

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

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sementis

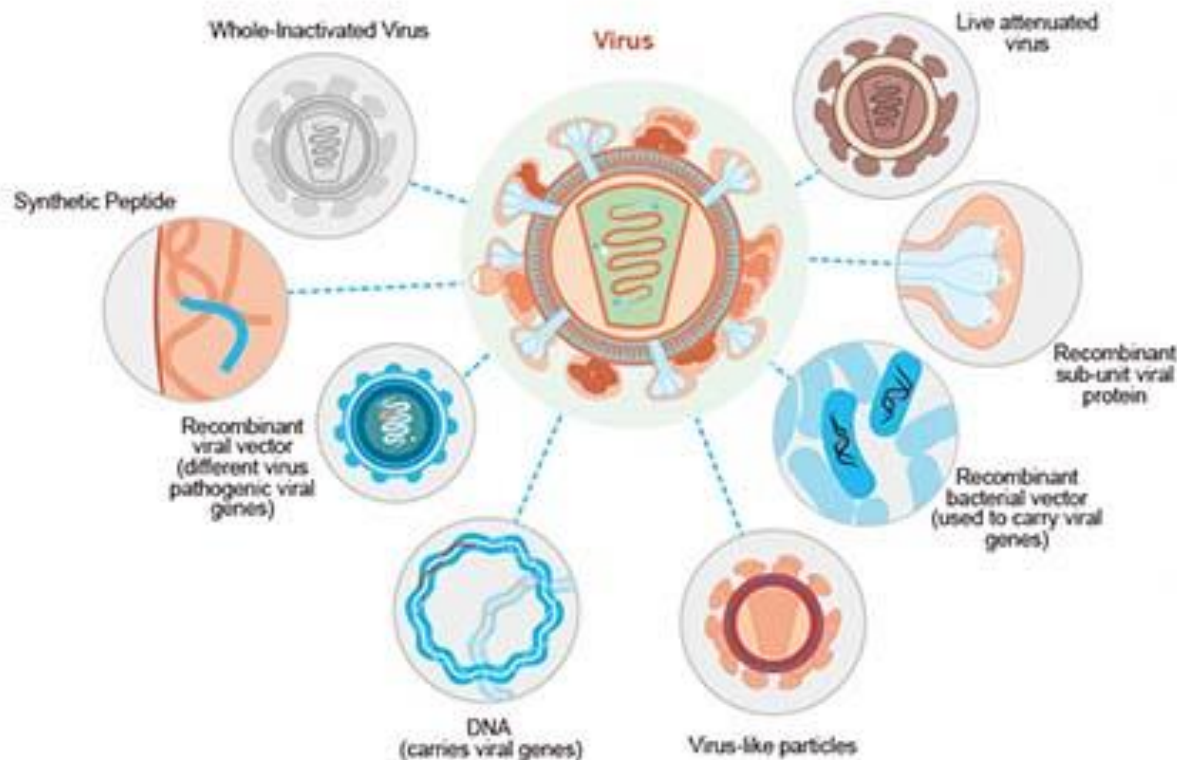


University of South Australia Cancer Research Institute

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)

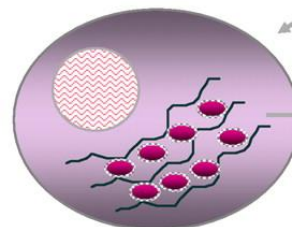


Chimeric cDNA → transcribe to RNA



Transfect mRNA

Envelope is heterologous virus
containing immunizing antigens

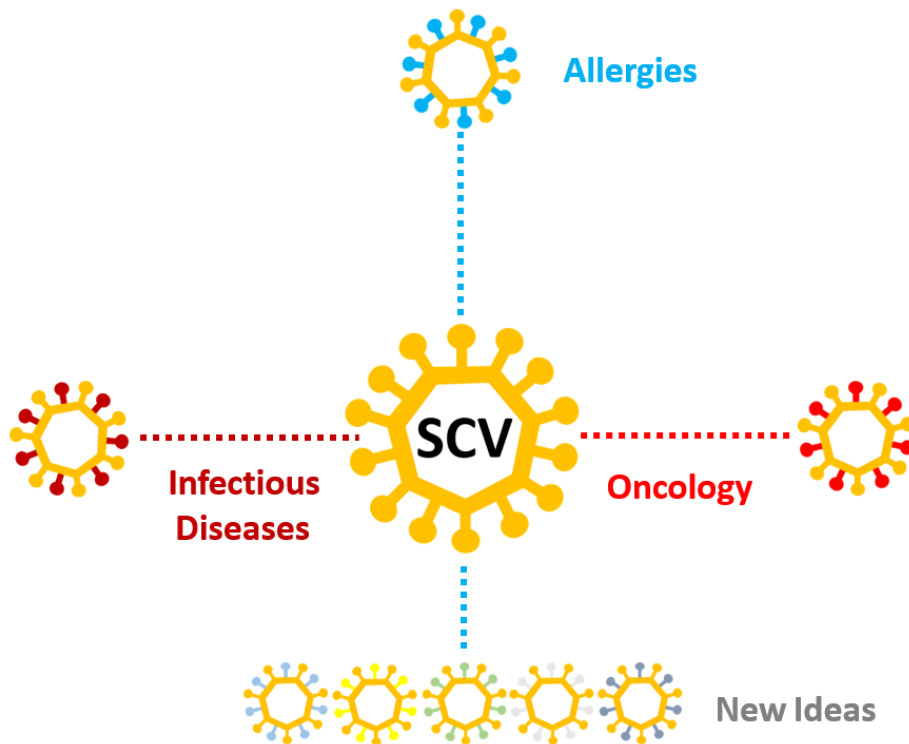
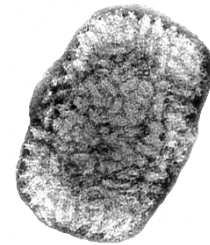


Grow virus
in cell culture



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:

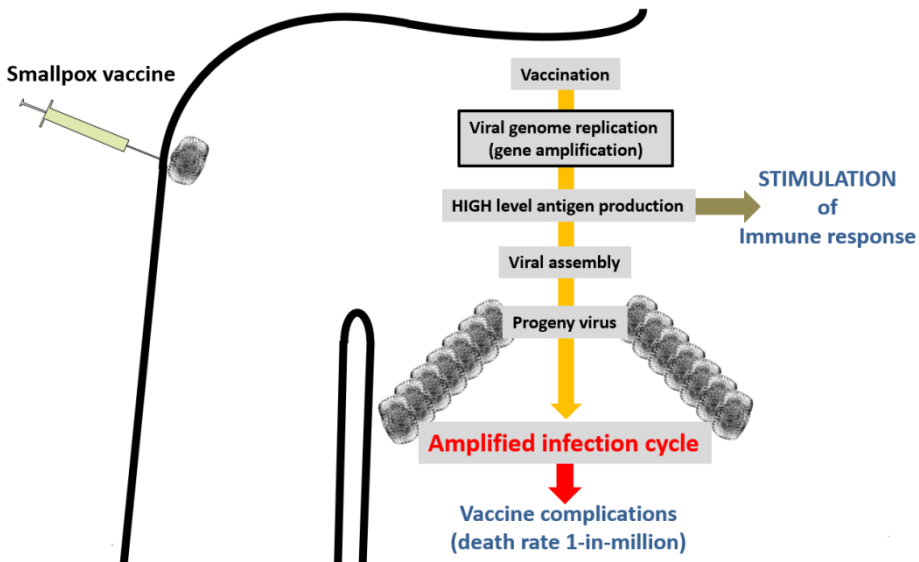
“The **CHO** biotechnology friendly cell substrate engineered to produce the SCV vector”

A first for the production of vectored vaccines!

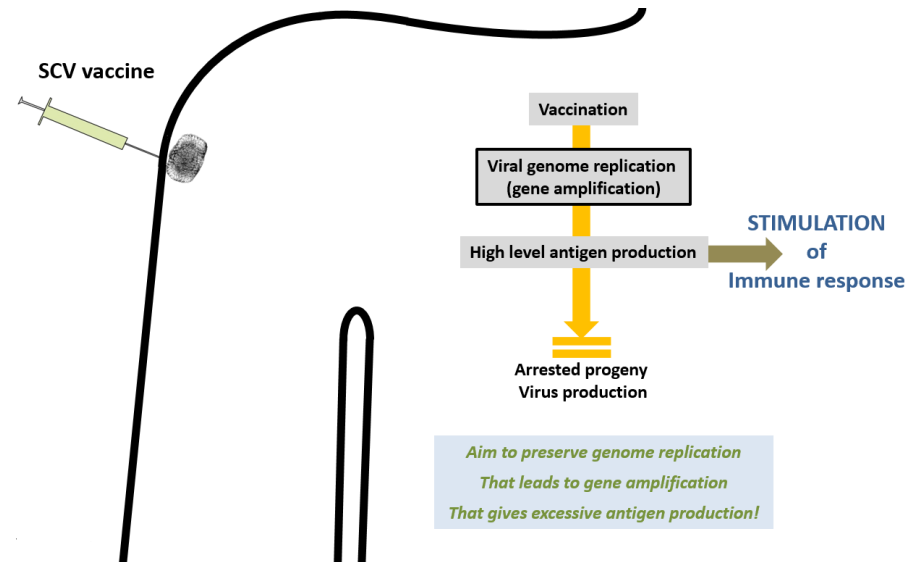
Declared COI: JD Hayball holds shares in Sementis Ltd and sits on the SciAdBrd

How does the SCV platform work?

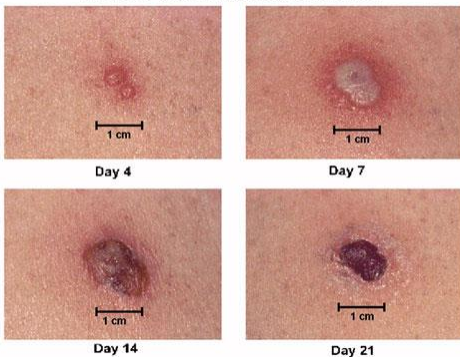
Smallpox Vaccine (Live replication competent)



SCV Vaccine (Live NON-replication competent)



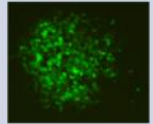

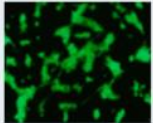
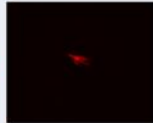
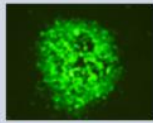

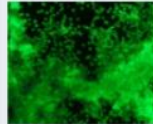

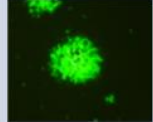

Primary Vaccination Site Reaction



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:

