



Preclinical Development of Next-Generation Rotavirus Vaccine

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October 1, 2025

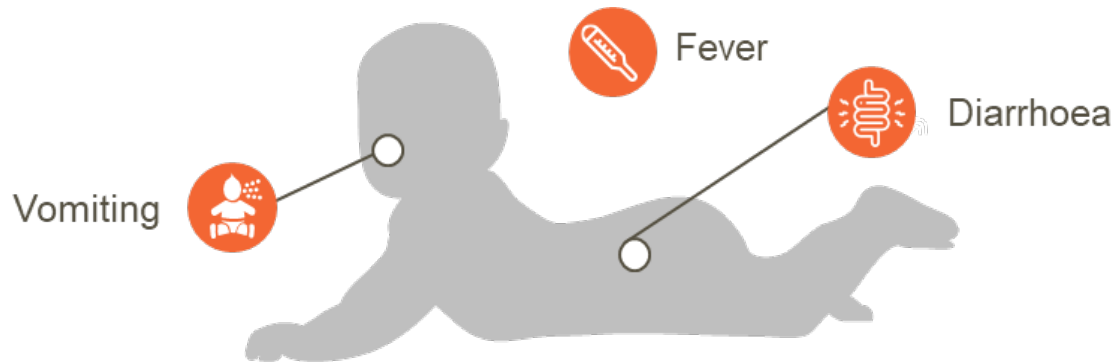
This work was undertaken at the request of and sponsored by GlaxoSmithKline Biologicals SA.

GSK Vaccines Institute for Global Health Srl is an affiliate of GlaxoSmithKline Biologicals SA.

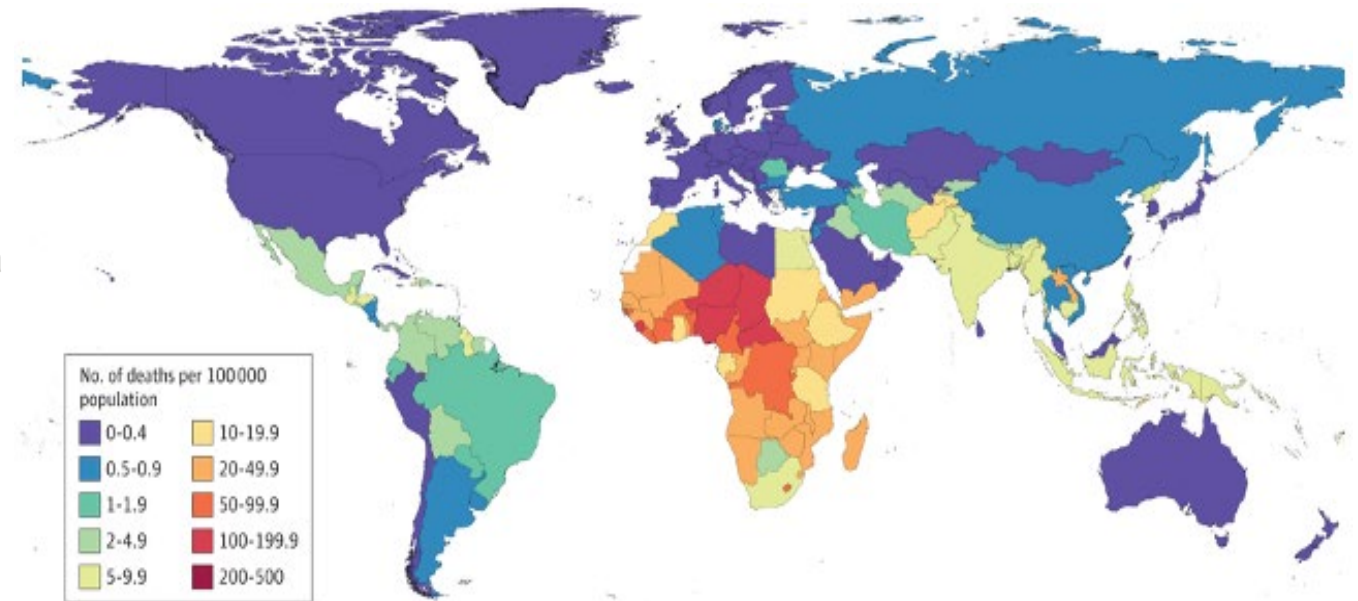
Rebecca Loomis is employed by the GSK group of companies and reports ownership of GSK shares.

