

Bristol Children's Vaccine Centre

**Structure-based design
of a quadrivalent fusion
glycoprotein vaccine for human
parainfluenza virus types 1-4**

<https://www.pnas.org/content/115/48/12265.long>

@adamhfinn

ECCMID, 13th April 2019

B

V

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C

Relevant interests

No funding relevant to first paper

Research funding (to University of Bristol and/or Univ Hospitals Bristol NHS Trust) from GSK Sanofi and Pfizer - incl. VZV studies.

Consultancies (paid to UoB) Bionet Asia, Takeda, Janssen, Sci-B Vac

Member, JCVI

Chair, WHO ETAGE

President, ESPID (whose meeting is sponsored by Sanofi, Merck, GSK & Pfizer amongst other companies)

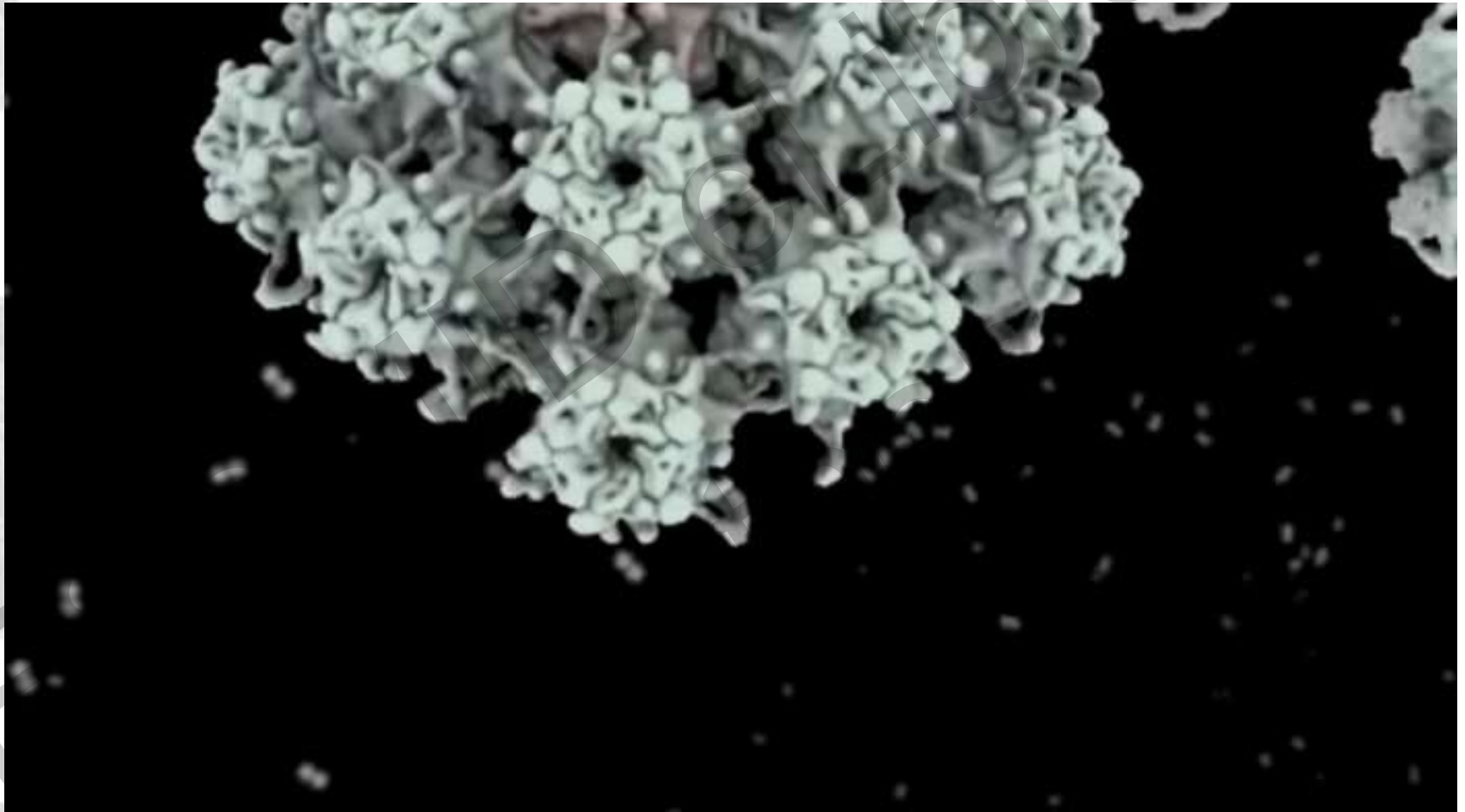
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Virus-like particles