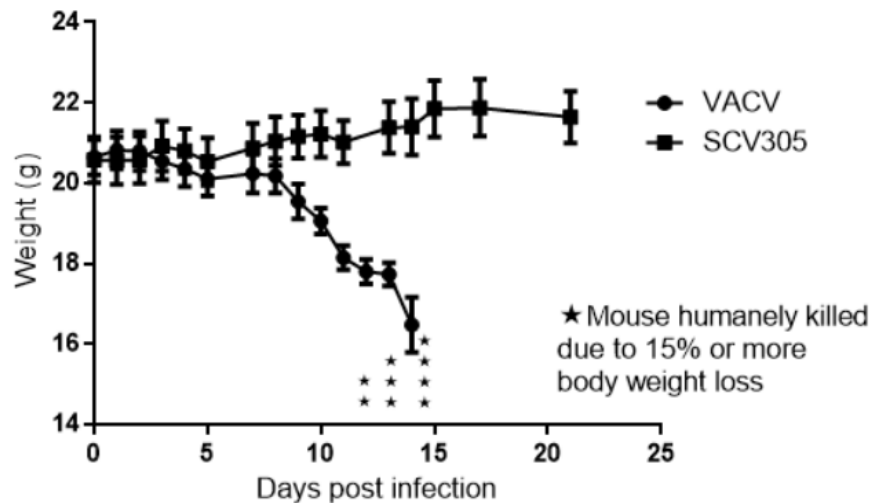
	Vaccinia Virus (Parent of SCV)	SCV
Human Bone cell	High Yields of virus (as <i>expected</i>)	No virus production!
Human Lung cells		
Human Kidney cells		
Human Skin cells		
Human Cervical cells		

		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

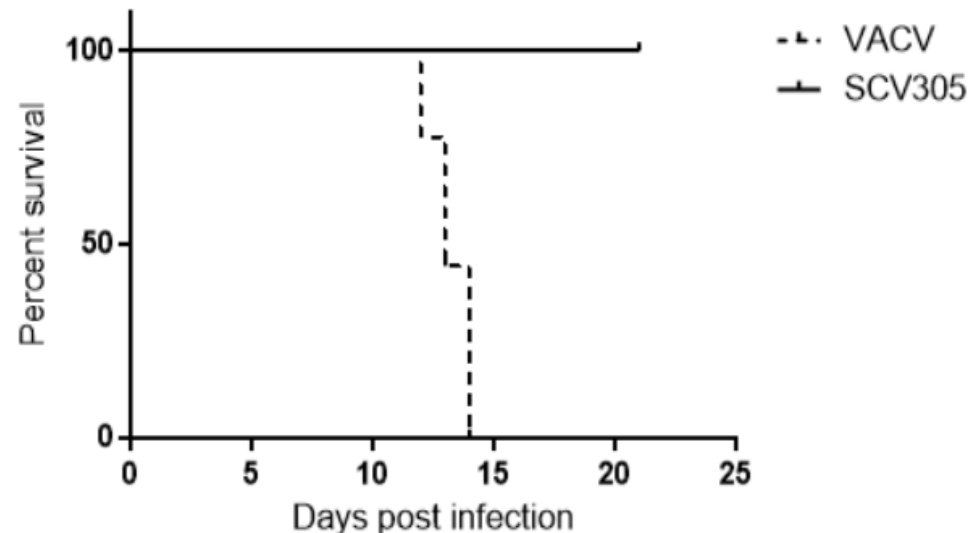
(biodistribution in immunocompromised mice)

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.

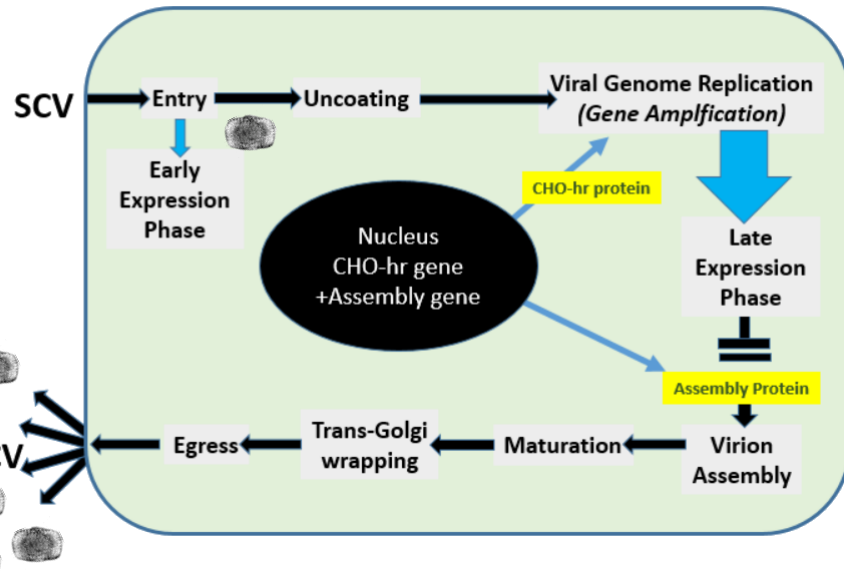
Survival Plot
(n=9 per treatment group)



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

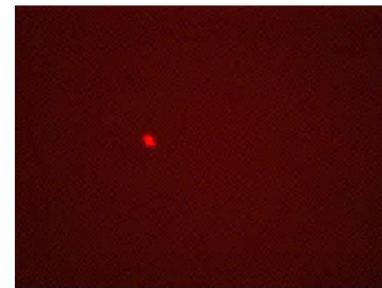
SCV cell substrate for manufacturing

SCV Production CHO Cell Line

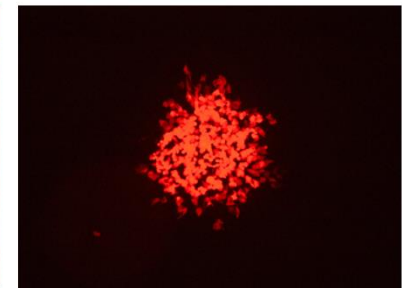


Infection with SCV

(Totally attenuated SCV expressing Red Fluorescent Protein)



CHO

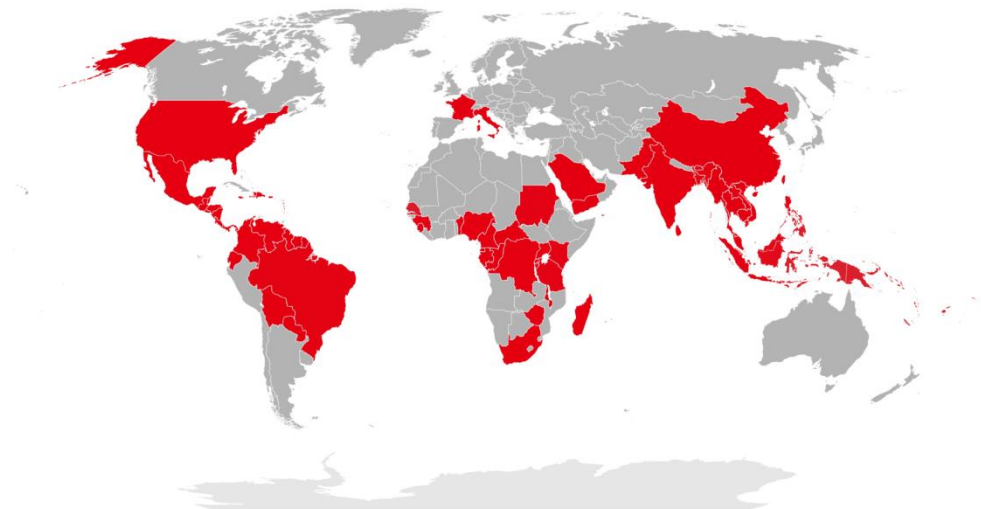
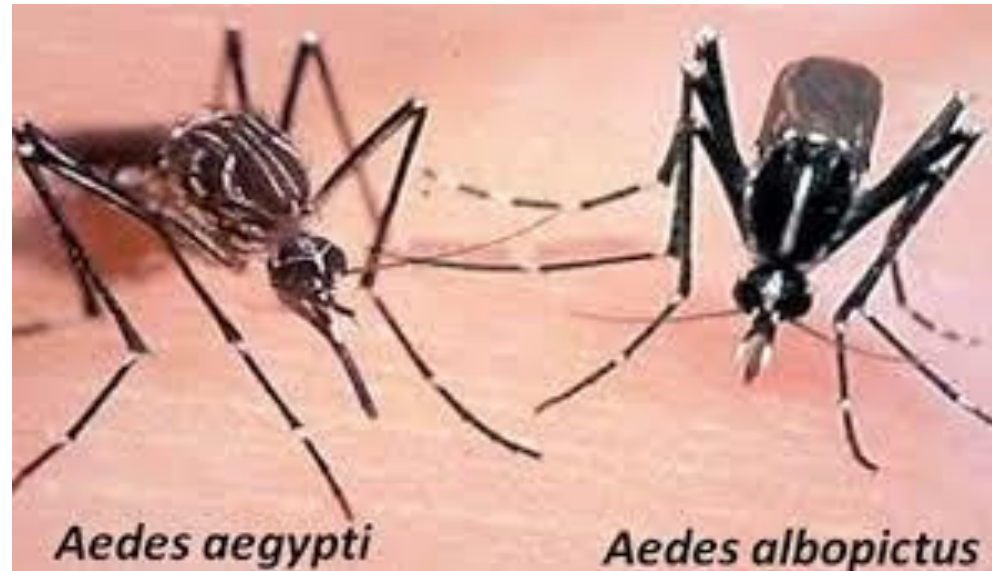
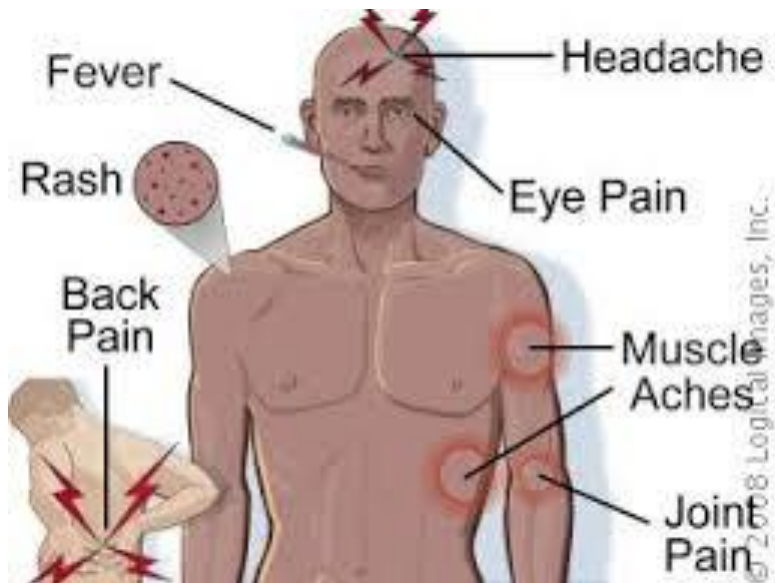
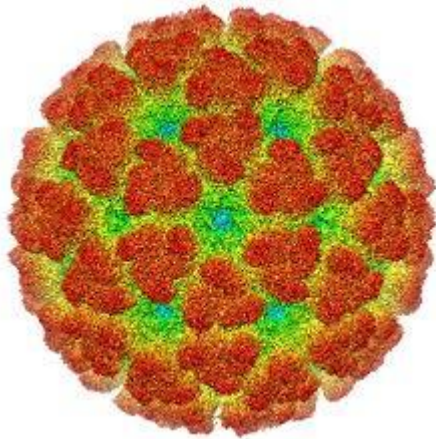