Rotavirus (RV) is a highly contagious virus causing acute, severe diarrhea in children <5 years

RV is transmitted via oral-fecal route.







Geographic Distribution of RV-Associated Mortality Rates Among Children Younger Than 5 Years



JAMA Pediatr. 2018;172(10):958-965. doi:10.1001/jamapediatrics.2018.1960

Limitations of current oral live-attenuated RV vaccines

- Vaccine efficacy against severe RV diarrhea in children <1 year of age

 Rotarix ^{1,2}	 RotaTeq ³⁻⁶	 Rotavac ⁷	 Rotasiil ^{8,9}
Single live-attenuated human strain	Human–bovine pentavalent reassortants	Single human strain reassorted with a bovine segment	Human–bovine pentavalent reassortants
HIC: ~95–100% LIC to MIC: ~49% (Africa) ~85% (Latin America)	HIC: ~89–98% LIC to MIC: ~40% (Africa) ~48% (Bangladesh, Vietnam)	~56% (India)	~36% (India) ~67% (Niger)

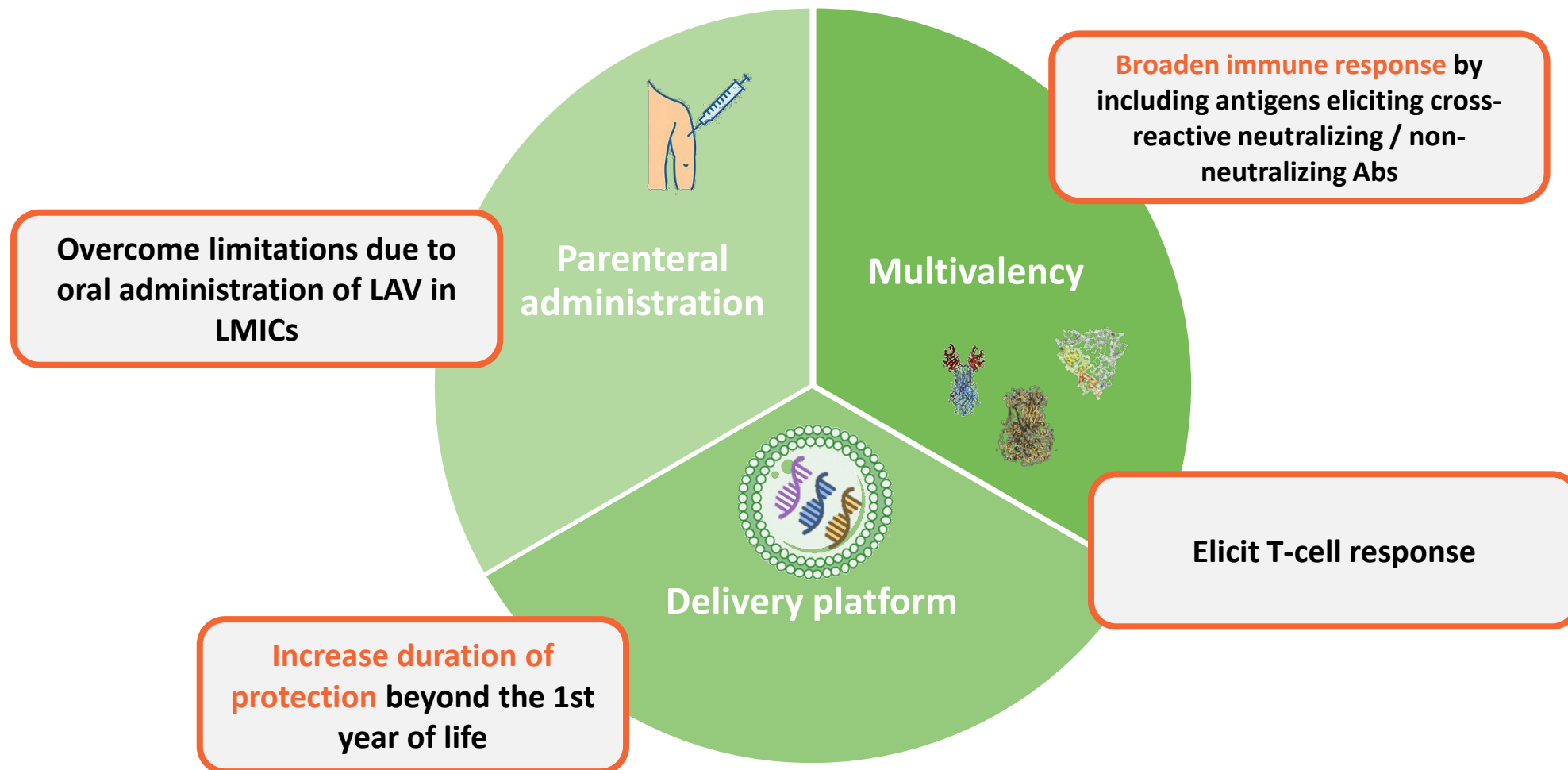
- Potential factors contributing to reduced vaccine efficacy in LMICs



