chikungunya vaccine protects against Chikungunya virus challenge viraemia

- SCV000-10<sup>7</sup> pfu/mouse
- SCV305-10<sup>5</sup> pfu/mouse
- SCV305-10<sup>6</sup> pfu/mouse

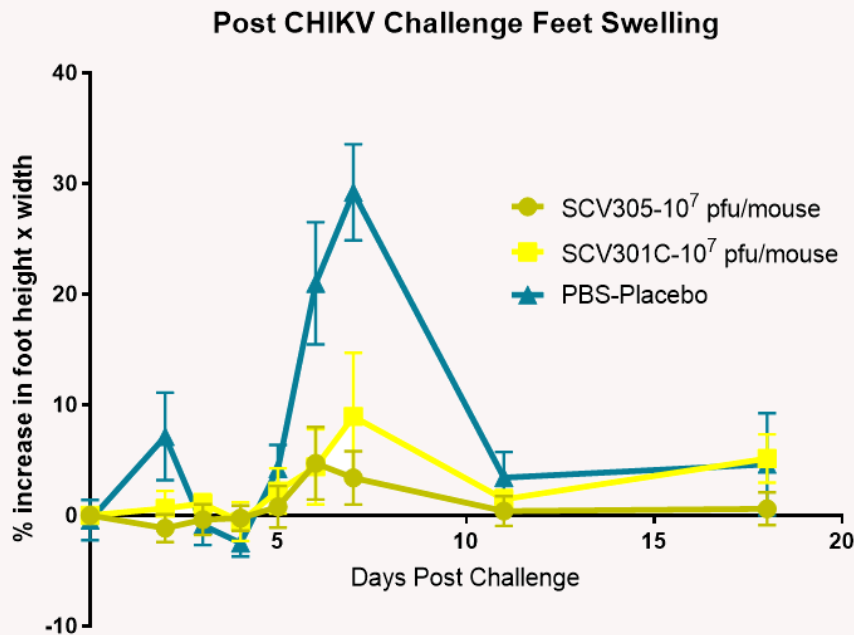


SCV-CHIK vaccine induced foot swelling (arthritis) after Chikungunya virus challenge

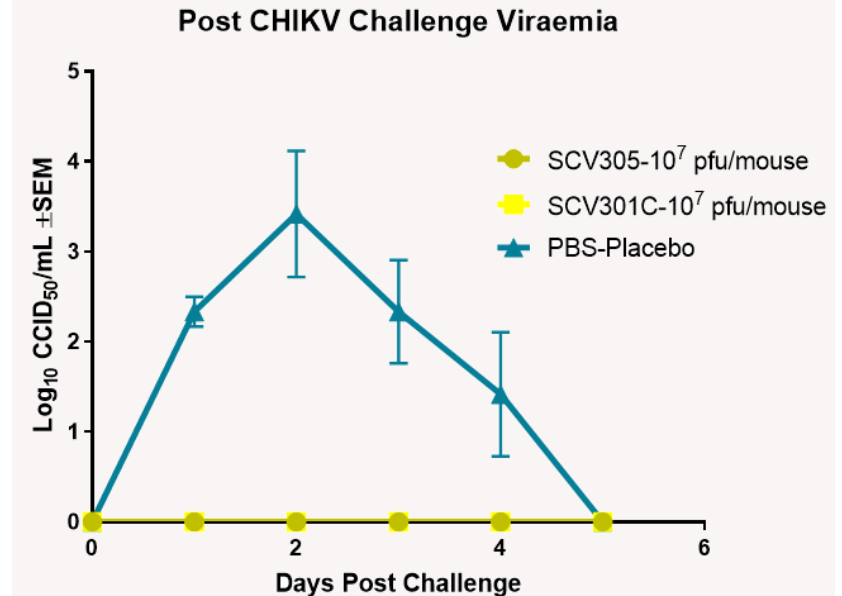


# A single shot of SCV-CHIKV still protects mice one year after vaccination

Immunization with SCV-CHIKV was fully protective against Chikungunya virus induced foot swelling 1 year after vaccination



Immunisation with SCV-CHIKV protects against Chikungunya virus challenge viraemia 1 year after vaccination





# Summary I

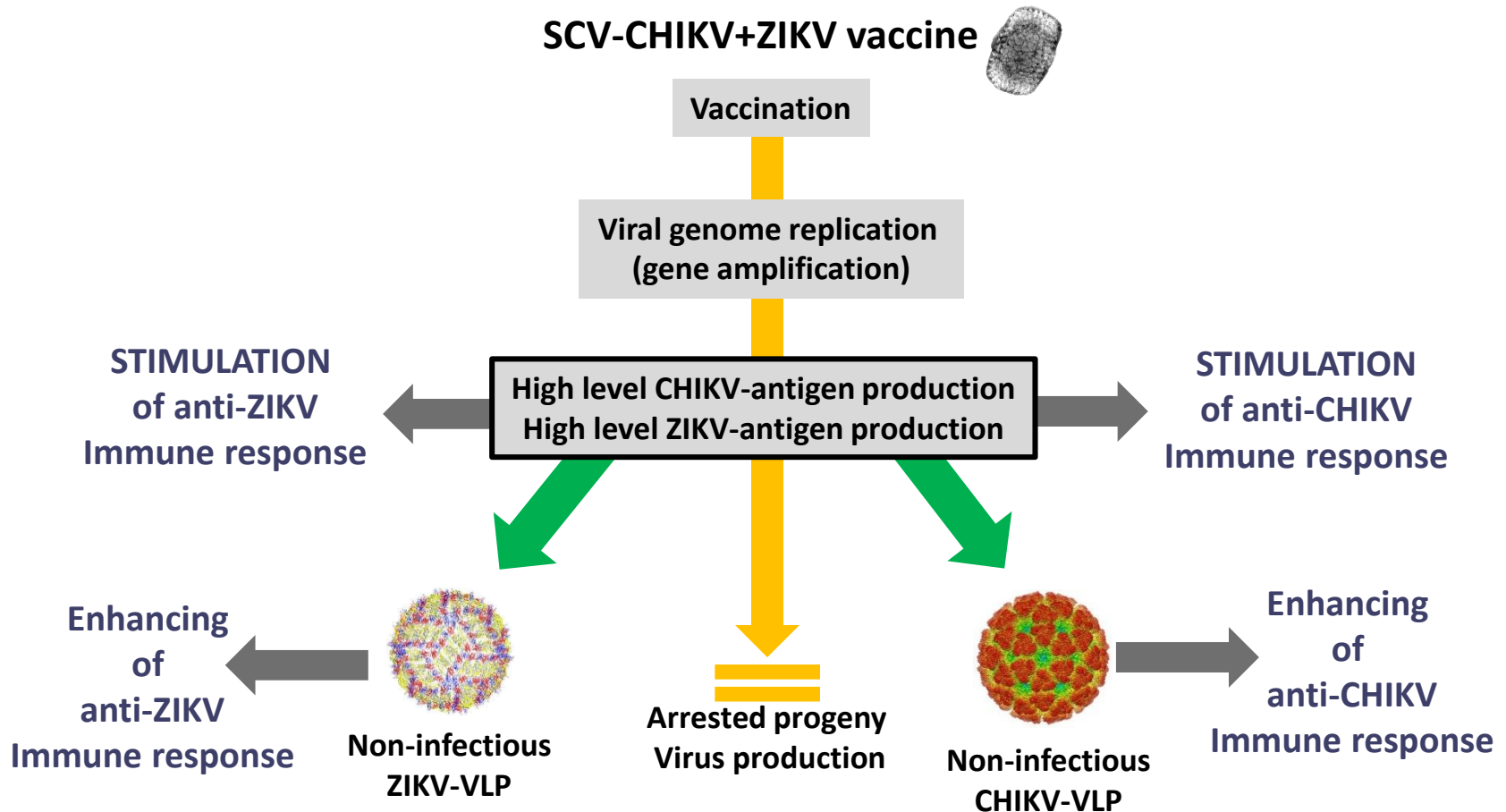
- SCV is replication-defective *in vitro* and *in vivo* - safe vaccine platform
- A stable rescue cell line derived from biotech-proven CHO cells provides for scalable commercial vaccine production
- SCV-CHIKV vaccination elicits single shot protective immune responses which last for at least one year
- Liu *et al*, BioTechniques, 2017.
- Eldi *et al*, Molecular Therapy, 2017.