SCV Rescue cell line

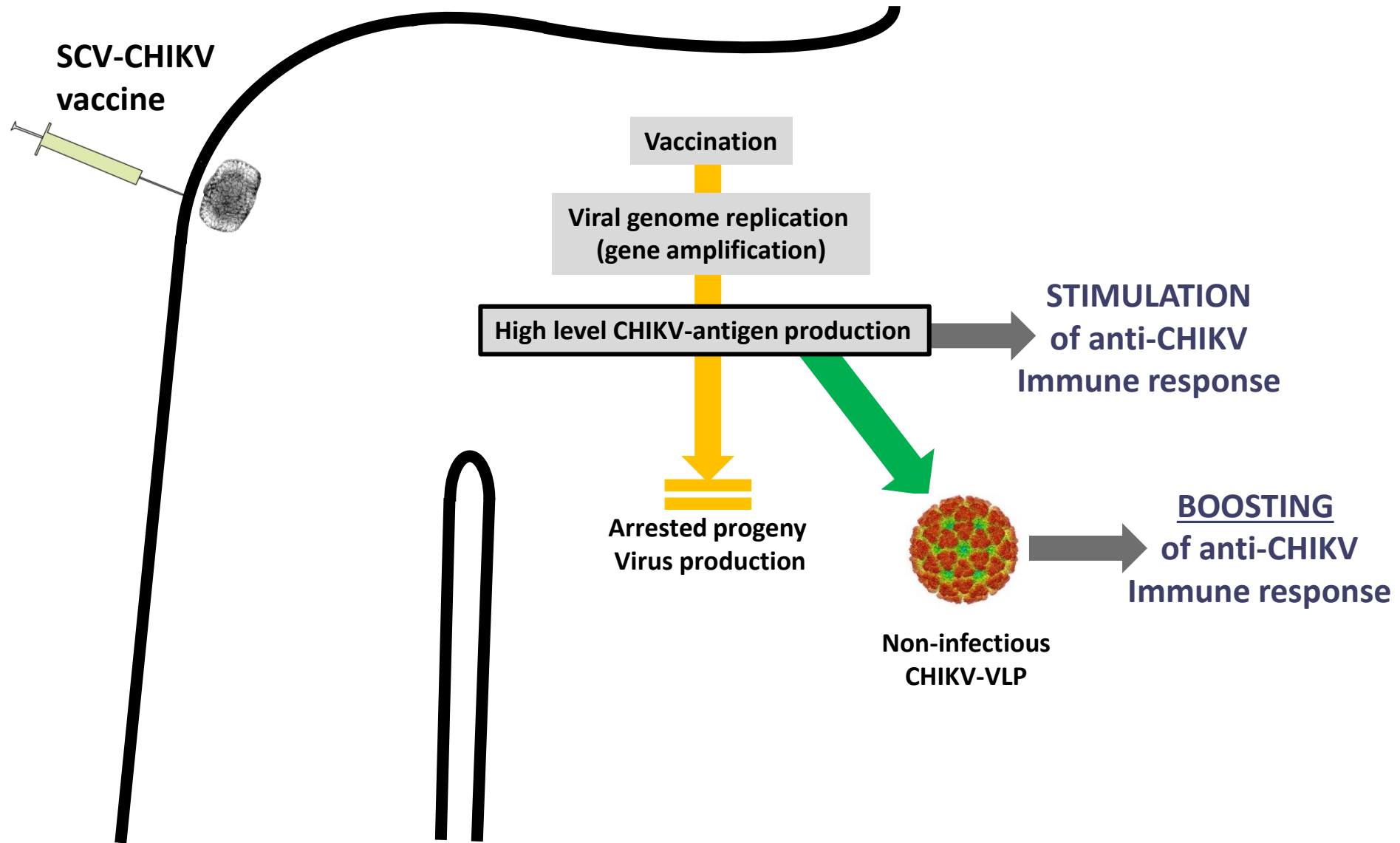
Sementis' SCV-cell substrate for manufacturing was derived from GMP produced CHO-S cell line :

- 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



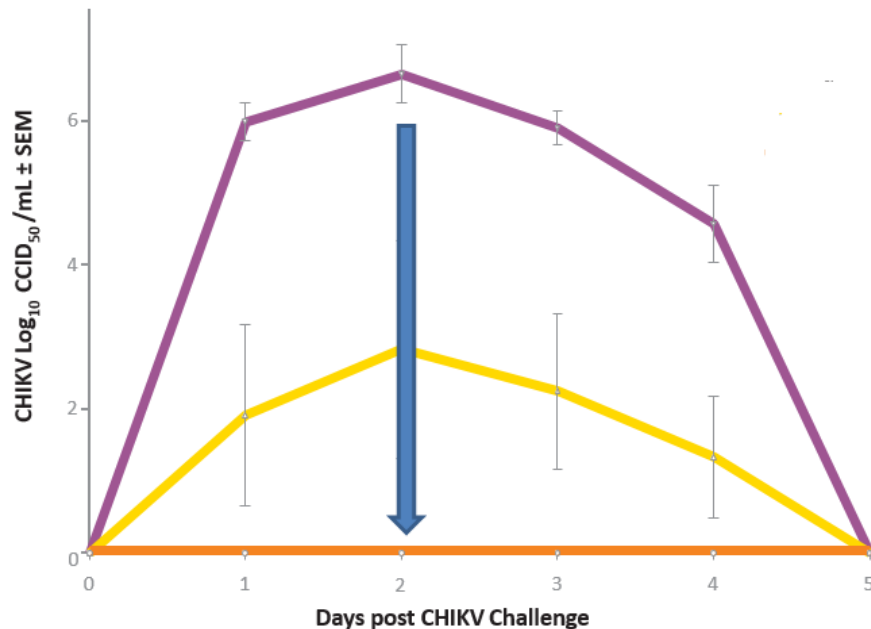
How our SCV-CHIKV vaccine works



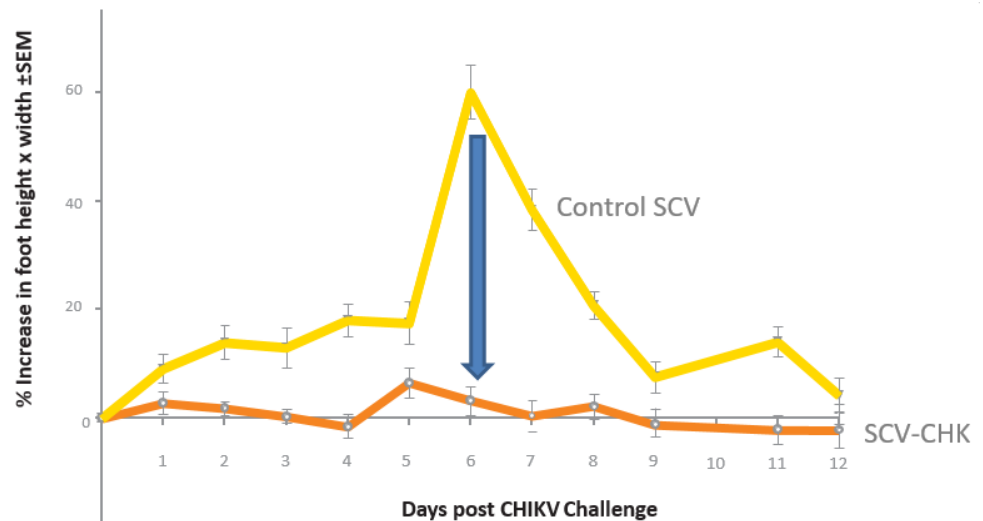
A single shot of SCV-CHIKV protects mice against viraemia and virus induced arthritis

Immunisation with Chikungunya vaccine protects against Chikungunya virus challenge viraemia

- SCV000-10⁷ pfu/mouse
- SCV305-10⁵ pfu/mouse
- SCV305-10⁶ pfu/mouse

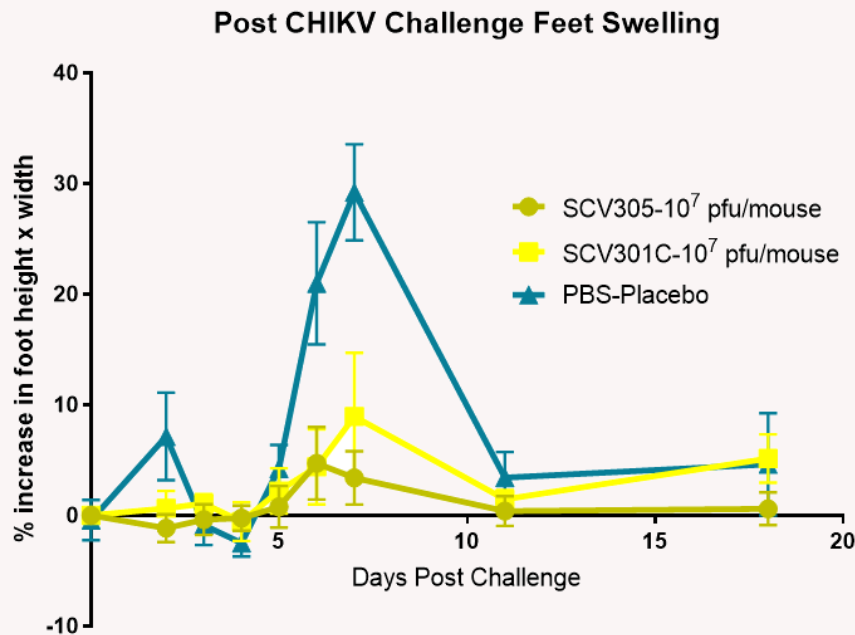


SCV-CHIK vaccine induced foot swelling (arthritis) after Chikungunya virus challenge