PMID 30420505

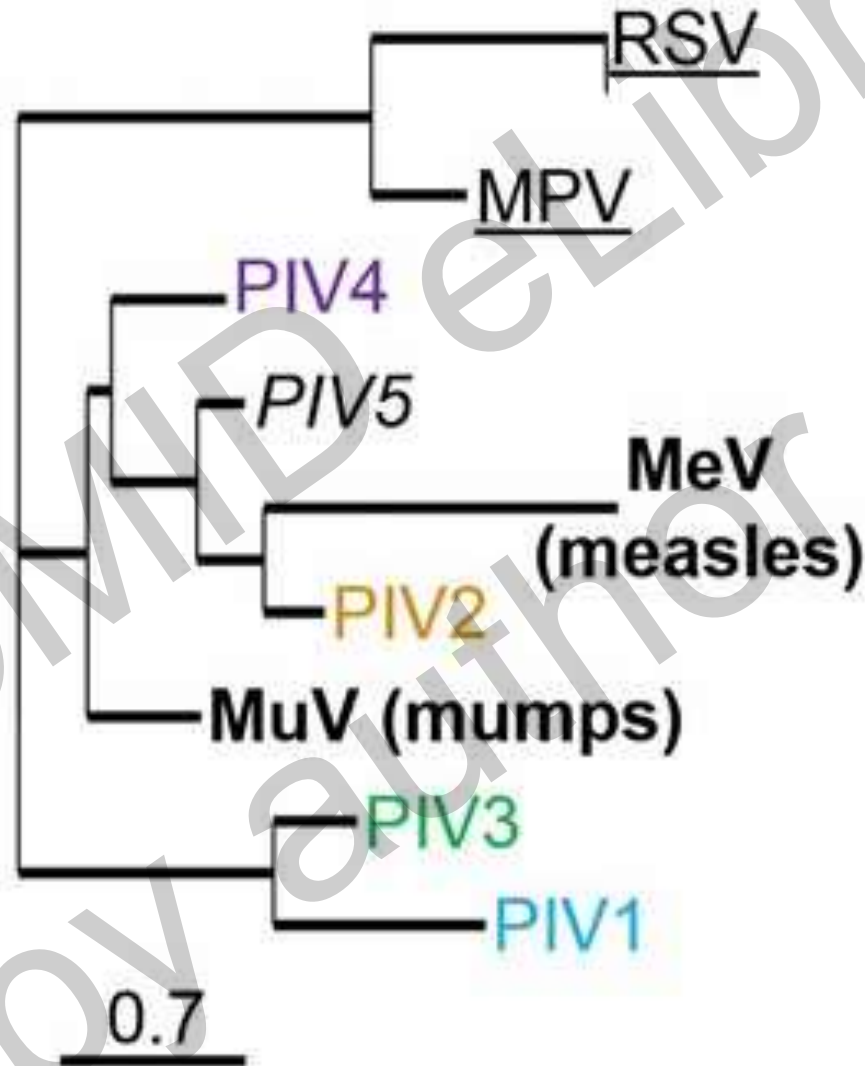
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Paramyxoviruses



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Human Parainfluenza viruses

...are the second main cause of hospitalisation in children under 5 years of age suffering from a respiratory illness (only *Human orthopneumovirus (RSV)* causes more respiratory hospitalisations for this age group)



Vaccine against RSV

NOVAVAX
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Novavax Announces Topline Results from Phase 3 Prepare™ Trial of ResVax™ for Prevention of RSV Disease in Infants via Maternal Immunization

- *Trial did not meet primary objective of prevention of medically significant RSV LRTI*
- *Trial did show efficacy against secondary objective (RSV LRTI hospitalization); first RSV vaccine to show Phase 3 efficacy*
- *Other pre-specified exploratory endpoints and post-hoc analyses highlight potential to improve global health against RSV disease*
- *Favorable safety and tolerability data*
- *Next step to meet with key regulatory authorities to discuss licensure pathways*
- *Investor conference call today at 8:00 am EST*

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RSV MPV

- Viral fusion glycoprotein
 - Metastable pre-fusion
 - Stable post-fusion conformations
- Merges virus and cell membranes
- Structure-based stabilisation in pre-fusion conformation used for RSV candidate vaccine - high titre neutralizing antibodies
- However no such improvement seen for stabilized metapneumovirus FuP