# The Zika virus outbreak-a new challenge



- No vaccines or approved therapies
- Co-circulates with chikungunya
  - What about dual vaccine?

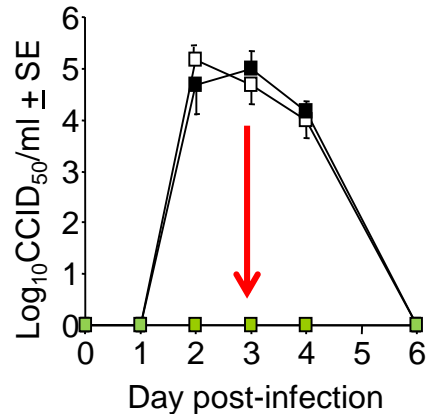
# How our dual SCV-CHIKV+ZIKV vaccine works



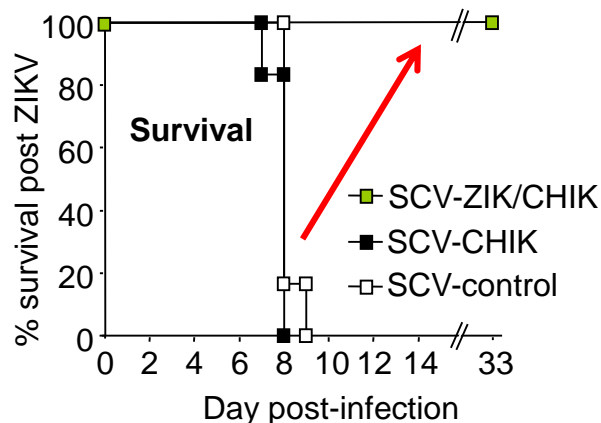
# A single dose of SCV-CHIKV+ZIKV protects against infection with both diseases