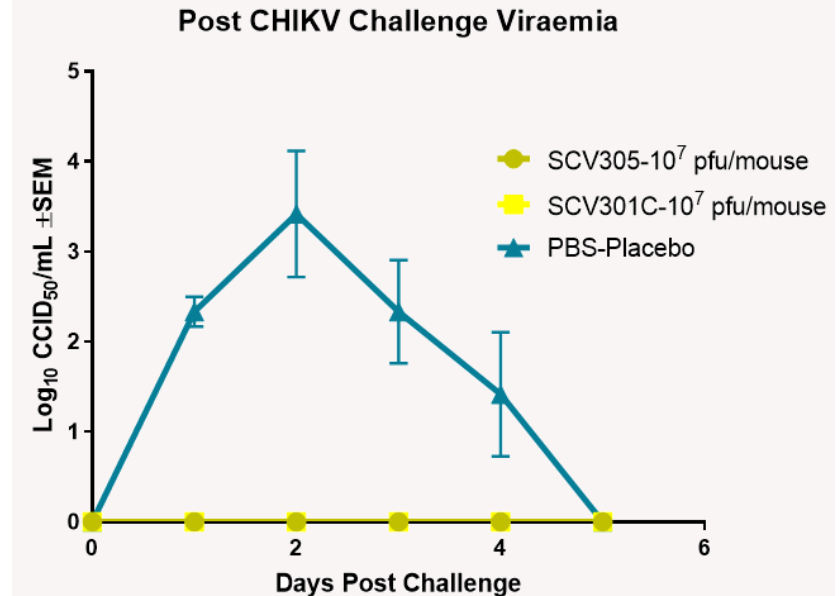


A single shot of SCV-CHIKV still protects mice one year after vaccination

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

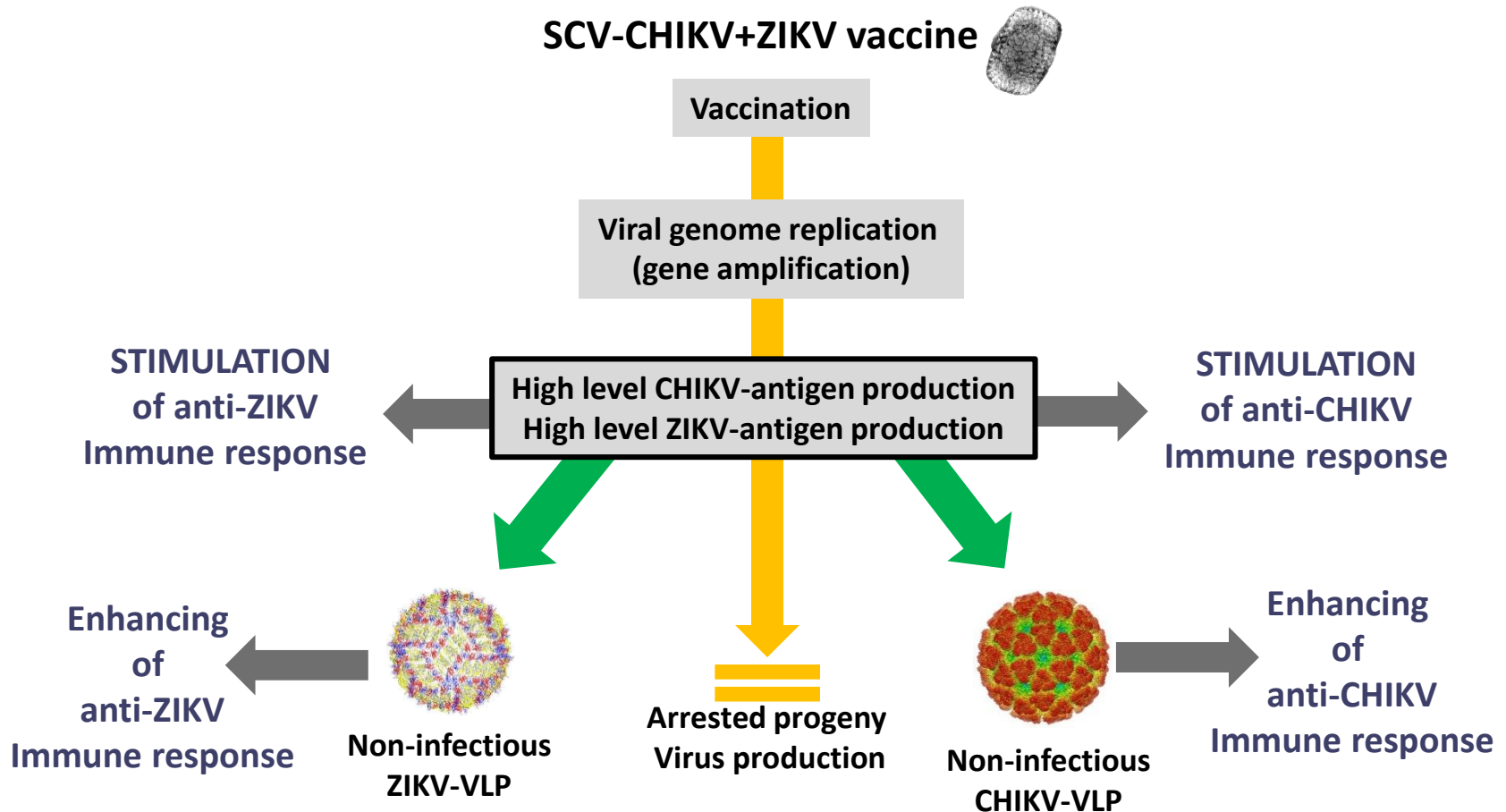
- SCV is replication-defective *in vitro* and *in vivo* - safe vaccine platform
- A stable rescue cell line derived from biotech-proven CHO cells provides for scalable commercial vaccine production
- SCV-CHIKV vaccination elicits single shot protective immune responses which last for at least one year
- 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?

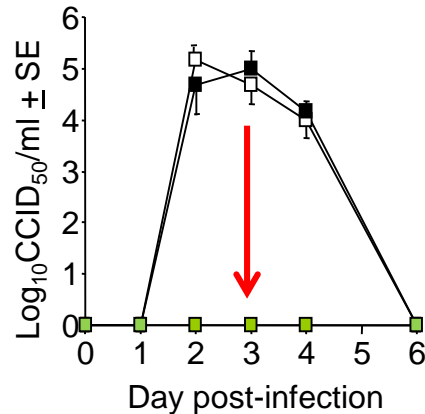
How our dual SCV-CHIKV+ZIKV vaccine works



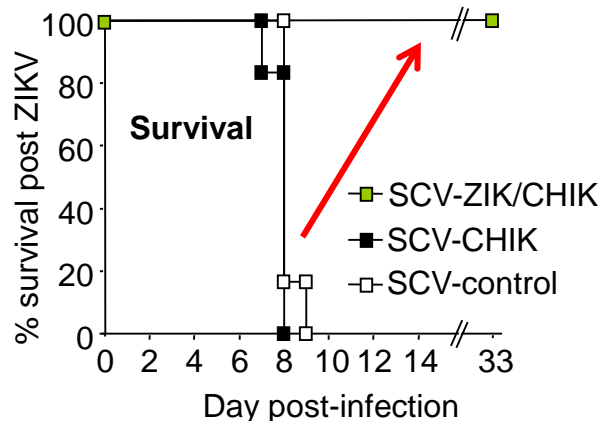
A single dose of SCV-CHIKV+ZIKV protects against infection with both diseases

- in IFNAR mice

Protection against viraemia

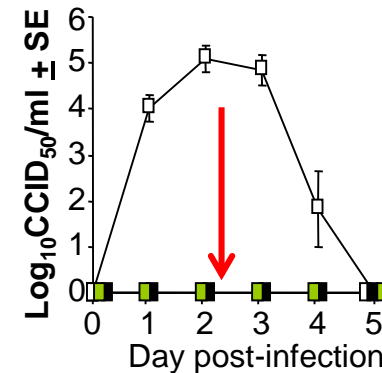


Protection against lethal ZIKV_{MR766}

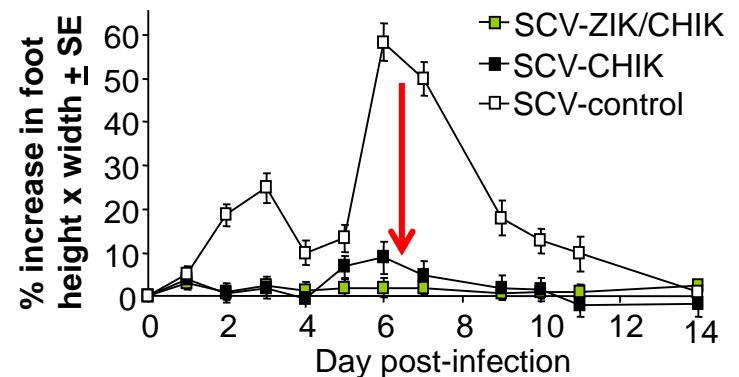


- in C57BL/6 mice

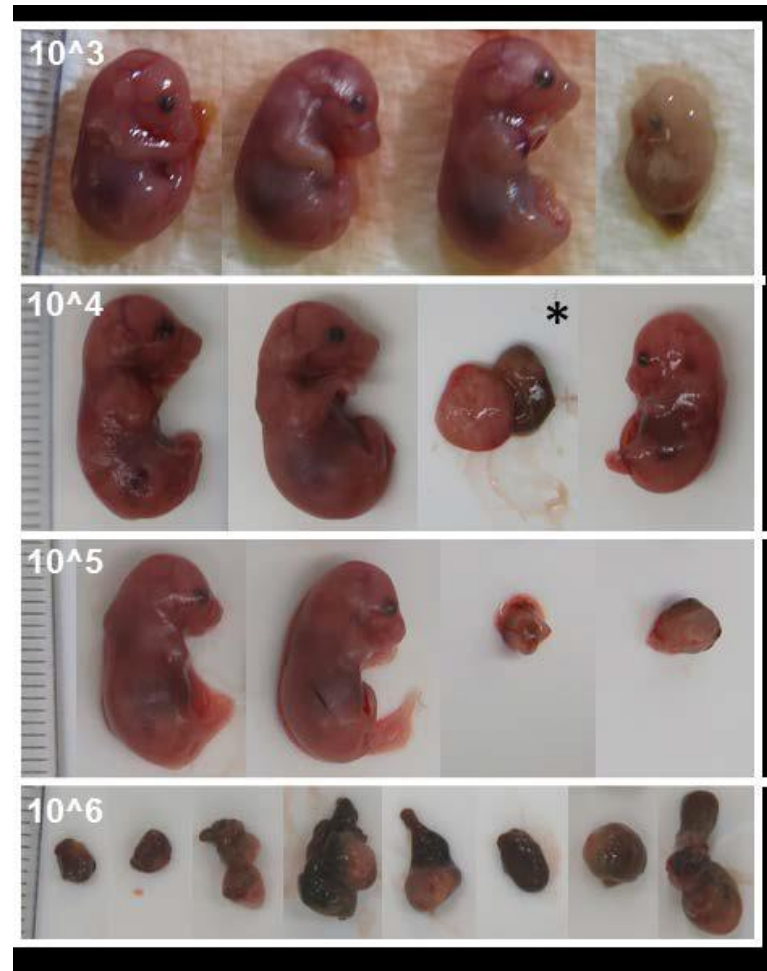
Protection against viraemia



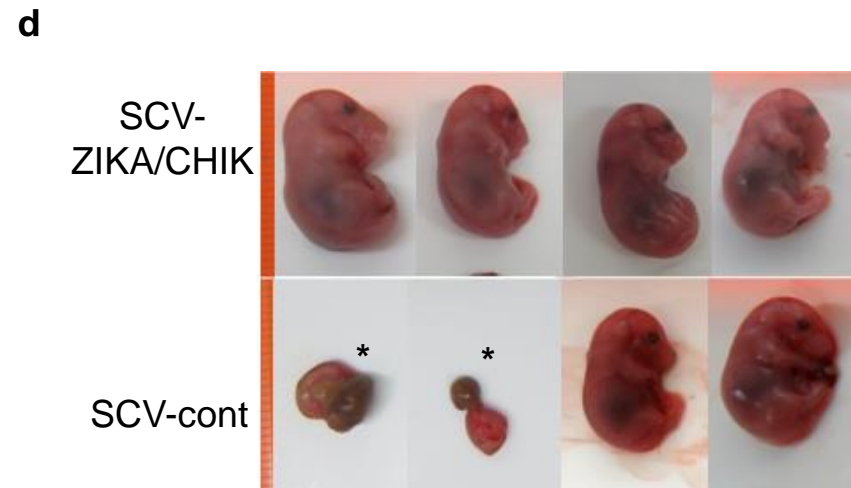
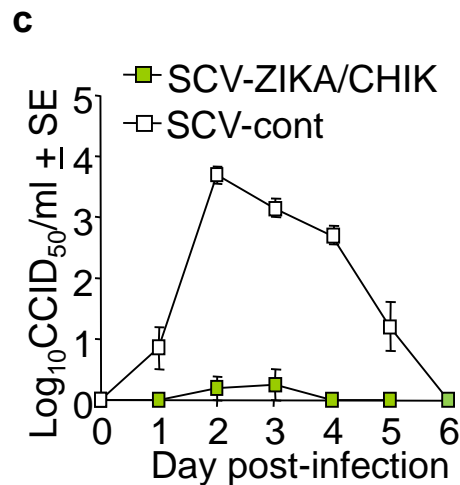
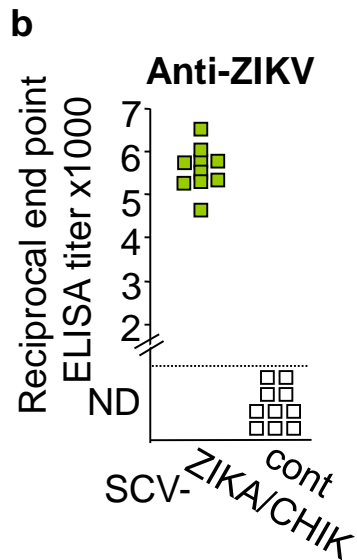
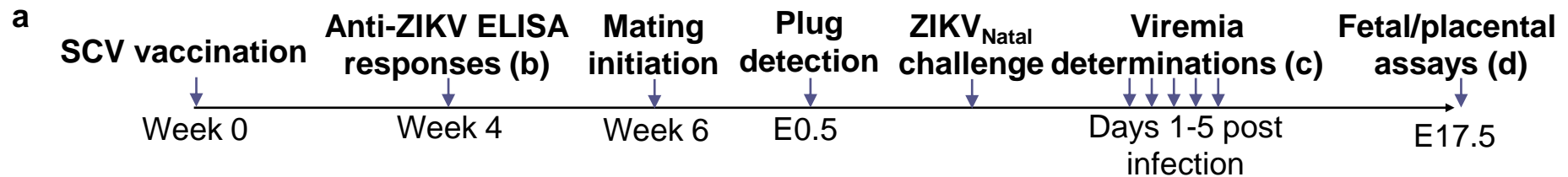
Protection against CHIKV arthritis