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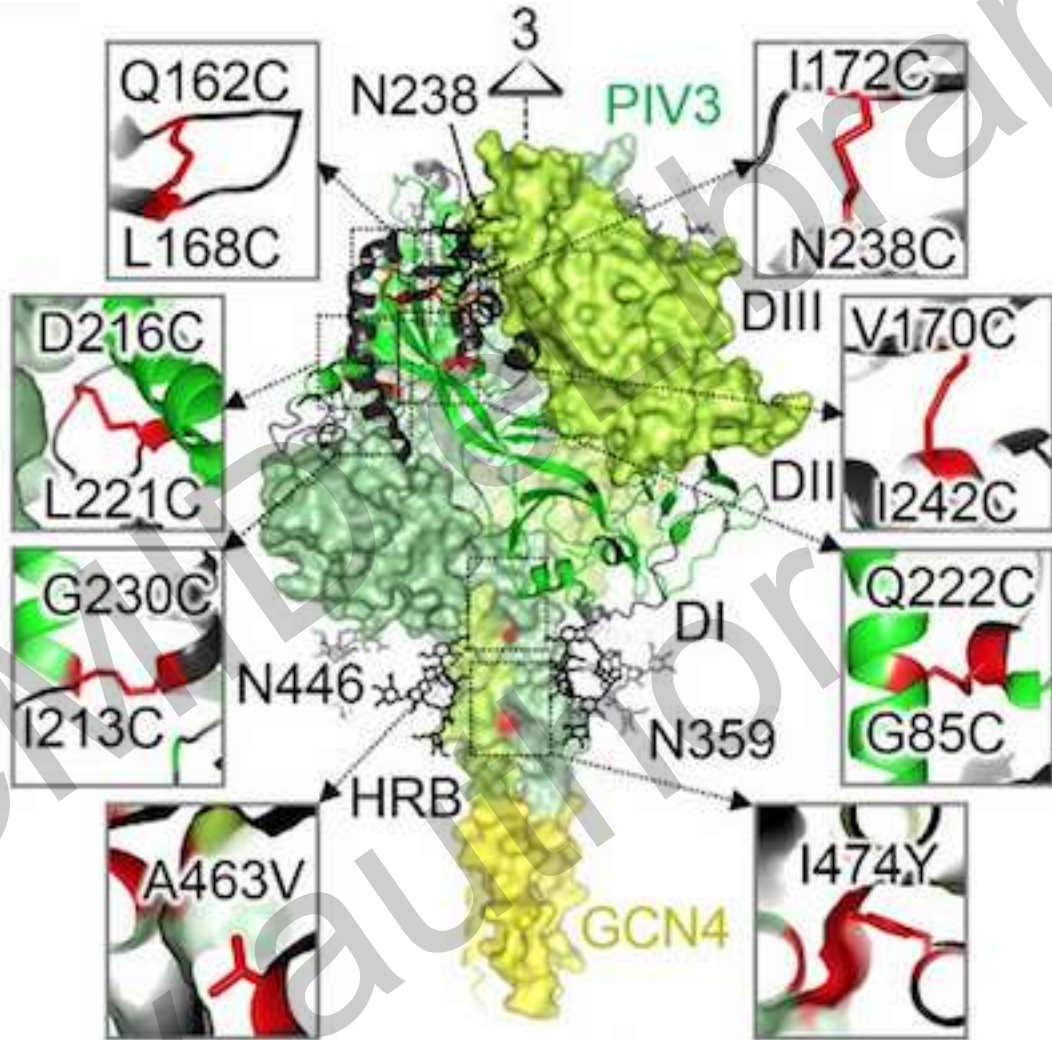
Paramyxovirus F-protein



Trimeric

B V C C

PIV3

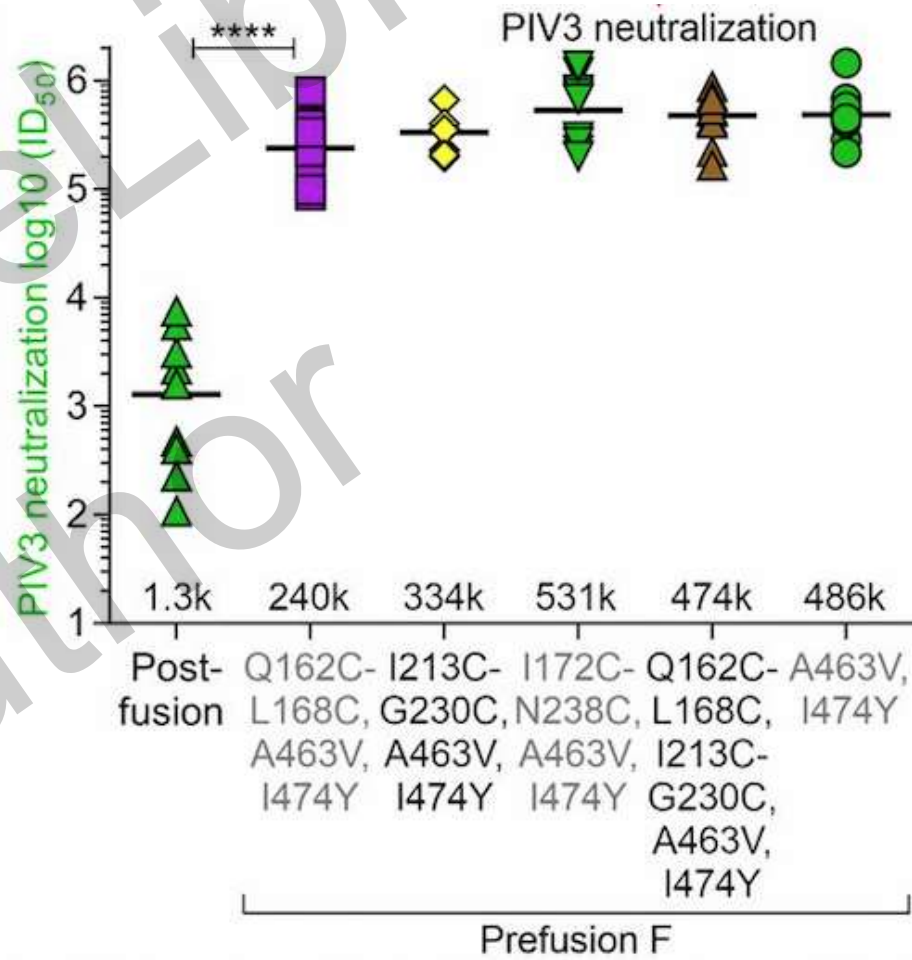
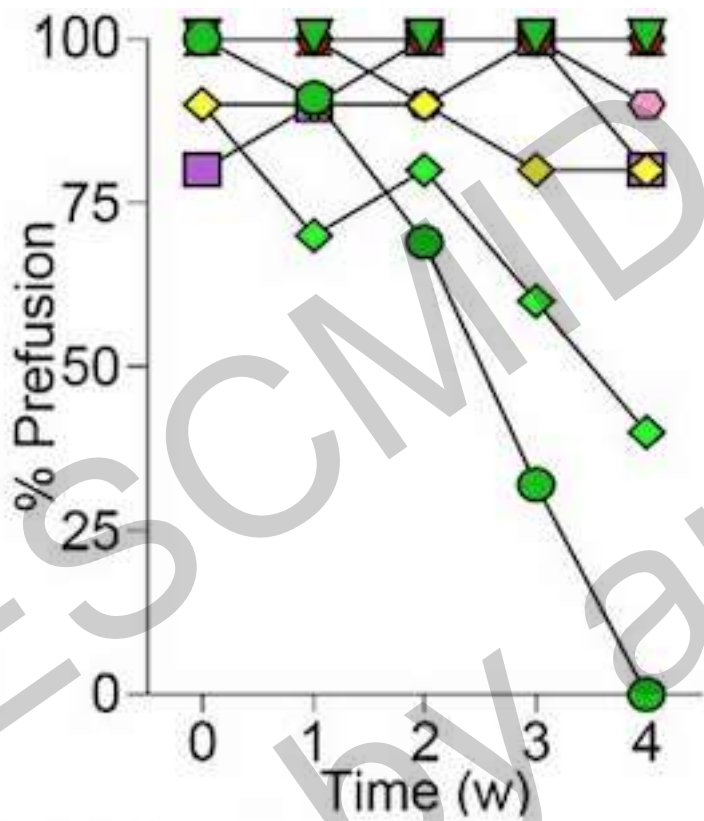