- in IFNAR mice

## Protection against viraemia

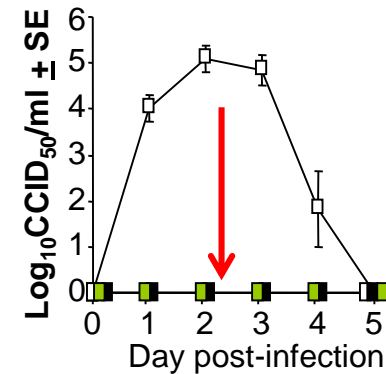


## Protection against lethal ZIKV<sub>MR766</sub>

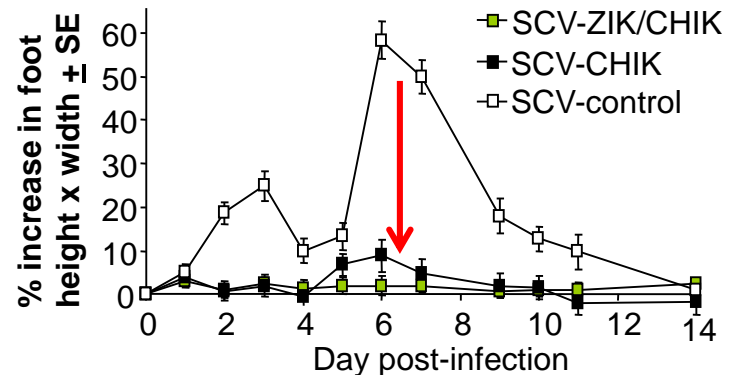


- in C57BL/6 mice

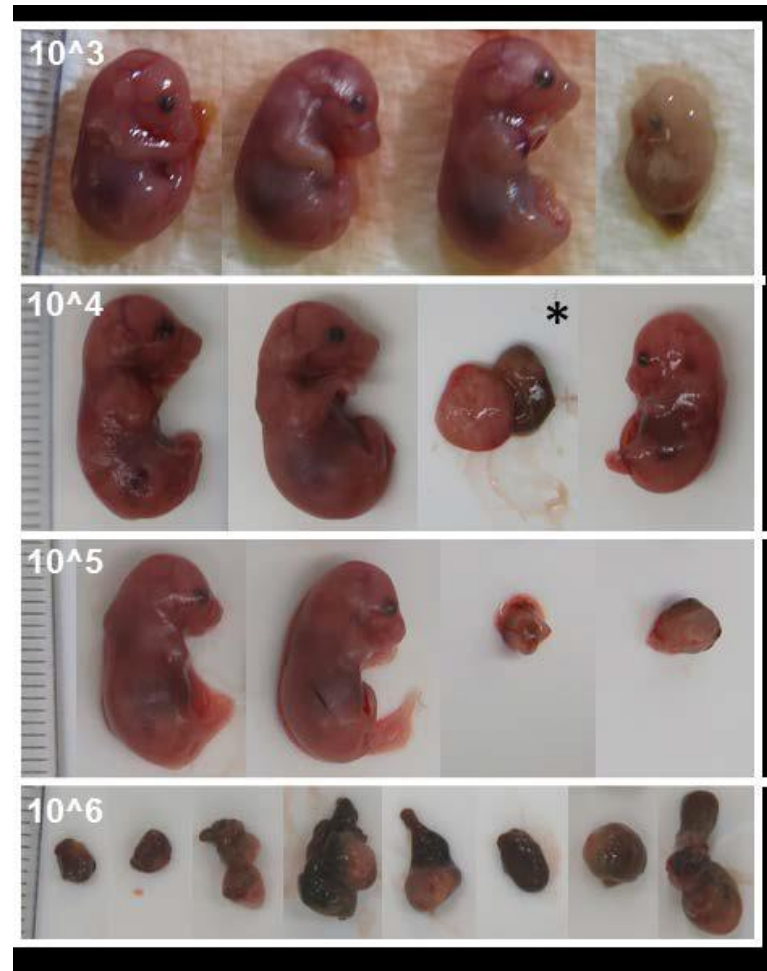
## Protection against viraemia



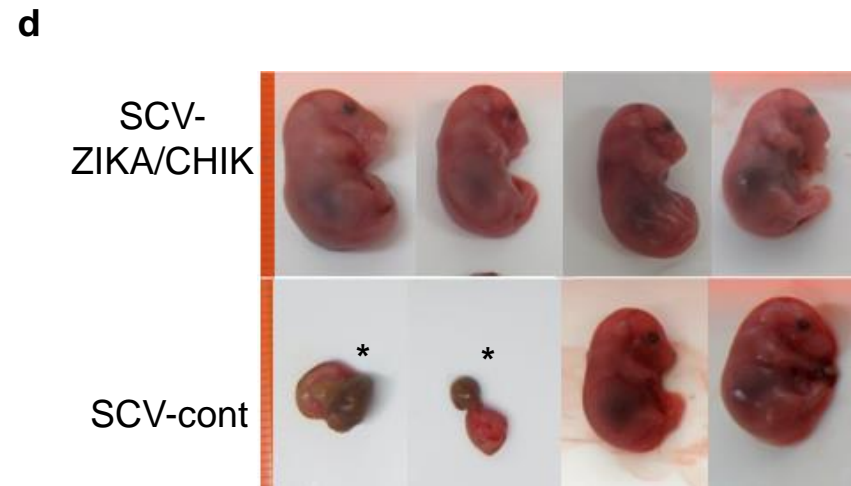
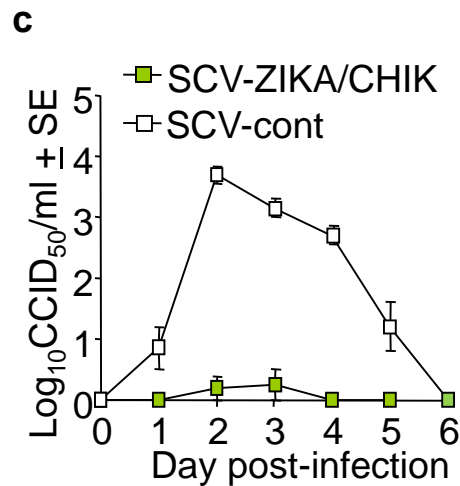
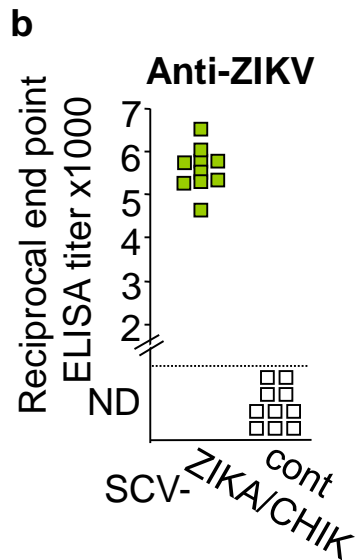
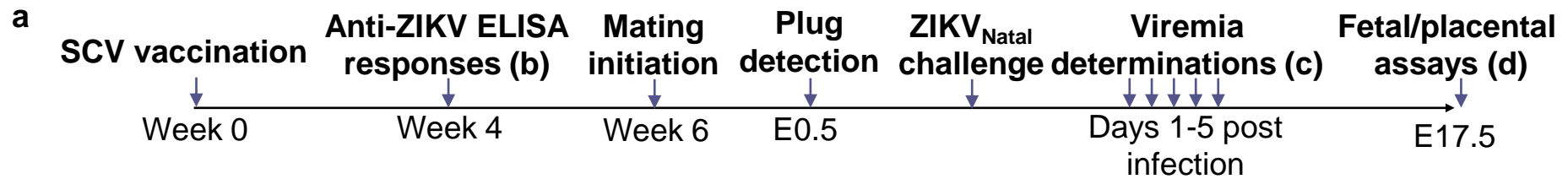
## Protection against CHIKV arthritis



# ZIKV Natal mouse model of foetal brain infection in IFNAR<sup>-/-</sup> x IFNAR<sup>-/-</sup> mice

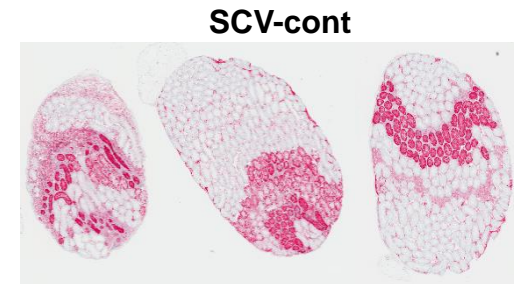
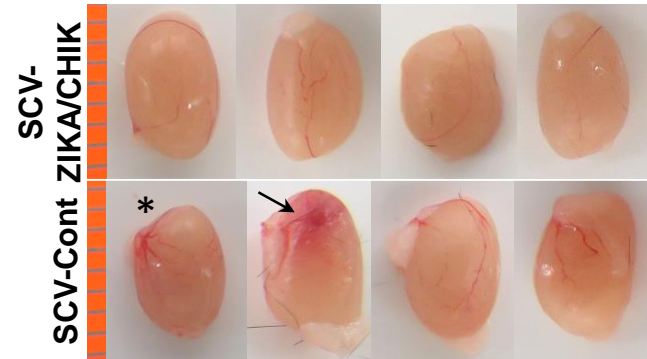
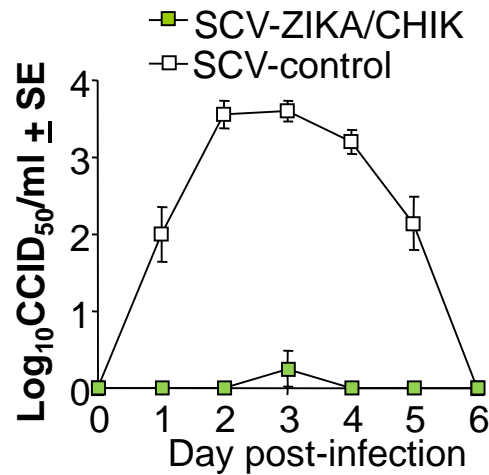
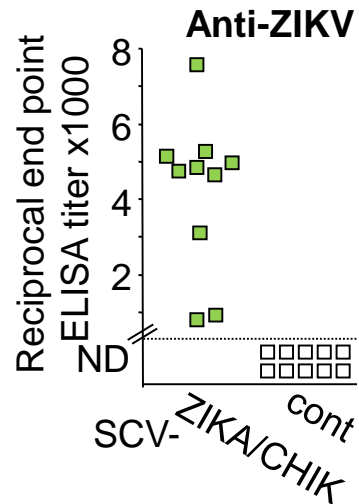