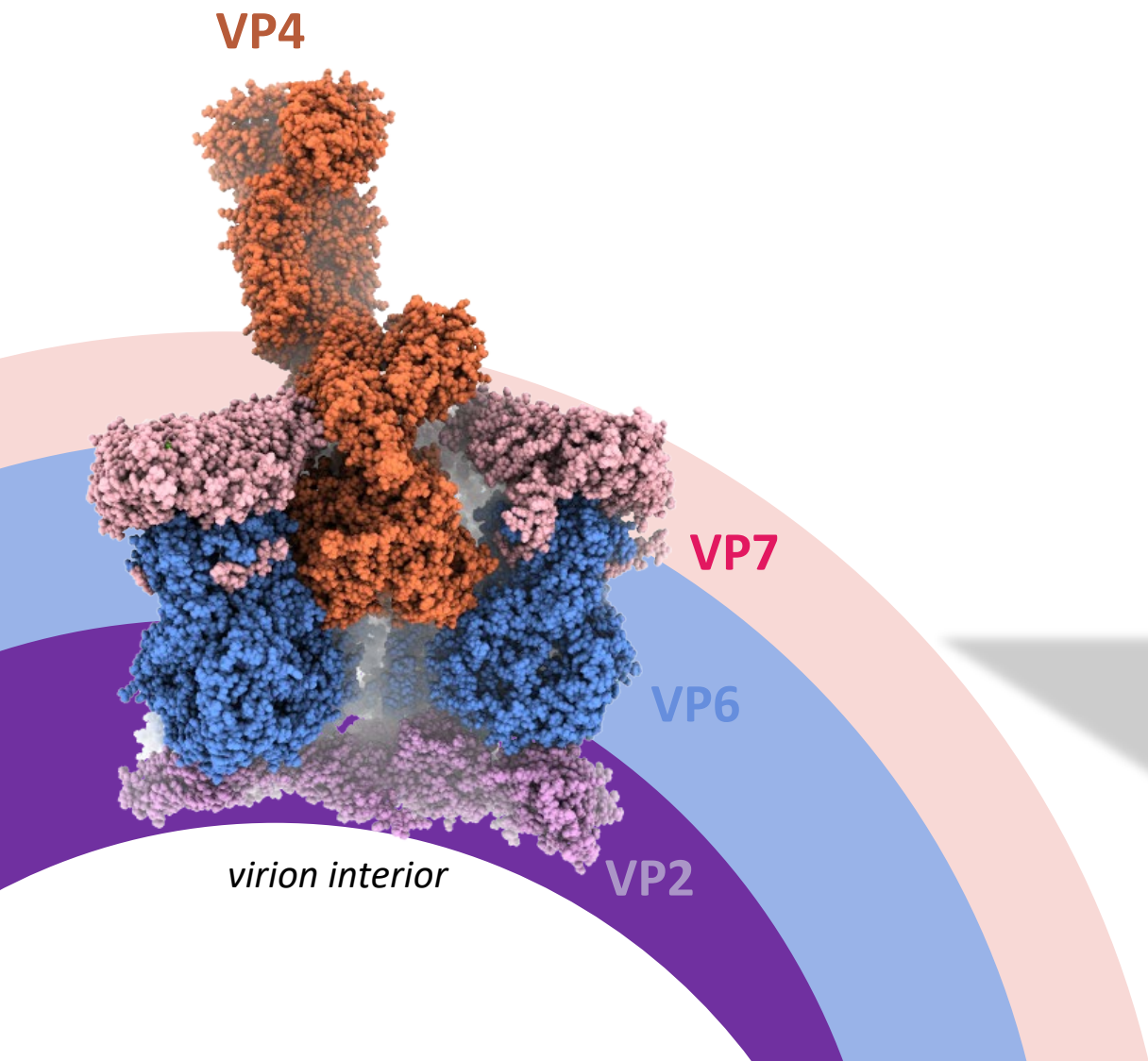
¹GSK. Rotarix EU SmPC. EMA, 2020. https://www.ema.europa.eu/en/documents/product-information/rotarix-epar-product-information_en.pdf; ²*N Engl J Med* 2010;362:289–298; ³MSD. RotaTeq EU SmPC. EMA, 2018. https://www.ema.europa.eu/en/documents/product-information/rotateq-epar-product-information_en.pdf; ⁴*Pediatr Infect Dis J* 2012;31:184–188; ⁵*Lancet* 2010;376:615–623; ⁶*Lancet* 2010;376:606–614; ⁷*Vaccine*. 2014;32 Suppl 1:A110-6. ⁸*Vaccine* 2017;35:6228–6237; ⁹*N Engl J Med*. 2017;376(12):1121-1130.