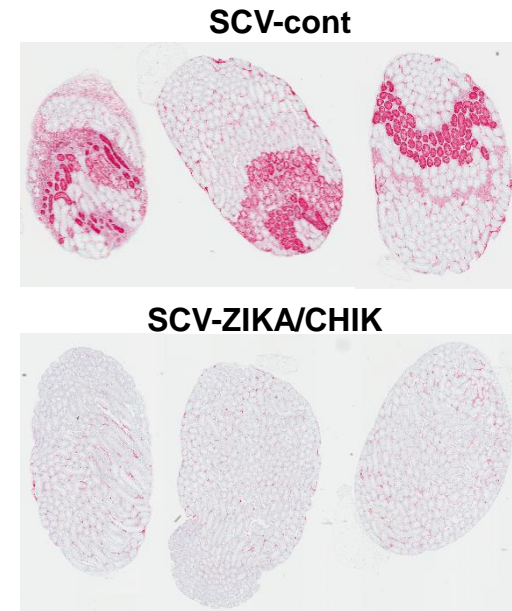
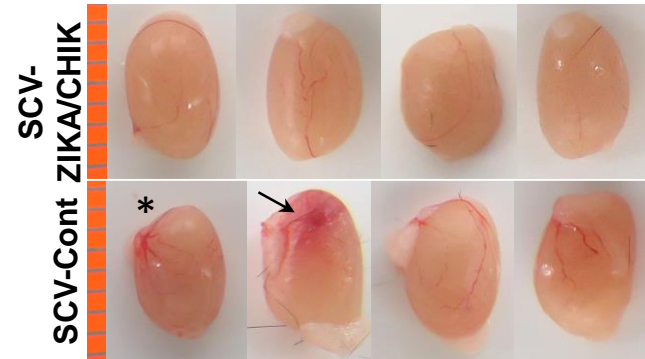
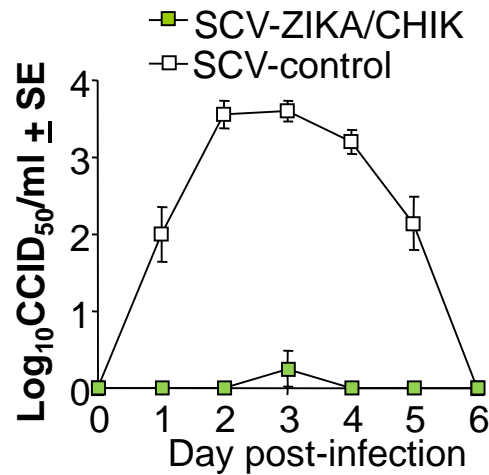
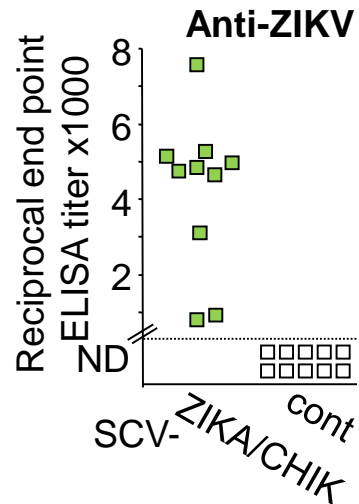
ZIKV Natal mouse model of foetal brain infection in IFNAR^{-/-} x IFNAR^{-/-} mice



A single shot vaccination protects against detrimental foetal outcomes



A single shot vaccination protects against testicular damage





- Implavax technology for SCV delivery
 - Enhanced stability?
 - Enhanced immune responses?
- Stage 1: Formulation of SCV into solid doses (Enesi)
- Stage 2: Immunogenicity study (Sementis)
 - CHIKV/ZIKV vaccine
 - Peanut vaccine

Summary II

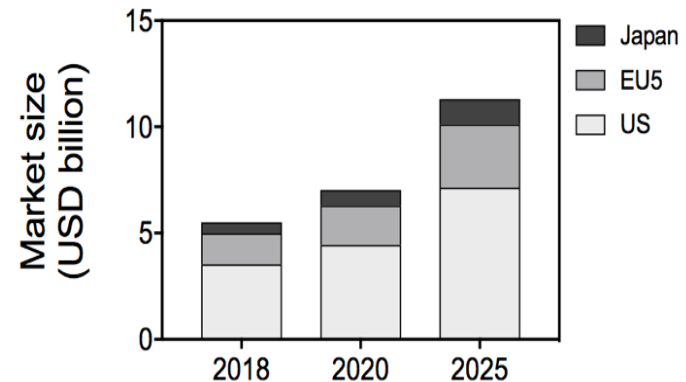
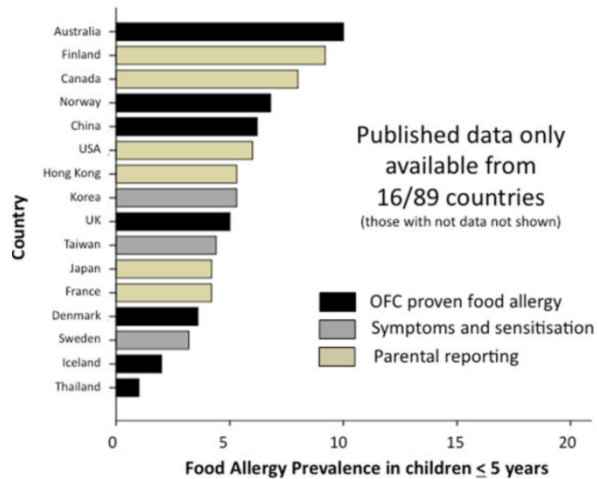
- SCV-CHIKV+ZIKAV vaccination elicits single shot protective immune responses
- Protects pregnant mice and their offspring from ZIKAV infection
- Protects the testis of male mice from ZIKAV infection-mediated damage
- No immune interference between CHIKV and ZIKV vaccine antigen expression nor booster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

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 ≤ 5 years

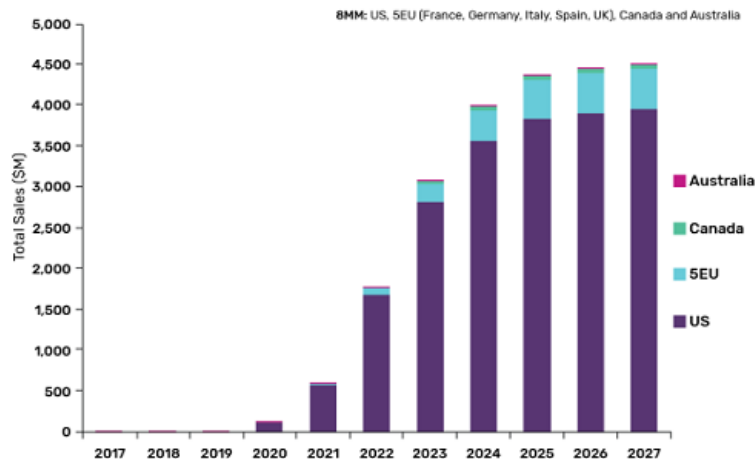


- ❖ Peanut allergy: high prevalence in Australia
- ❖ 3% of children are peanut allergic
- ❖ Of which, 80% remain allergic for life

By 2025:

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

Sales forecast for peanut allergy in 8MM, 2017-2027



Source: GlobalData, Pharma Intelligence Centre

"This incredible growth stems from the projected entry of four new peanut immunotherapy products into a previously empty marketplace. These new therapies include three oral immunotherapy (OIT) products—Aimmune Therapeutics' AR-101, Prota Therapeutics' PPOIT, and Camallergy's CA-002—and one epicutaneous immunotherapy product—DBV Technologies' Viaskin Peanut."

Vaccine (company)	Technology	Mode of action	Route of administration	Stage
Viaskin® Peanut/ DBV-712 (DBV Technologies)	Epicutaneous immunotherapy	Desensitization	Transdermal	Phase III
Aimmune	CODIT-characterised oral desensitisation immunotherapy	Desensitization	Oral	Phase III
HAL-MPE-1 (HAL Allergy Group)	Hypoallergenic peanut extract	Desensitization	Subcutaneous	Phase I
Peanut allergen vaccine (Tunitas Therapeutics)	Ara h2-human FC gamma 1 chimeric fusion protein vaccine	IgE-Fc receptor 1 antagonist	Parenteral	Phase I
Ara-LAMP-vax (Immunomic Therapeutics/Astellas)	Lysosomal associated membrane protein DNA vaccine	Immuno-modulation	Parenteral	Phase I

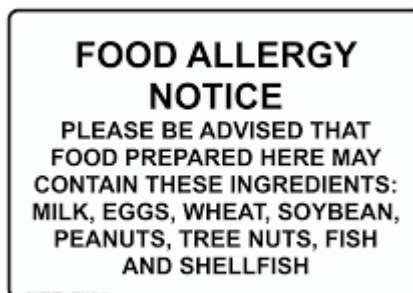
Current treatment: total avoidance



THIS SCHOOL IS
NUT FREE



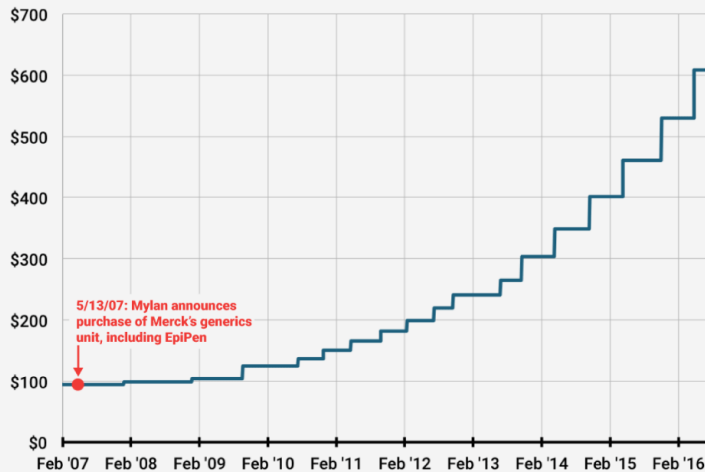
THANK YOU
for keeping our school safe!