■ >5 Å movement to postfusion
■ <5 Å movement to postfusion

...disulfide and cavity-filling changes in the head and stem, respectively

Stability, immunogenicity

PIV3



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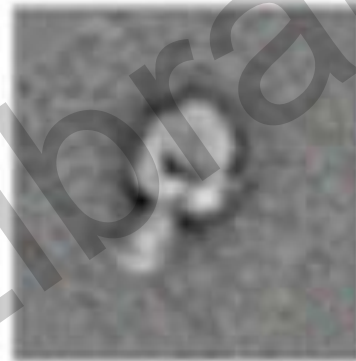
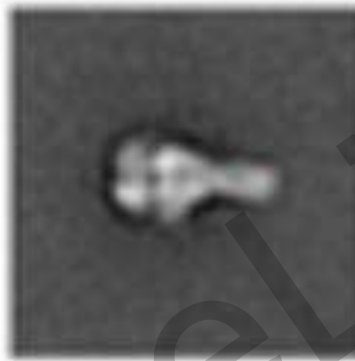
C

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PIV 1
23x

Postfusion F

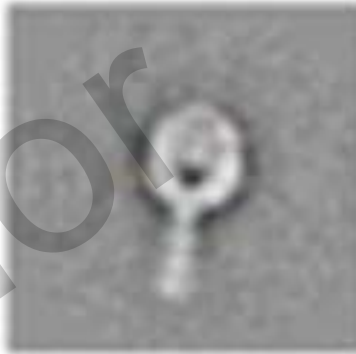
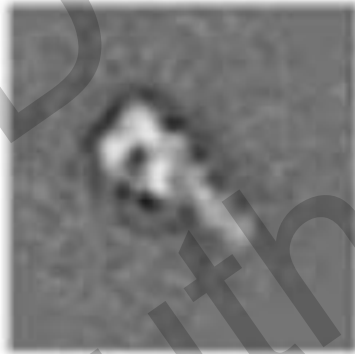
Prefusion F