Strategy for a next generation RV vaccine

Lessons learned from the oral live-attenuated and PATH P2-VP8* vaccines



RV is composed of a triple-layered capsid



Rotavirus Antigens

VP4

Two antigenic regions: VP5* and VP8* that contain most of the **cross-reactive and strain-specific neutralization epitopes**, respectively.

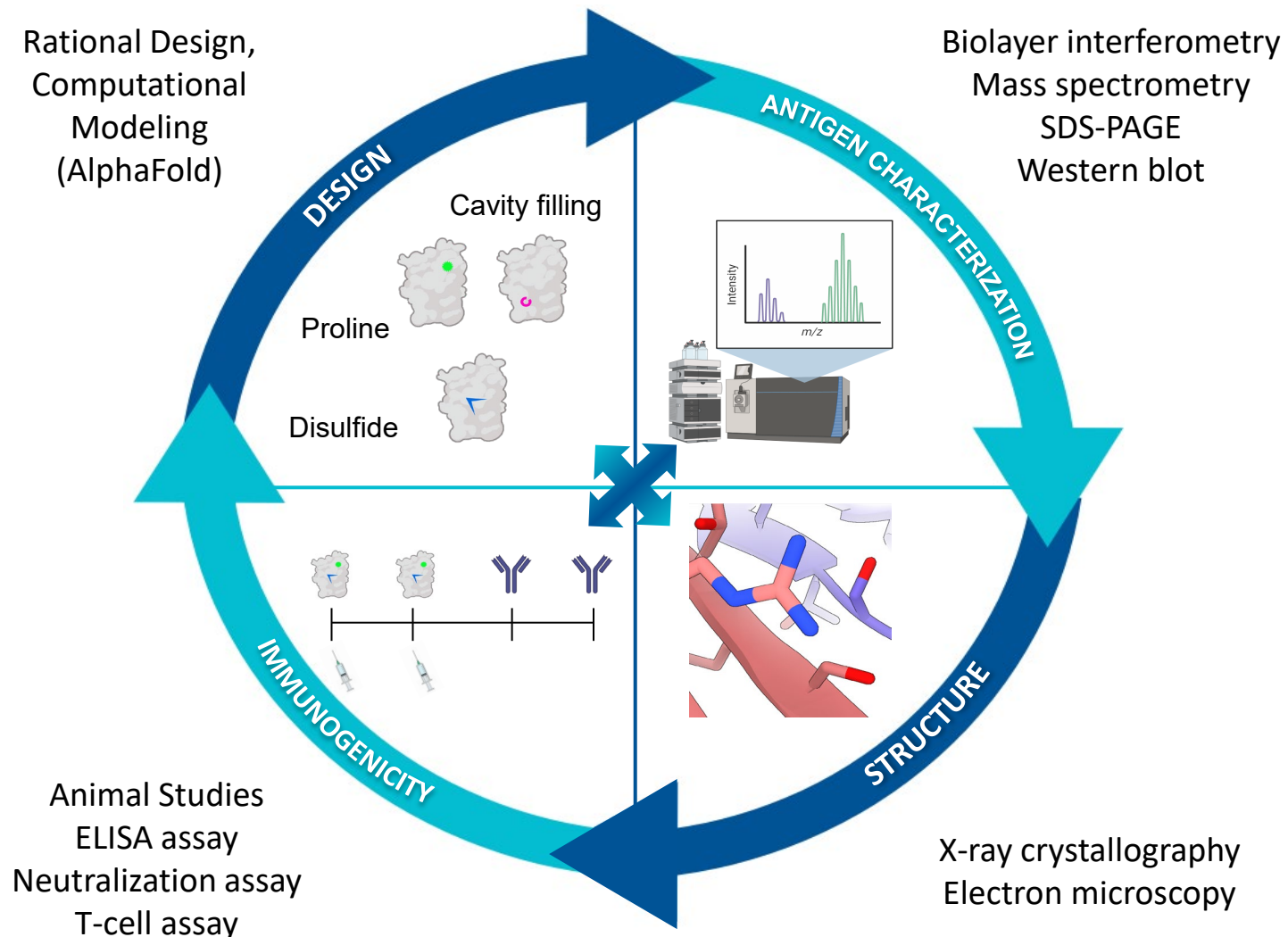
VP7

Outer capsid glycoprotein, highly antigenic, important **target for neutralizing antibodies**

VP6

Immunodominant, highly conserved, and contributes to **cross-protection** without virus entry neutralization.

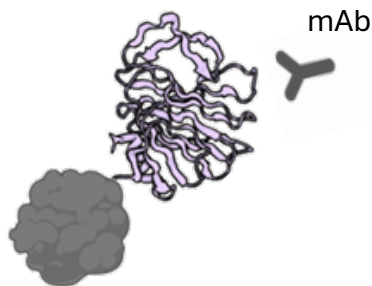
Iterative process of structure-based antigen design



Adapted from DOI: 10.1101/cshperspect.a029470. Created with BioRender.com.