# A single shot vaccination protects against detrimental foetal outcomes





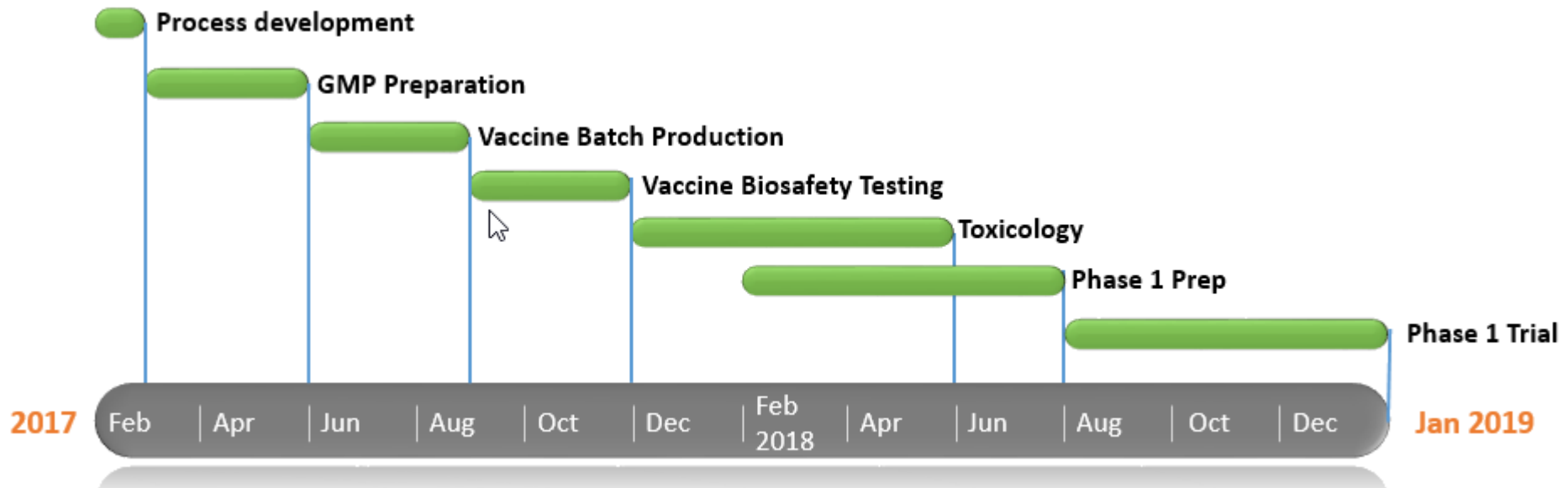
# A single shot vaccination protects against testicular damage



## Summary II

- SCV-CHIKV+ZIKAV vaccination elicits single shot protective immune responses
- Protects pregnant mice and their offspring from ZIKAV infection
- Protects the testis of male mice from ZIKAV infection-mediated damage
- No immune interference between CHIKV and ZIKV vaccine antigen expression nor booster responses (**data not shown**)
- Prow *et al*, Nature Communications, 2018.
- US NIH/NIAID-sponsored NHP challenge study, July/August 2018.

## Indicative SCV Vaccine GMP scale up and Phase I Timeline cost \$2.5M AUD

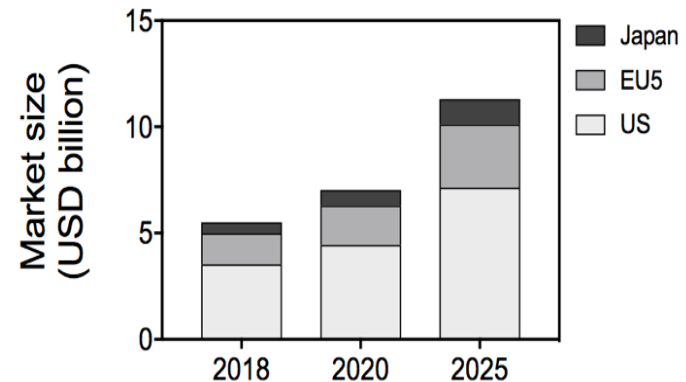
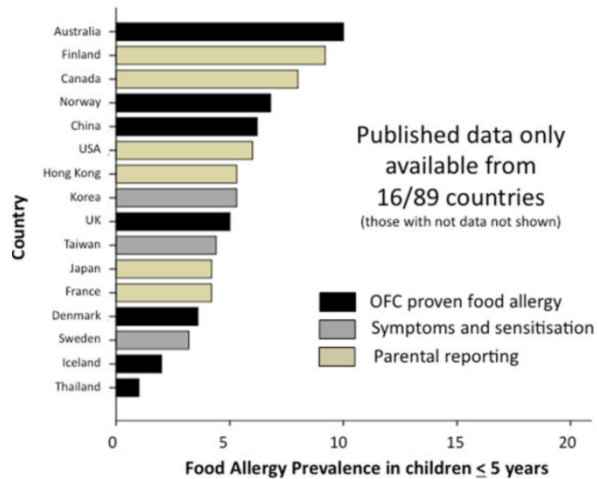


# A new SCV-based vaccine to treat and prevent peanut allergy?



food allergy affects about 1 in 10 infants

Studies reporting Food Allergy Prevalence  
in preschool children  $\leq 5$  years



- ❖ Peanut allergy: high prevalence in Australia
- ❖ 3% of children are peanut allergic
- ❖ Of which, 80% remain allergic for life

By 2025:

- ❖ Projected 8 million peanut allergic individuals in the 7 major markets
- ❖ Projected market size of 11.3 billion USD

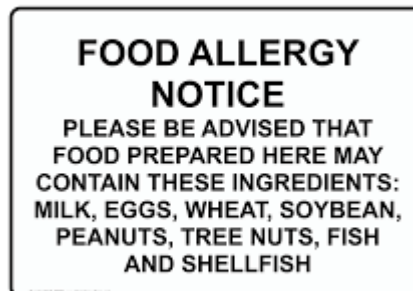
# Current treatment: total avoidance



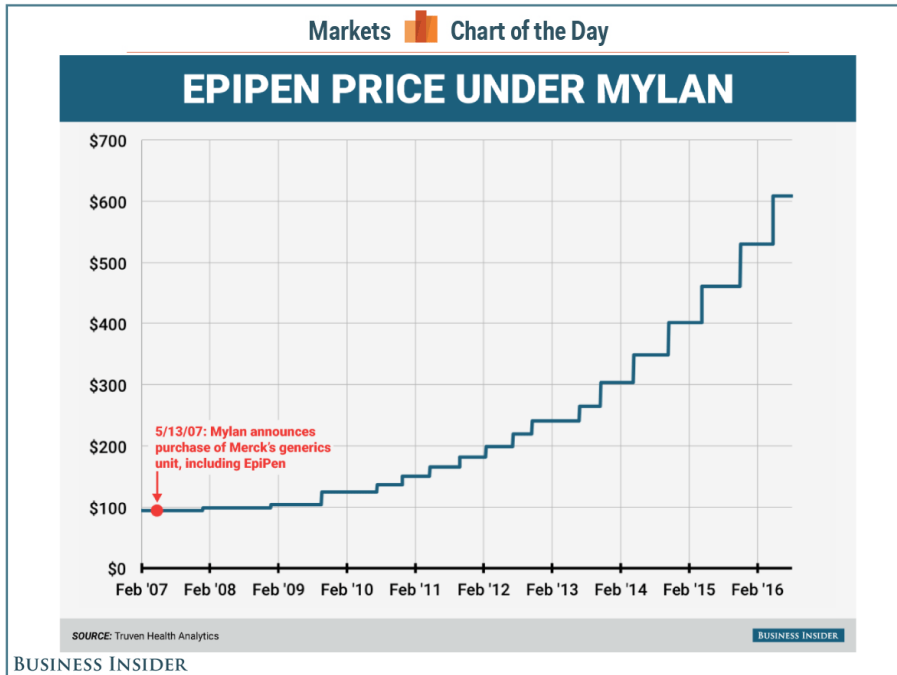
**THIS SCHOOL IS  
NUT FREE**



**THANK YOU**  
for keeping our school safe!



# Current treatment: EpiPen adrenaline



**R<sub>x</sub>**

PATIENT NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

Prescription:

\*3 EpiPen 2-Pak cartons  
2-Pak carton for home  
2-Pak carton for school or gym bag  
2-Pak carton for relative's house work

**Write DAW**  
for 6 total EpiPen Auto-Injectors

Date \_\_\_\_\_ Signature \_\_\_\_\_

The more specific the prescription, the greater the likelihood the pharmacist will fill it as intended

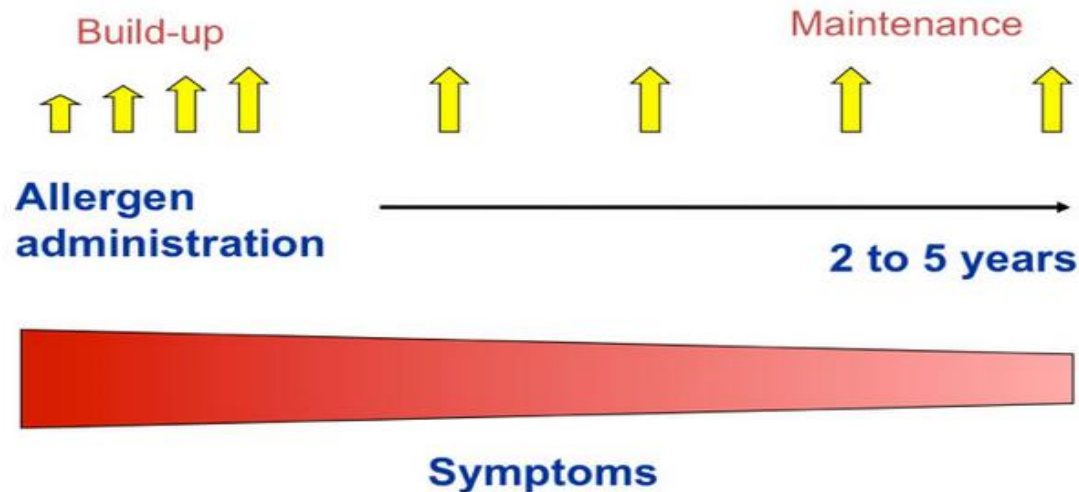
Prescribe an EpiPen 2-Pak® for each location where your patient may need immediate access

- ☒ "HOME" ☒ "SCHOOL"
- ☒ "WORK" ☒ "GYM BAG"