Postfusion F

Prefusion F

PIV 2
9.5x



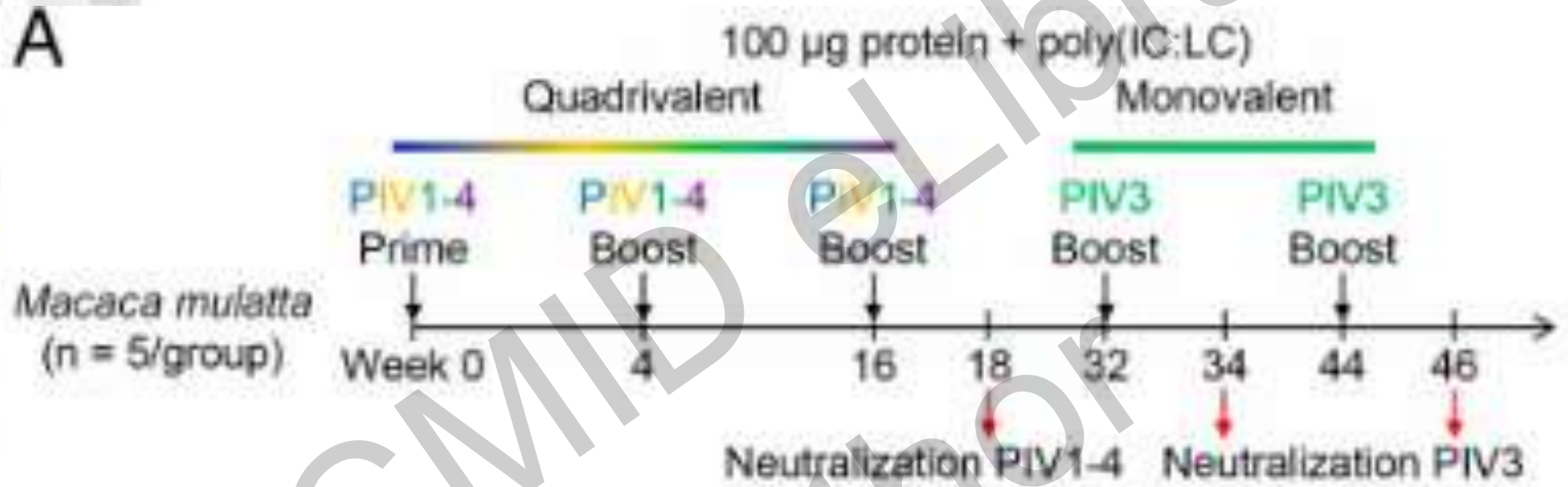
Postfusion F

Prefusion F

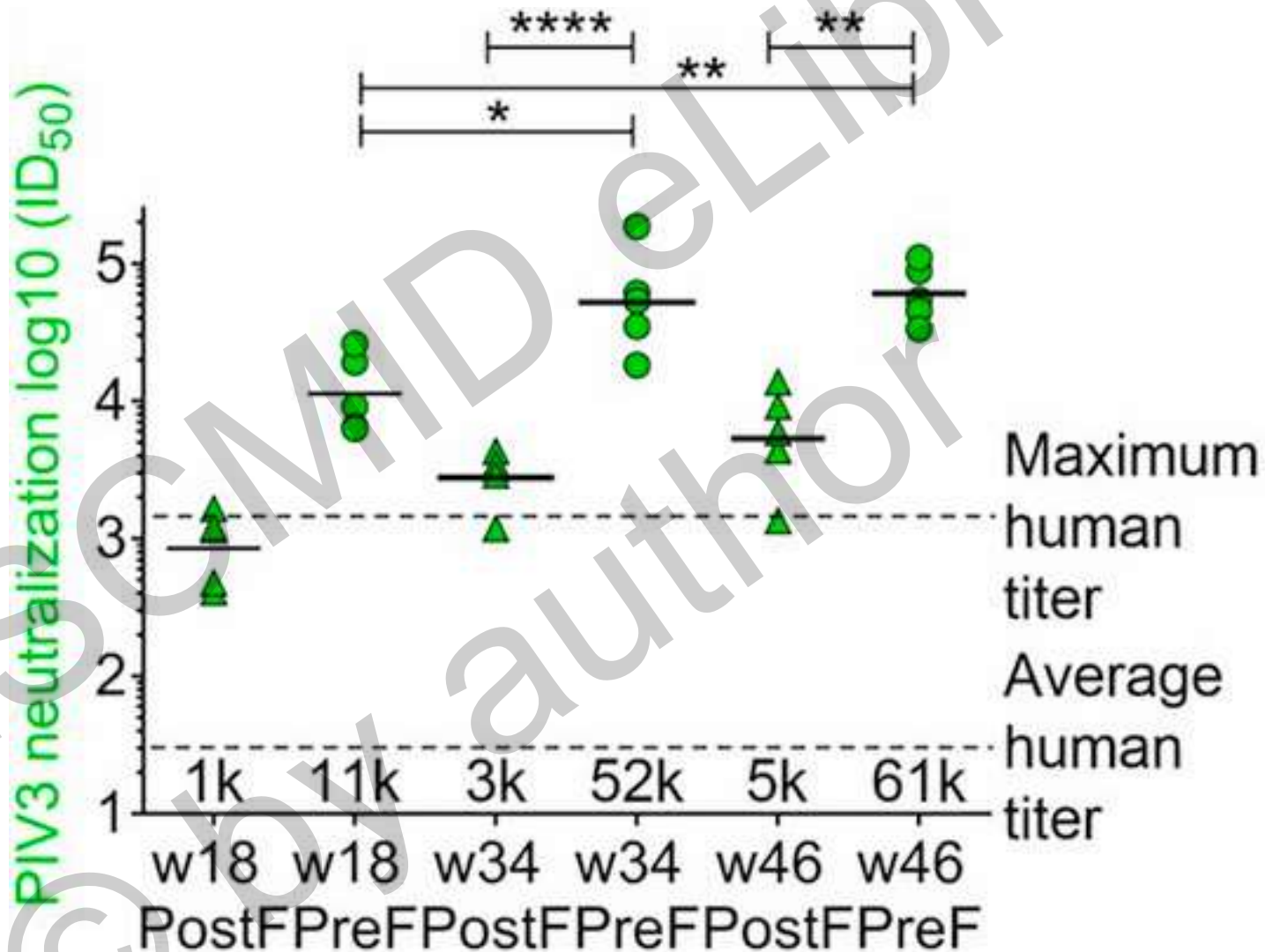
PIV 4
2.6x



Quadrivalent PIV vaccine x3 in non-human primates



PIV3 Responses compared to AB titres in humans



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Conclusions

- F-proteins from PIV 1-4 can be engineered to stabilize them in their pre-fusion configuration
- This changes their antigenic characteristics such that they induce much higher concentrations of neutralizing antibodies in mice
- In non-human primates the 4 antigens combined induce higher concentrations of nAB than found in healthy humans



Th1 memory
differentiates recombinant from
live herpes zoster vaccines

Published 19th July 2018

<https://www.jci.org/articles/view/121484>

@adamhfinn

ECCMID, 13th April 2019

B


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Why does zoster in the elderly matter for children?

1. Observational studies, reinforced by mathematical epidemiological models have suggested that exposure to children with varicella may protect adults against zoster
2. Zoster and especially post herpetic neuralgia are very expensive for health services
3. This theoretical concern has held back implementation of varicella prevention by universal vaccination in childhood