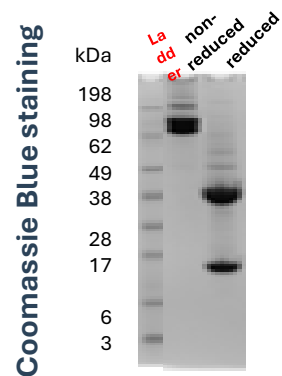
In vitro evaluation of P2-VP8 antigen

1. Antigen design

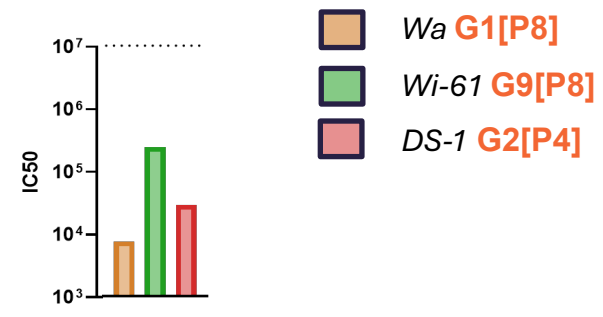


P2-VP8

2. Production of Antibodies

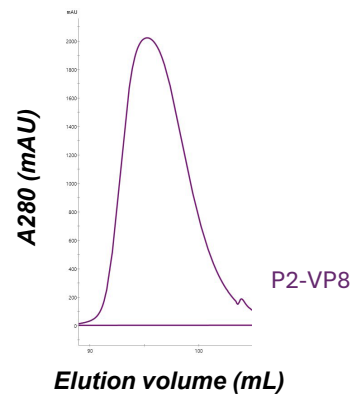


Neutralization assay

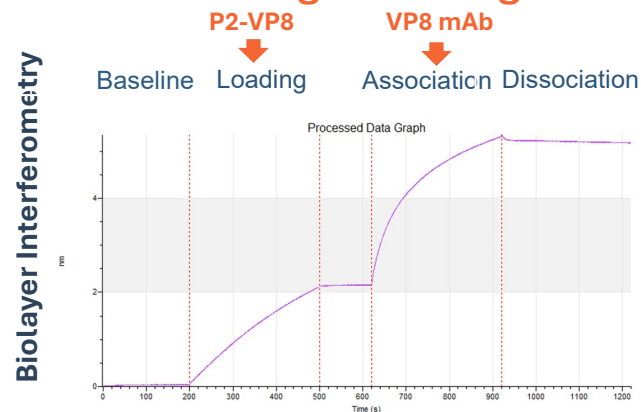


3. Antigen purification

Affinity chromatography

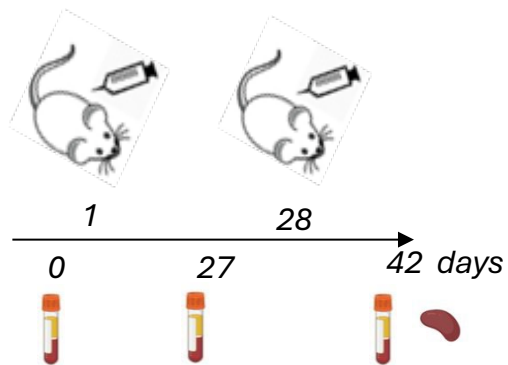


4. Antigen binding



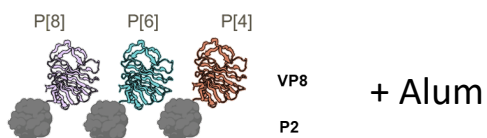
In vivo evaluation of the P2-VP8 antigen to set-up immunoassays

CB6F1/J mice
20 animals per group



• P2-VP8 IMMUNIZED:

• CTRL: Alum



Humoral

- Binding → ELISA
- Functionality → Neutralization test



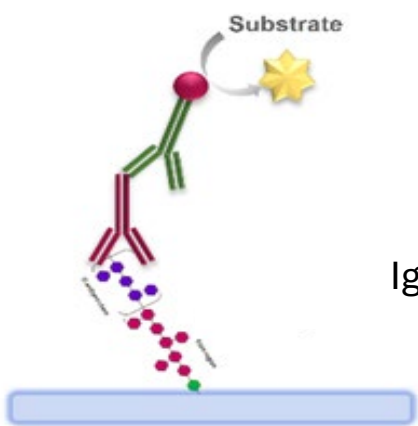
Cellular

- T cells → Flow Cytometry

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on Care, Welfare and Treatment of Animals.