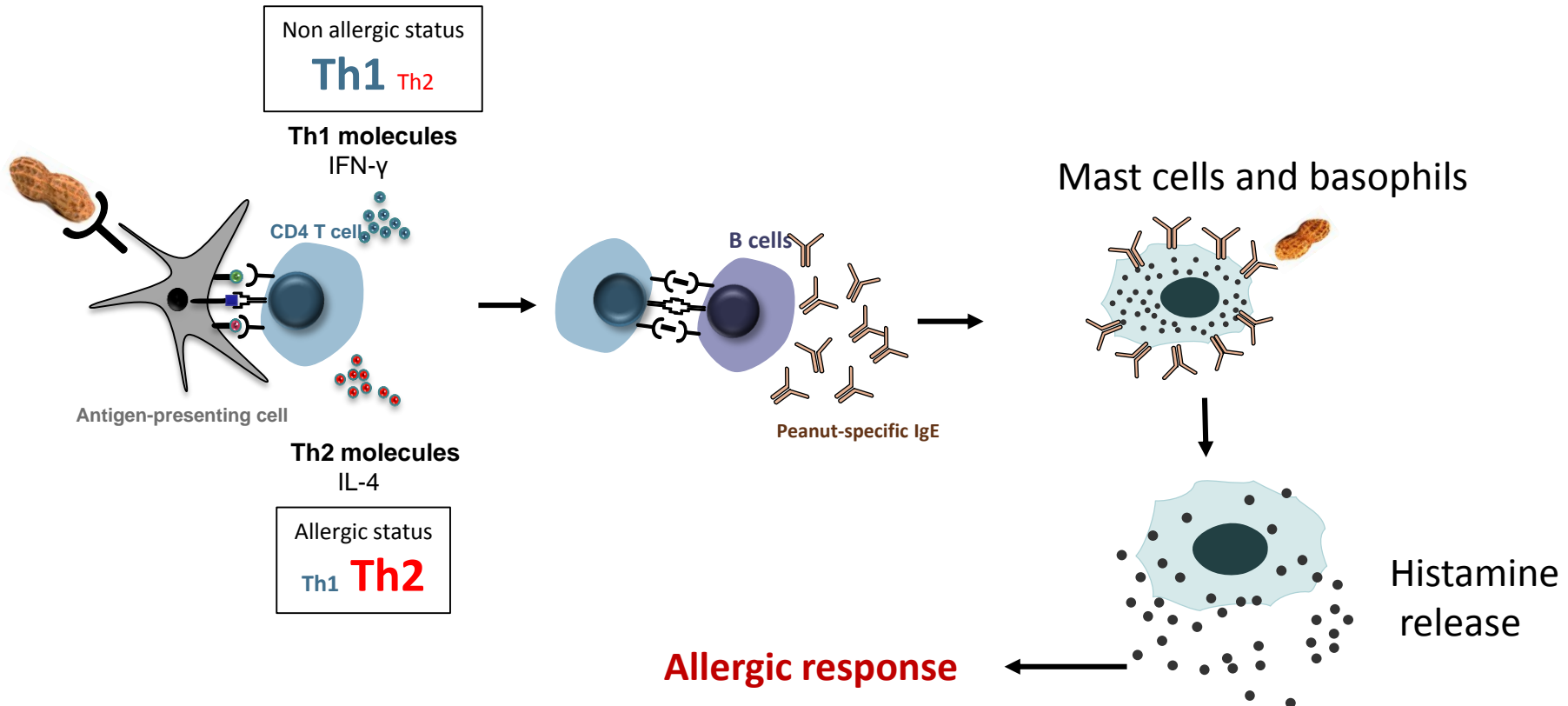


# Desensitization-oral immune therapy

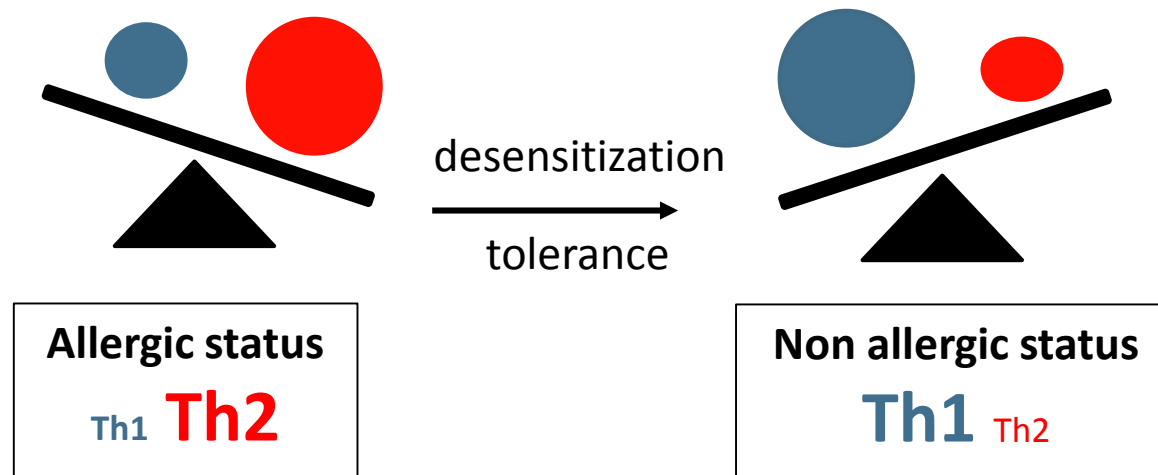
- Intense and costly administration of allergen
- Requires maintenance
- Benefit not a long term solution
- This treatment has safety concerns and is not approved by the FDA
- Sub lingual oral immunotherapy at home, 3 years duration (dust mite and pollen) compliance as low as 7%



# Allergic reactions are T cell-mediated diseases

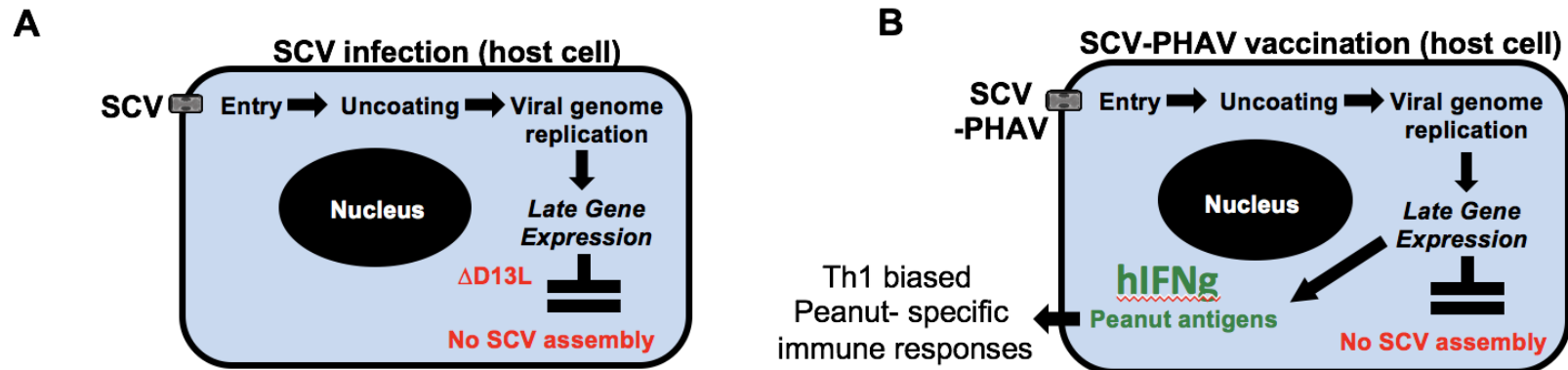


# Permanent desensitization by re-educating the allergic T cell response?



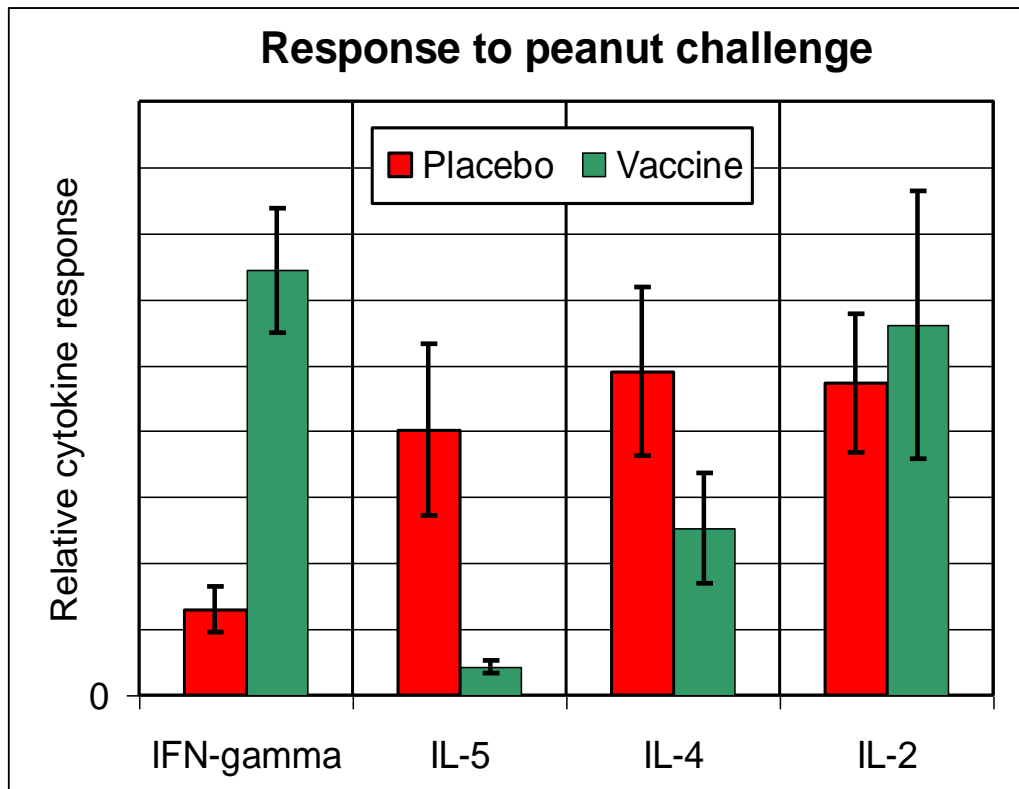
# How do we introduce a Th1 bias to peanut antigens ?