Current treatment: EpiPen adrenaline

Markets  Chart of the Day

EPIPEN PRICE UNDER MYLAN



SOURCE: Truven Health Analytics

BUSINESS INSIDER

BUSINESS INSIDER



R_x

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 _____

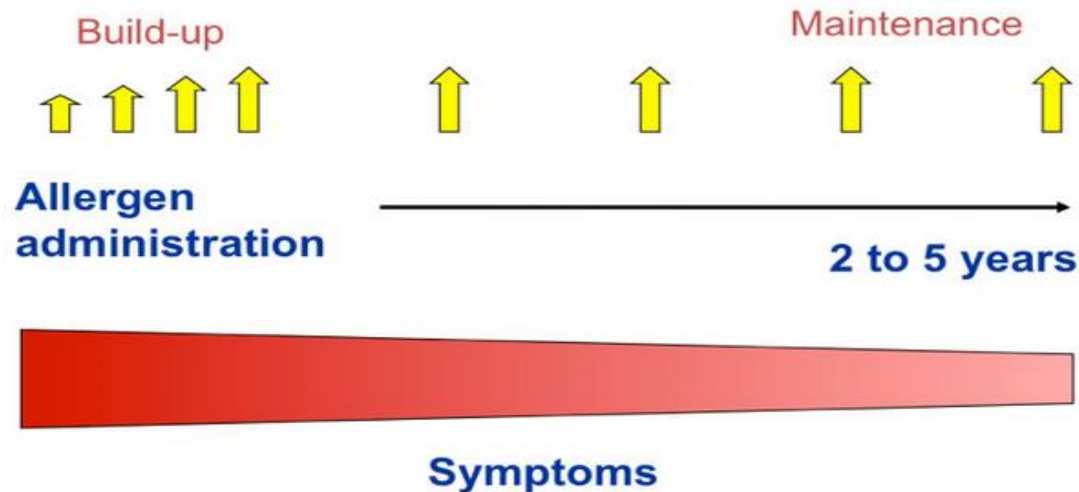
The more specific the prescription, the greater the likelihood the pharmacist will fill it as intended

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

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

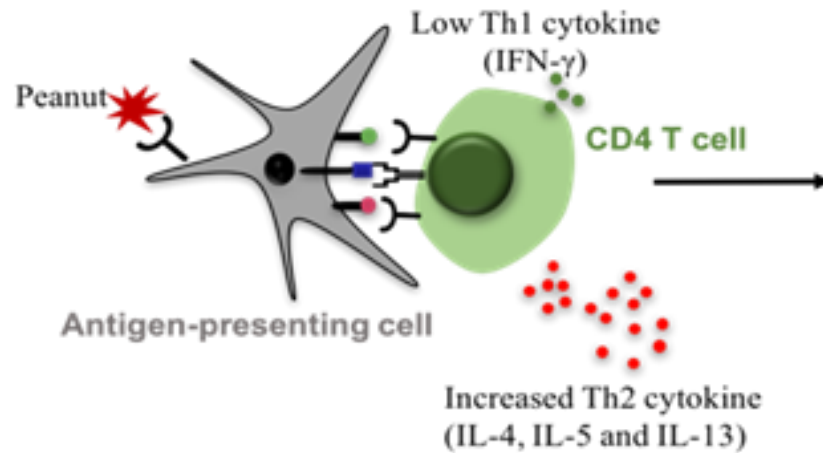
Desensitization-oral immune therapy

- 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%

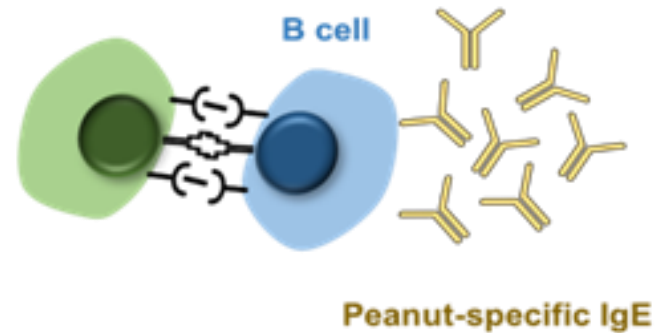


Permanent desensitization by re-educating the allergic T cell response with a vaccine?

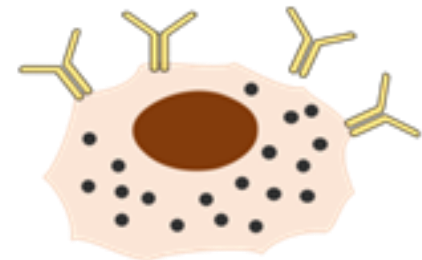
1. Induction of Th2 biased peanut-specific T cells



2. IgE production



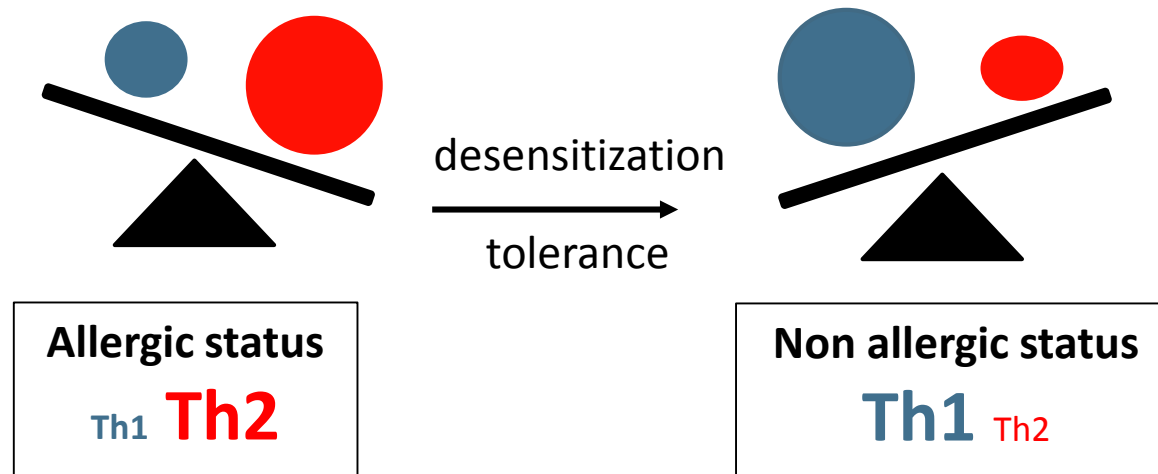
Peanut exposure



4. Mediator release leading to allergic symptoms

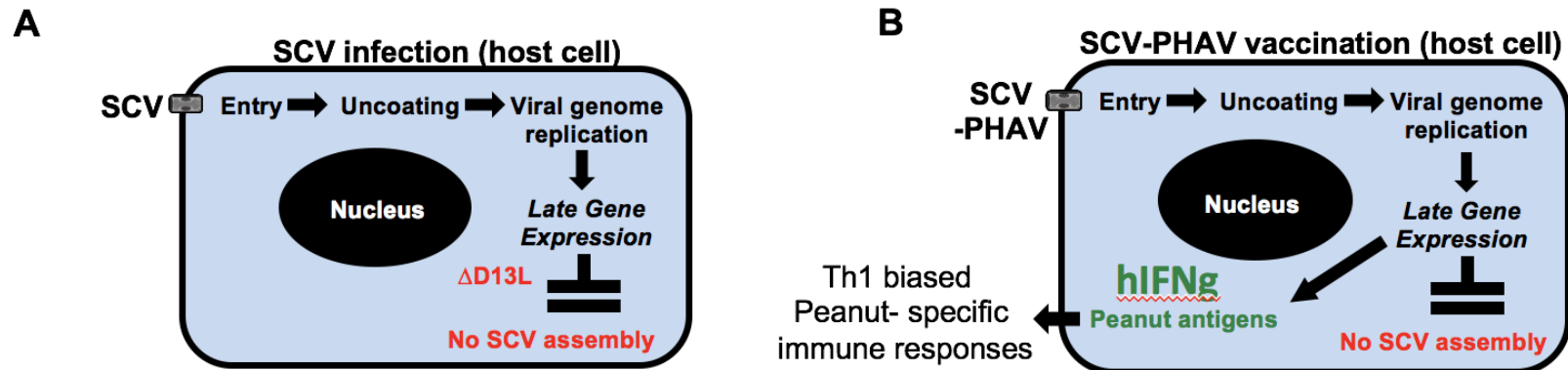
3. Mast cell priming with IgE

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



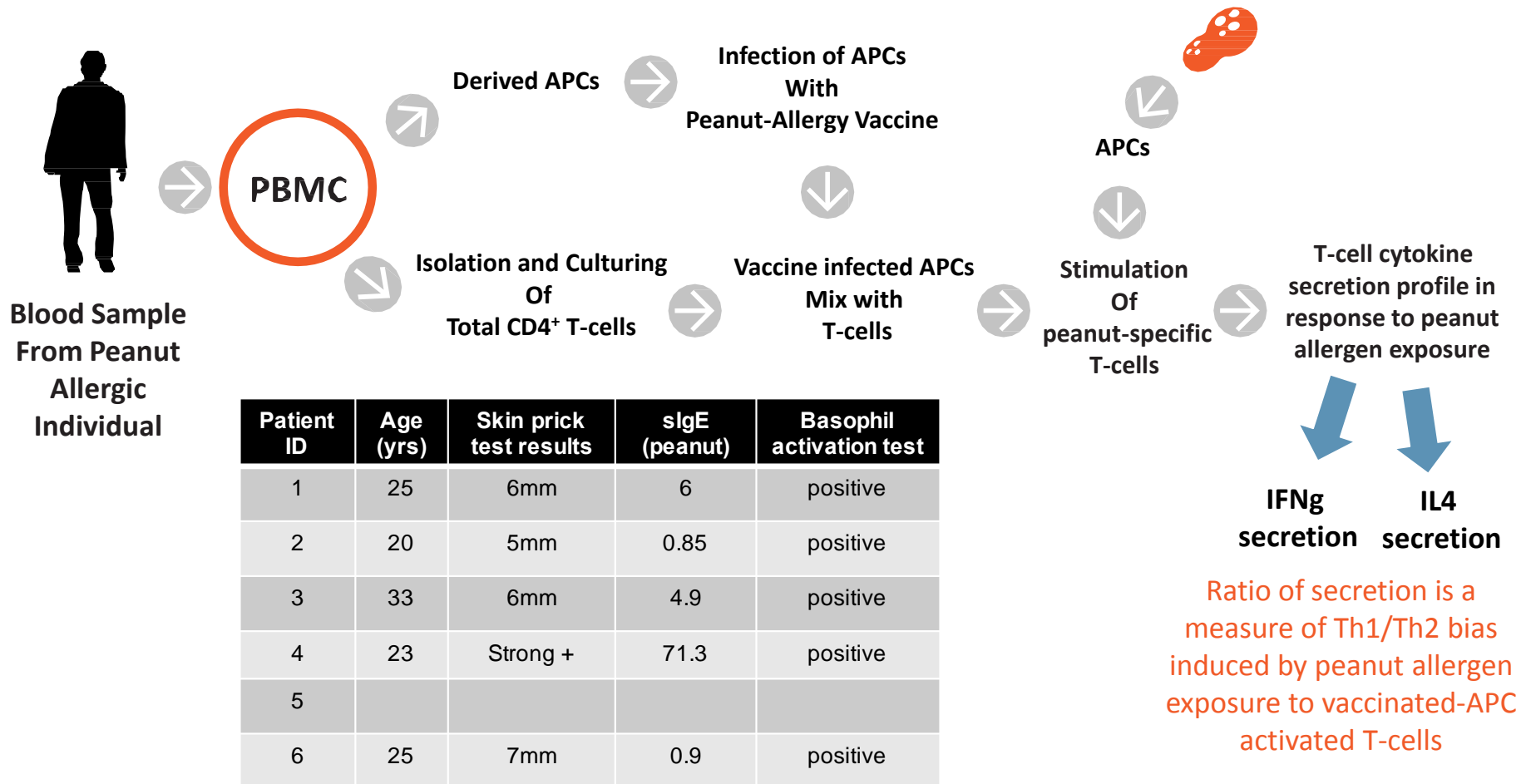
How do we introduce a Th1 bias to peanut antigens ?