Quantitation of antigen-specific Abs by automated high-throughput ELISA

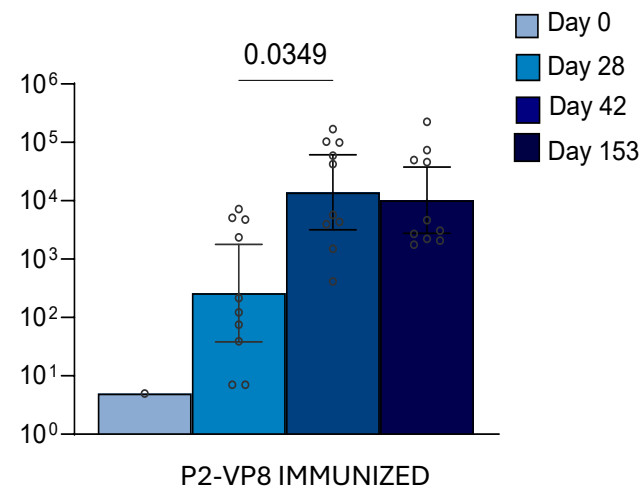
Humoral immune response



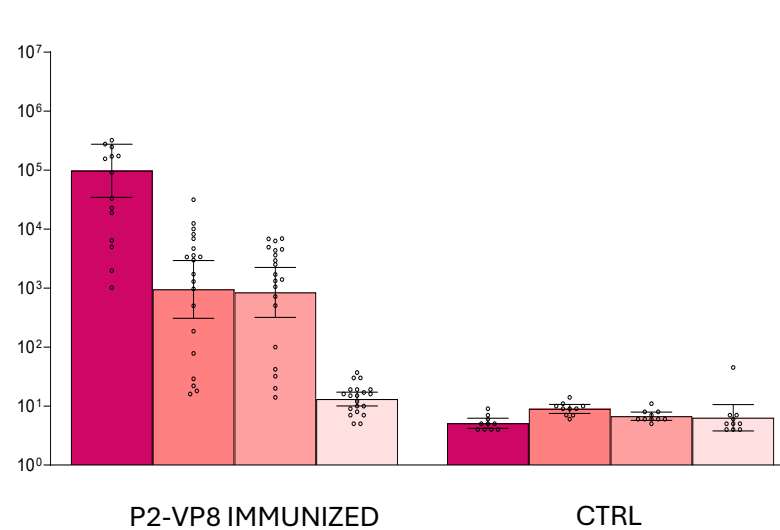
IgG subclasses

IgG

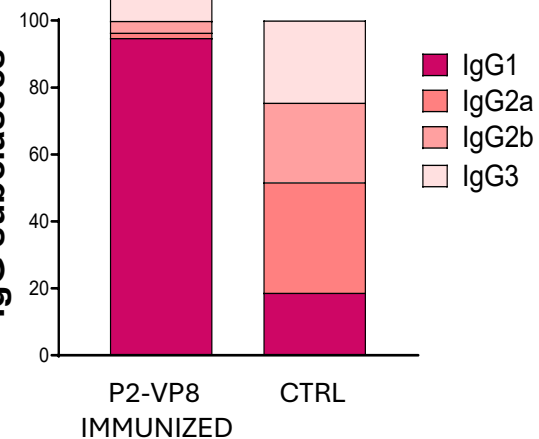
Antigen-specific total IgG (EU/ml)



Antigen-specific IgG (EU/mL)