Problems with Live Attenuated Zoster Vaccine (ZV)

1. This theoretical problem could be solved by using ZV in the elderly
2. Efficacy 51% in >60 year olds and falls with increasing age of administration
3. Protection wanes 6-8 years after vaccination
4. New vaccine may solve this - how?



The diagram shows a protein structure with four subunits labeled B, V, and C. Subunit B is in a blue box, V is in a green box, and the two C subunits are in orange and brown boxes respectively. They are arranged in a chain-like structure.

gpE subunit ZV (HZ/su)

- Single recombinant VZ antigen
- ASO1_B adjuvant (MPL & liposomal QS21)
- 97% efficacy in >50y olds. 89% in >80yos
- Efficacy maintained to 4y (so far) and immune responses to 9y (so far)
- One way to try to understand why/how new vaccine works so much better is to compare T cell immune responses to the 2 vaccines.
- Also might help indicate how to make other vaccines for elderly work too...

B

V

C

C

Study design

- 3 groups (80 + 80)
 - 50-59y no previous ZV
 - 70-85y no previous ZV
 - 70-85y previous ZV >5y previously
- Randomised 50:50
 - ZV (1 dose, day 0)
 - HZ/su (2 doses, days 0 and 60)
- Measured immune responses at
 - days 30 & 90 (ie 30 days after each dose)
 - and day 365

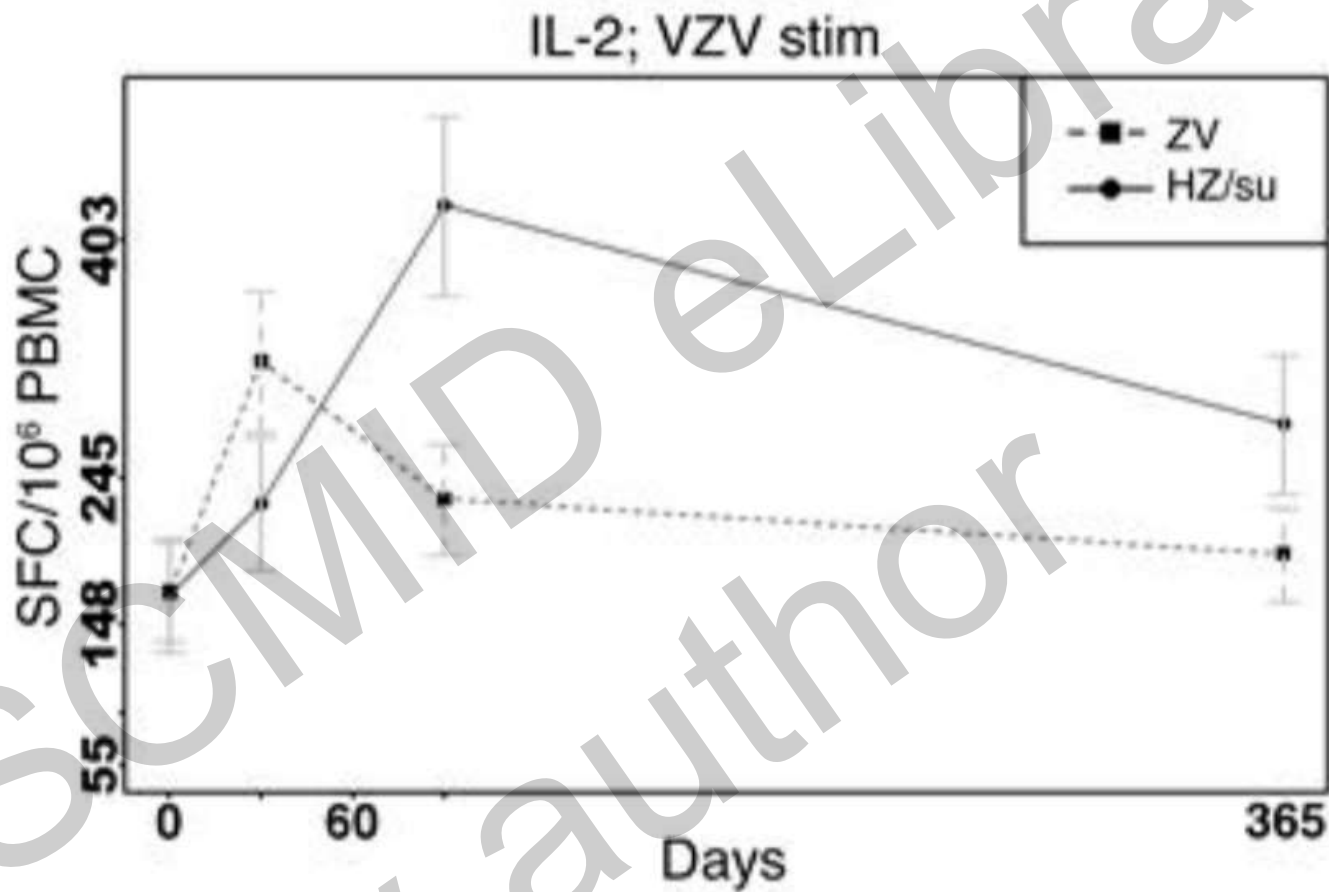
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TH1 VZV memory responses