- 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)



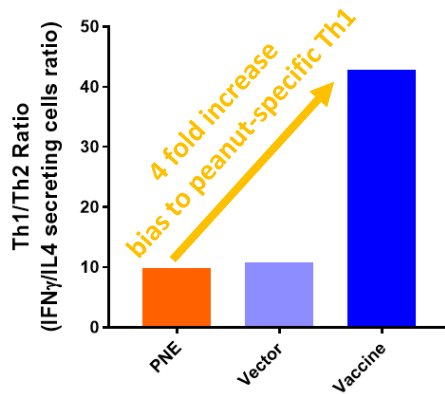
SCV-PHAV expresses a ubiquitinated, multi-peanut antigen fusion protein expressing:
Ara h 1, 2, 3, 5, 6, 7, 8, 8.1, 9, 10, 11

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

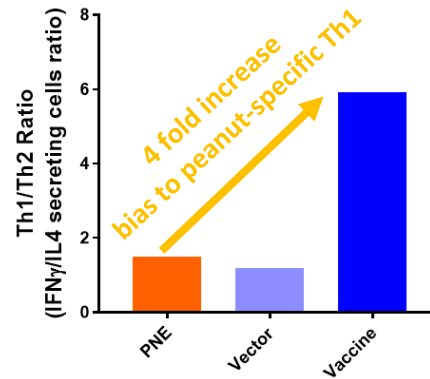


Th1/Th2 profiles for SIX peanut allergic volunteer

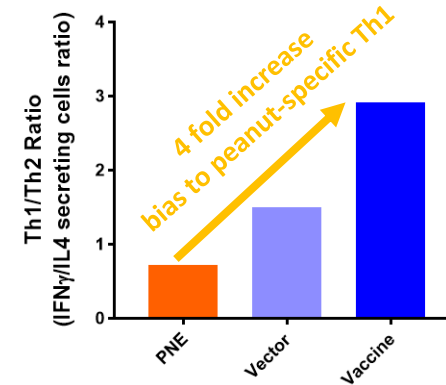
Peanut Allergic Volunteer: MD (female)
Ex Vivo Th1/Th2 Profile



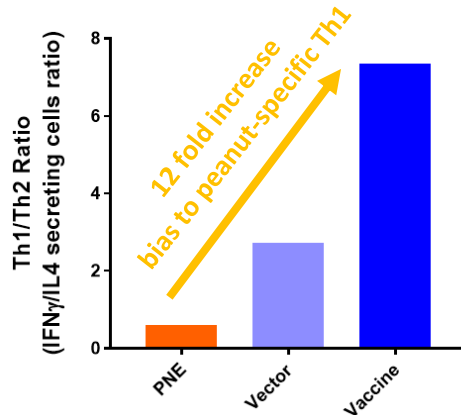
Peanut Allergic Volunteer: JD (female)
Ex Vivo Th1/Th2 Profile



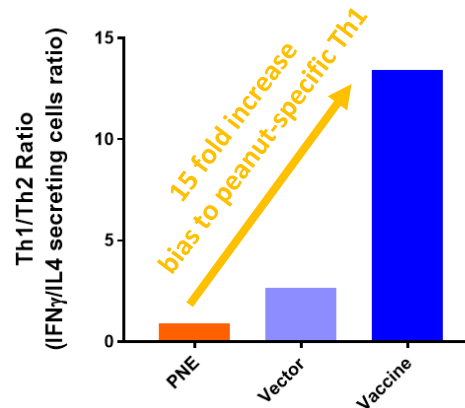
Peanut Allergic Volunteer: AB (female)
Ex Vivo Th1/Th2 Profile



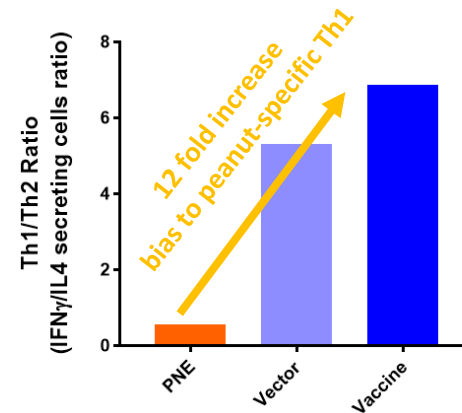
Peanut Allergic Volunteer: MA (male)
Ex Vivo Th1/Th2 Profile



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

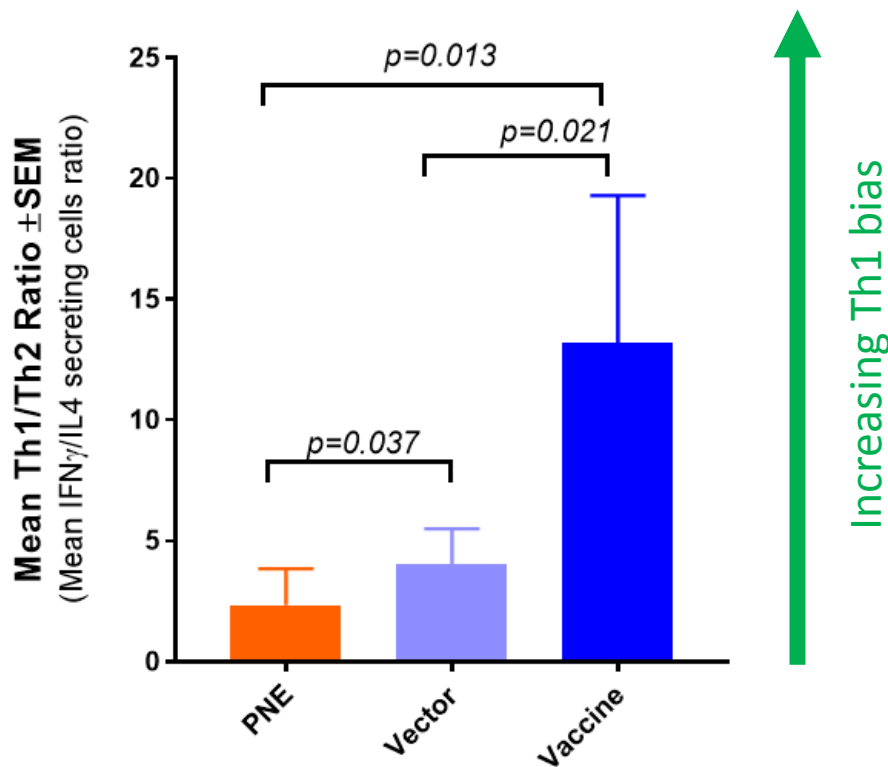


Peanut Allergic Volunteer: KD (female)
Ex Vivo Th1/Th2 Profile



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

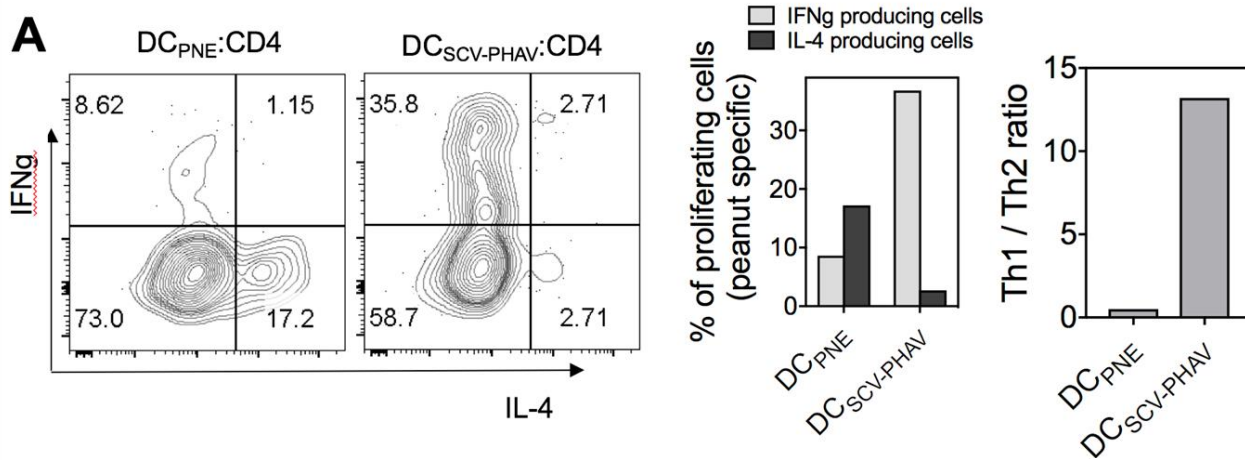


Significance was determined using one-tailed Mann-Whitney T-test
Significance = $p < 0.05$

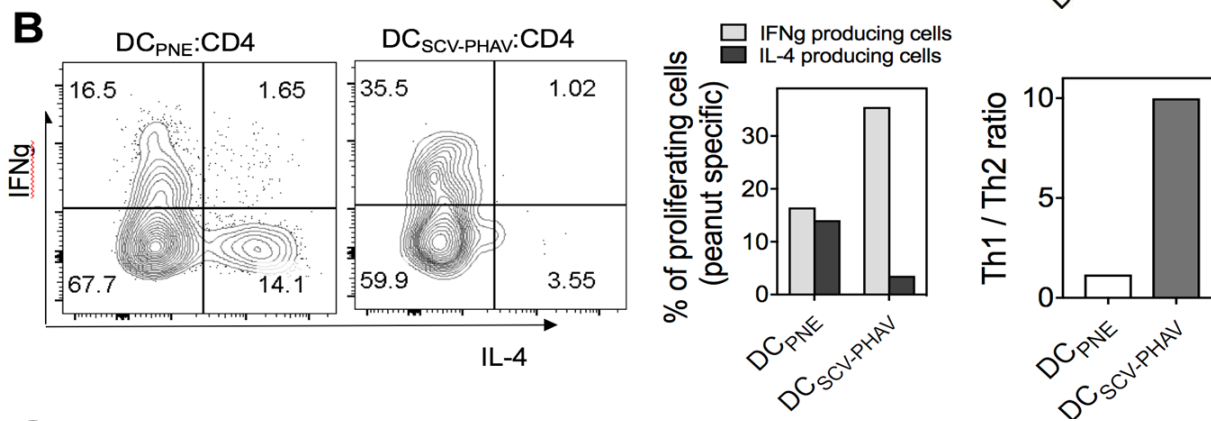
Conclusion:

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**.