- Response to vaccinia virus infection is usually dominated by a Th1 response
- SCV expressing the major peanut antigens as ubiquitinated multi-antigens  
**SCV-Peanut hypoallergenic vaccine (SCV-PHAV)**



# Exploratory study of prophylactic SCV-peanut allergy vaccine in sensitized mice

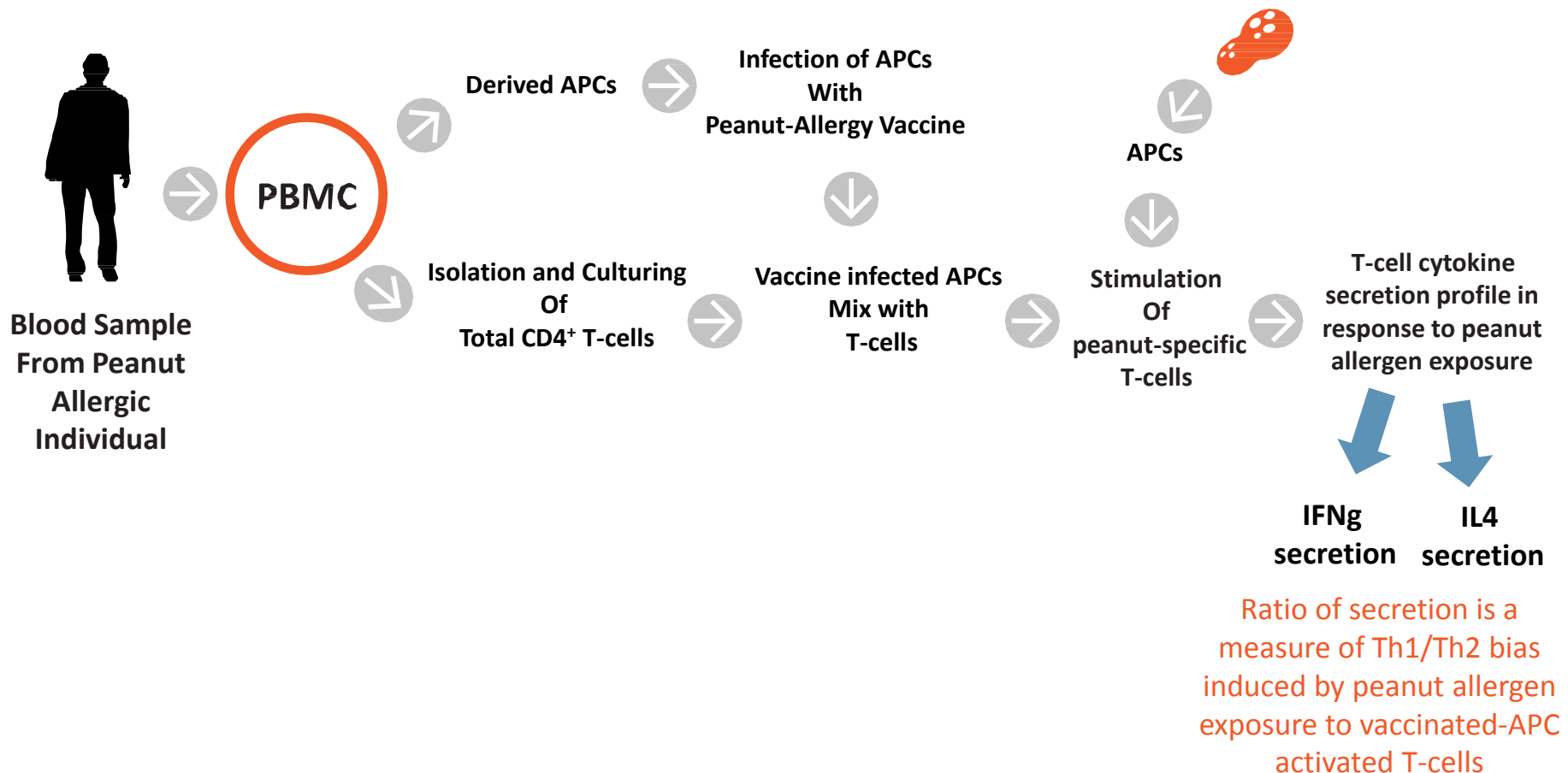
Comparison of the cytokine profiles that signal TH1 and TH2 responses for groups of five mice vaccinated with SCV-peanut allergy vaccine or placebo



- IFN- $\gamma$  is central to TH1
- IL-5 is specific for TH2
- IL-4 create TH2
- IL-2 secreted by all proliferating T-cells
- Results show that after vaccination, the immune response to peanut protein is TH1 specific

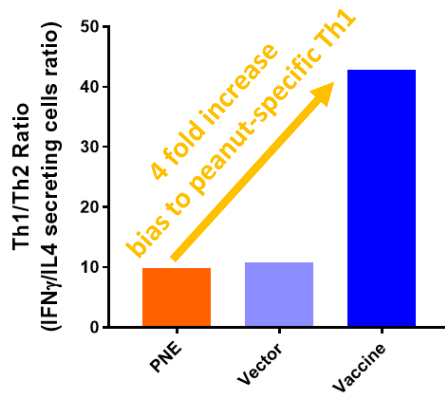
# Confirming vaccine mechanism of action using APC and total T-cells from blood of a peanut allergic individual

## Methodology

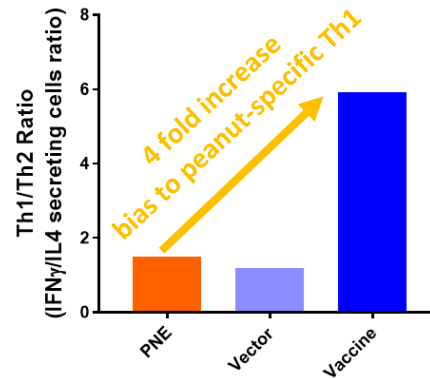


# Th1/Th2 profiles for SIX peanut allergic volunteer

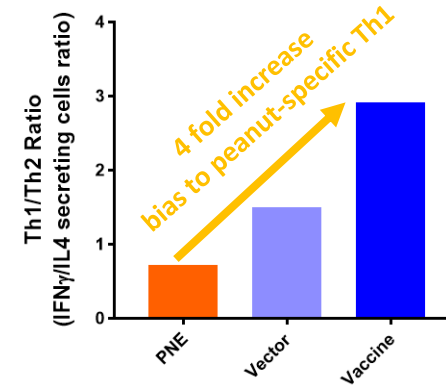
Peanut Allergic Volunteer: MD (female)  
Ex Vivo Th1/Th2 Profile



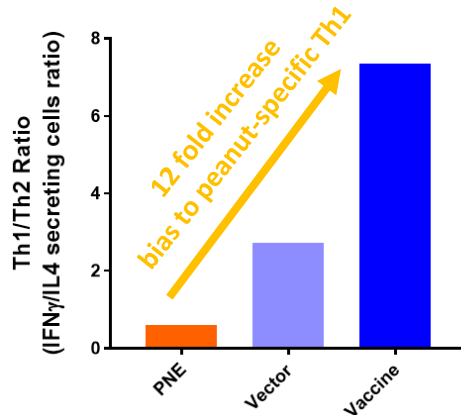
Peanut Allergic Volunteer: JD (female)  
Ex Vivo Th1/Th2 Profile



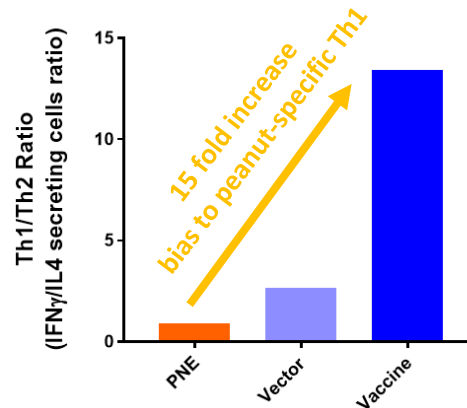
Peanut Allergic Volunteer: AB (female)  
Ex Vivo Th1/Th2 Profile