- Response after 1 dose ZV > HZ/su

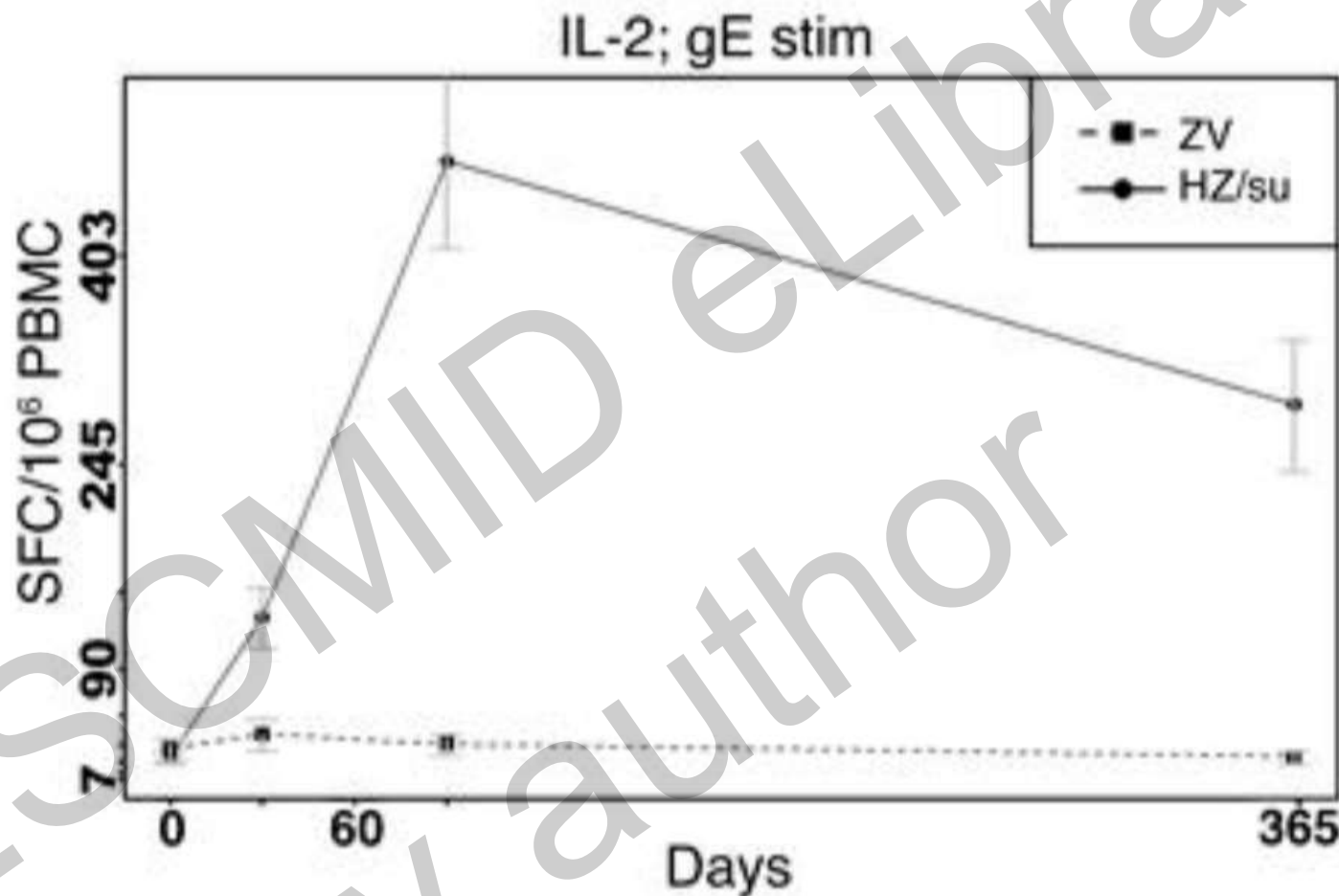
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TH1 gpE memory responses