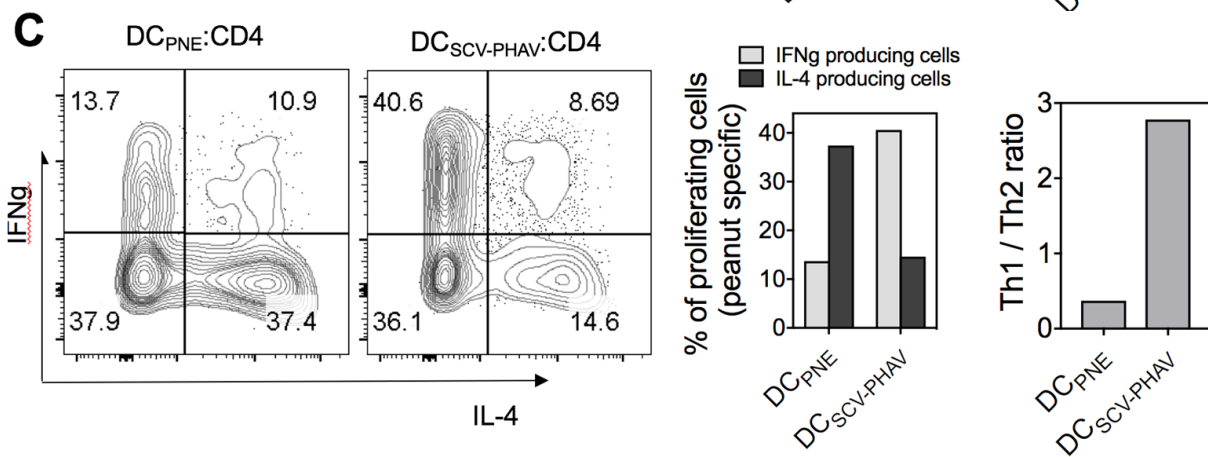
Assay done in 2016

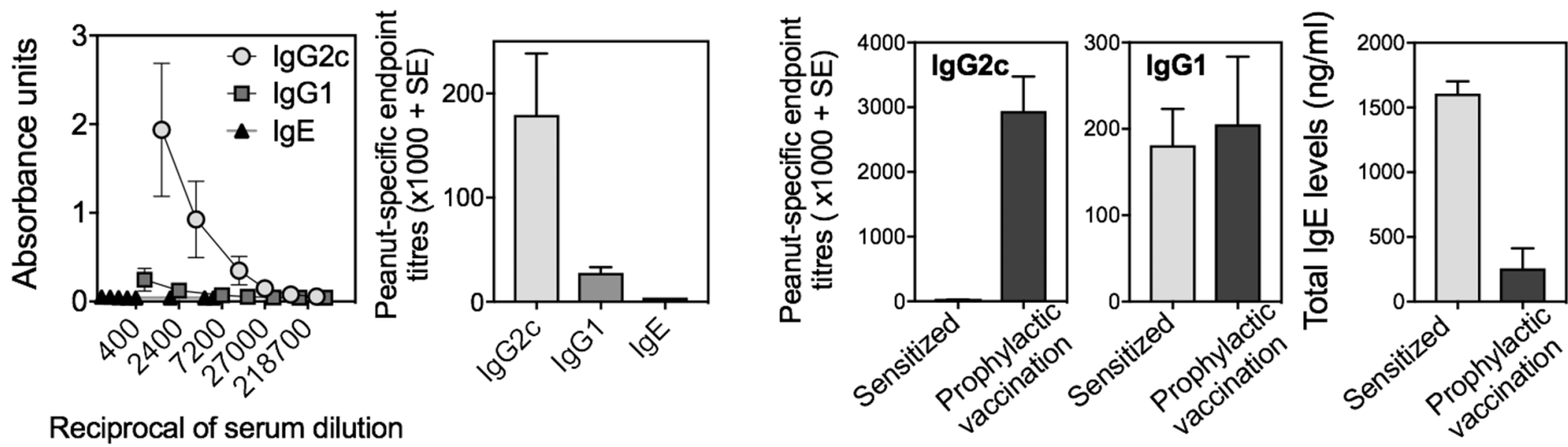
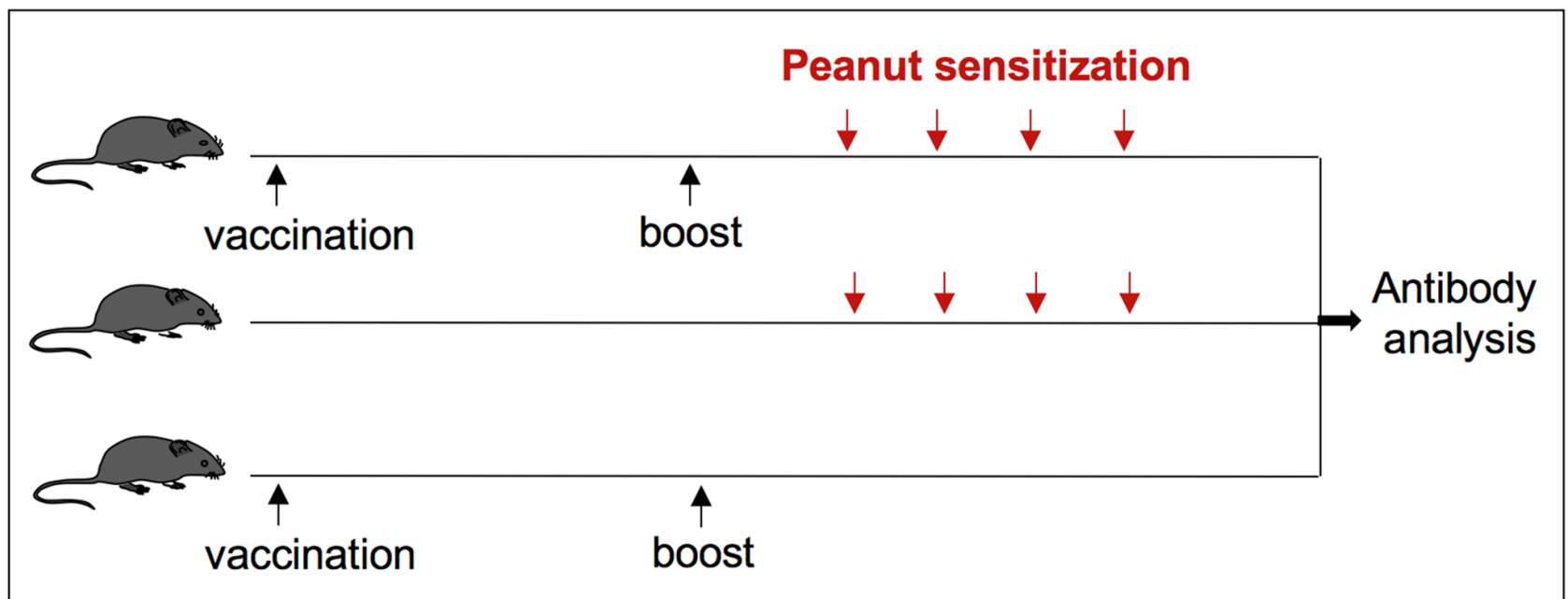


Assay done in Jan 2017

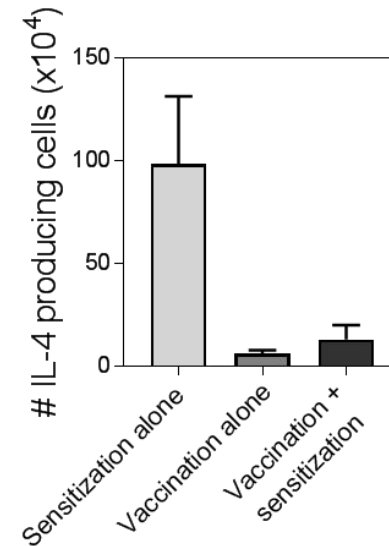
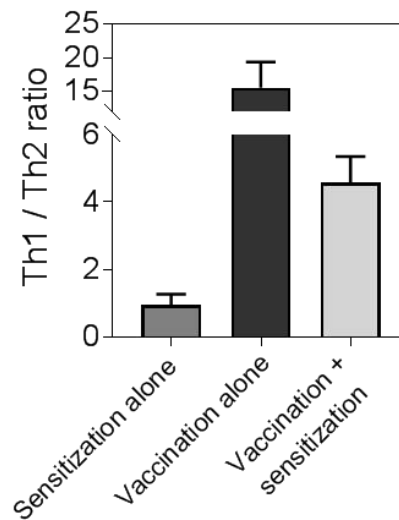
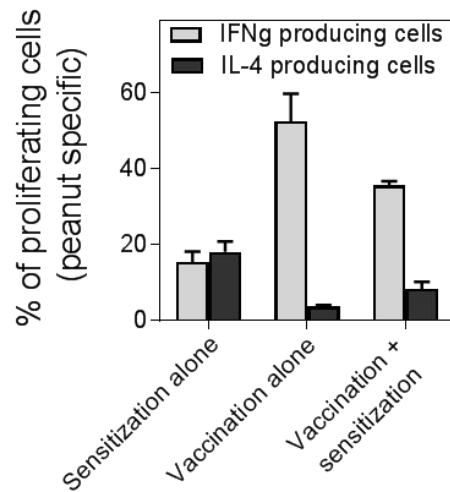
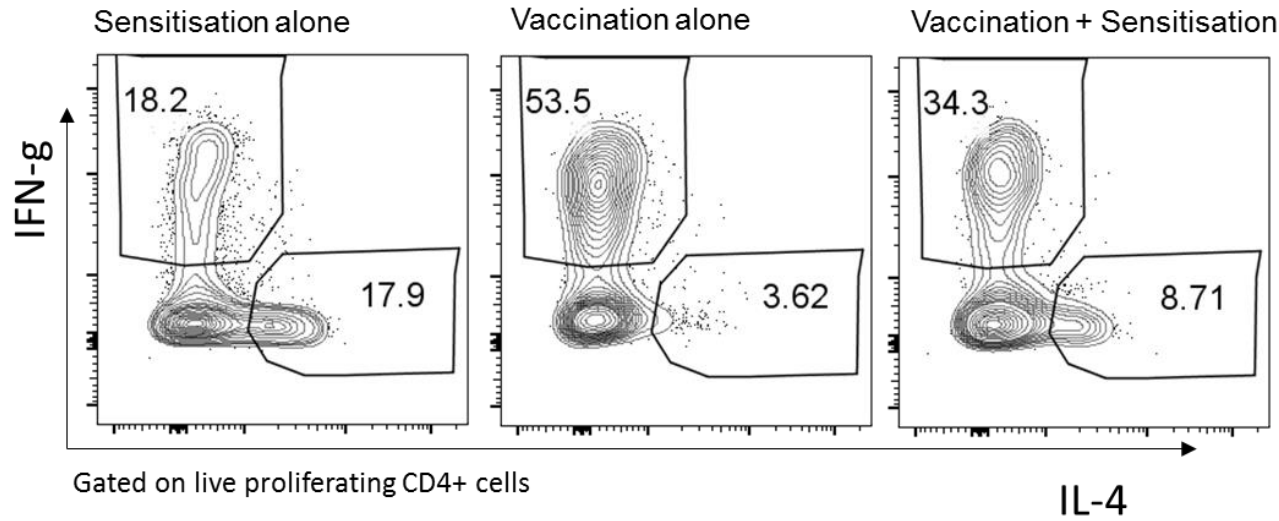


Assay done in Aug 2017





Ex-vivo stimulation antigen specific CD4 T cell cytokine analysis



Summary II

- 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
- SCV-PHA *in vivo* vaccination delivers a skewed Th1 vsTh2 response in peanut allergic mice
- Eldi *et al*, manuscript in preparation.

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