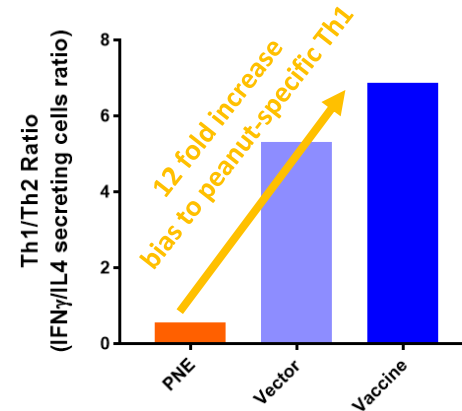
Peanut Allergic Volunteer: MA (male)  
Ex Vivo Th1/Th2 Profile



Peanut Allergic Volunteer: SN (male)  
Ex Vivo Th1/Th2 Profile



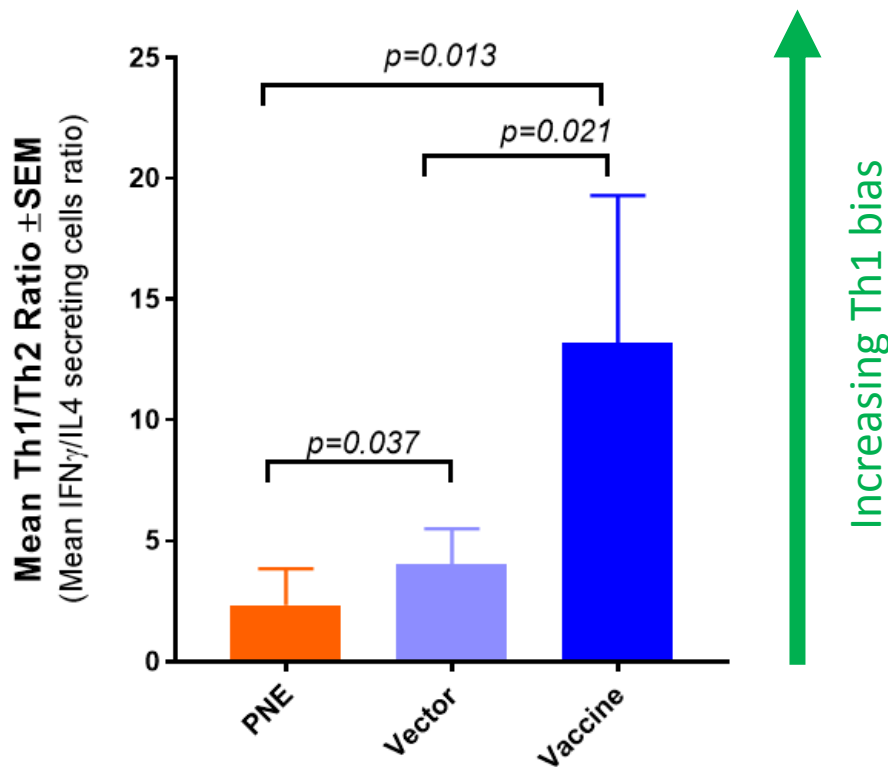
Peanut Allergic Volunteer: KD (female)  
Ex Vivo Th1/Th2 Profile





# Vaccine inducing Th1 efficiency in a sample population of 6 peanut allergic volunteers

## The Mean Ex Vivo Vaccination Induced Th1/Th2 Profile of 6 peanut allergic Volunteers



Significance was determined using one-tailed Mann-Whitney T-test  
Significance =  $p < 0.05$

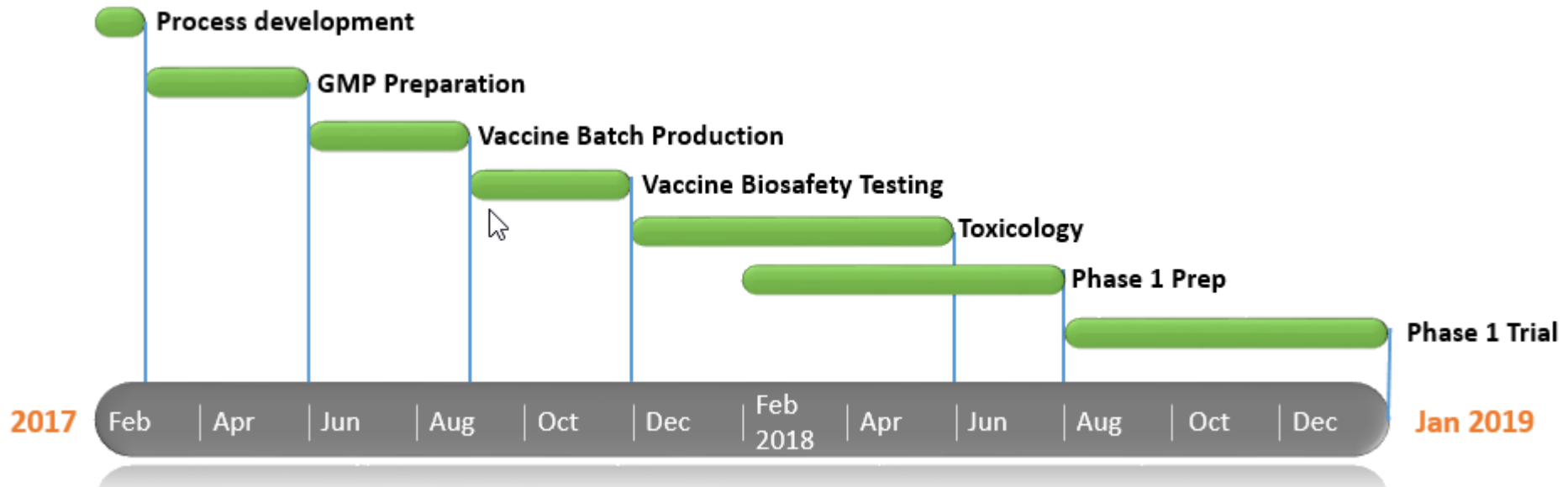
### Conclusion:

1. The **peanut hypoallergy vaccine** treated DCs induces a significant increase in a peanut-specific Th1 response over and above the T-cells treated with **PNE-treated DCs** (peanut protein extract).
2. The **peanut hypoallergy vaccine** treated DCs also induced a significant increase in a peanut-specific Th1 response over and above the T-cells treated with **SCV-vector only DC**.

## Summary III

- SCV-PHA *in vivo* vaccination delivers a skewed Th1 vsTh2 response in peanut allergic mice
- SCV-PHA *ex vivo* vaccination induces Th1-skewed response in a sample population of 6 peanut allergic volunteers
- The same Th1-skewed response pattern is observed in the same donor when tested three times over a 12month period
- Eldi *et al*, manuscript in preparation.

## Indicative SCV Vaccine GMP scale up and Phase I Timeline cost \$2.5M AUD



# Experimental Therapeutics Laboratory



sementis

Dr Paul Howley, *Sementis Ltd., Vic.*  
Prof Andreas Suhrbier, *QIMR Berghofer, Qld.*  
Dr William Smith, *Royal Adelaide Hospital, SA.*



University of  
South Australia