- Very few pre-vaccine gpE mem cells
- Very small responses to ZV

T cell differentiation

Differentiation stage

Mean of ZV/HZ/su results

Effector CD4

2.07

Tem cells CD4

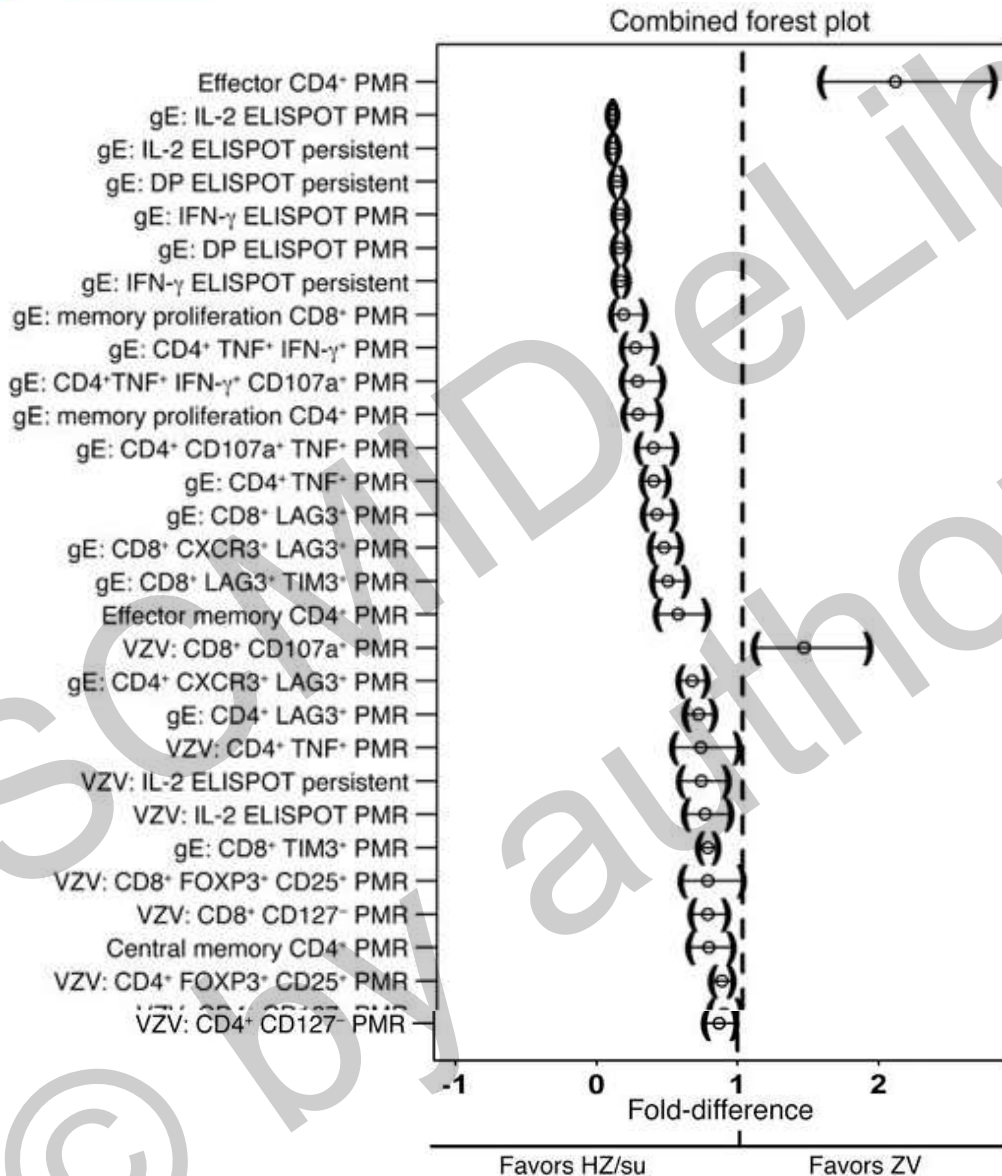
0.55

Tcm cells CD4

0.76

- ZV induces more effector cells
- HZ/su induces more memory cells
- CD4 & CD8 proliferation to gpE greater in HZ/su groups

Summary of differences



- IL2 peak memory responses were good predictors of 1 year persistence of TH1 VZ and gpE cells



B

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So what?

- gpE T cell responses are not found after ZV or natural infection.
- High memory responses may be the key to the high and sustained protection induced by HZ/su.
- 2 doses are probably important.
- Exogenous boosting - if it matters at all - need not worry us any more - we have a solution!