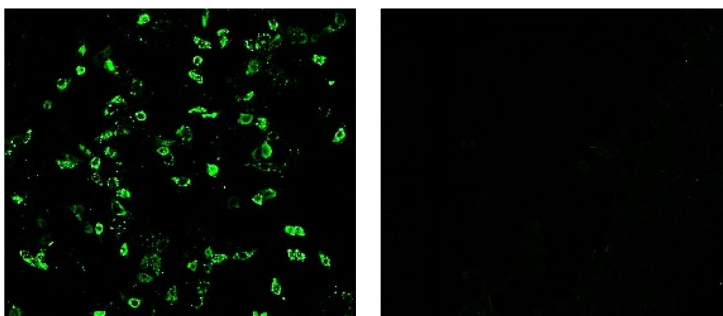


% Antigen-specific IgG subclasses



RV-immunization induces different classes of Ag-specific IgG (day 42)

Virus neutralization assay with fluorescent readout

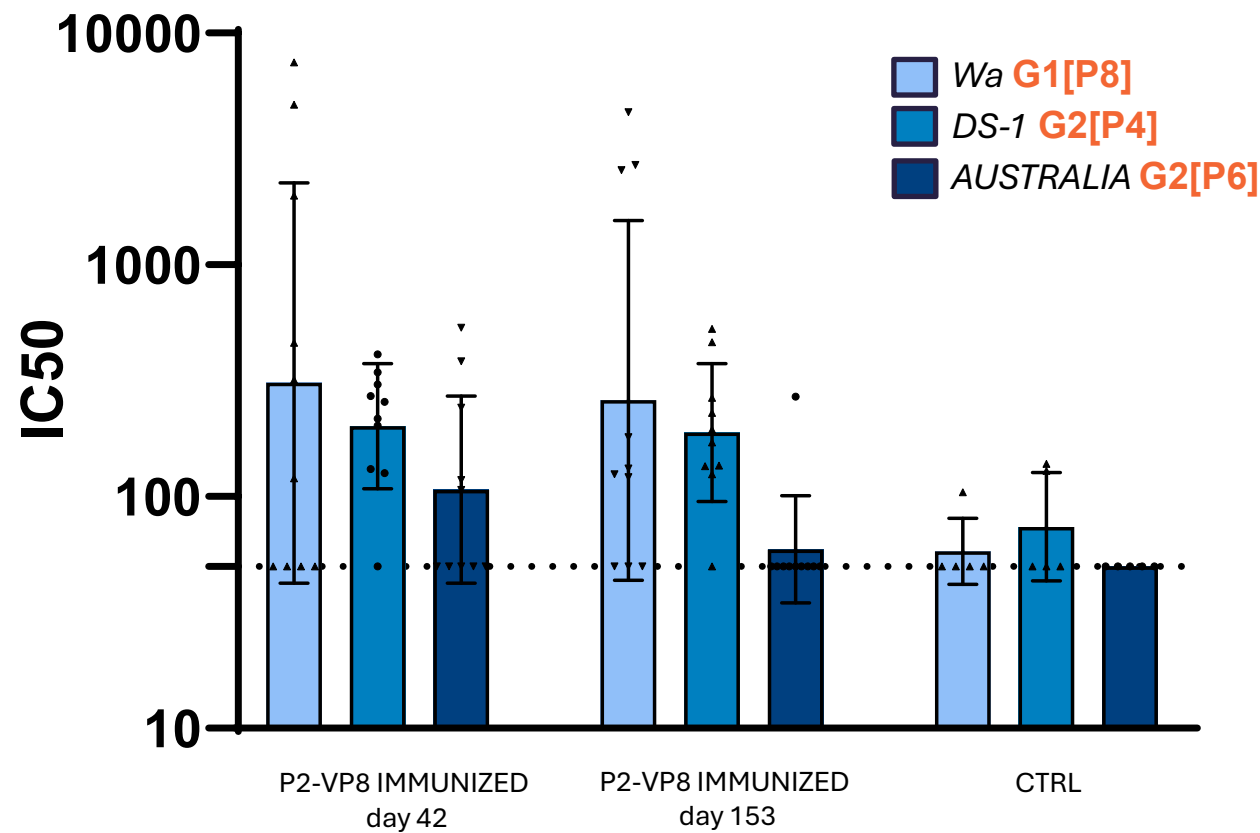


Only virus

Virus + serum

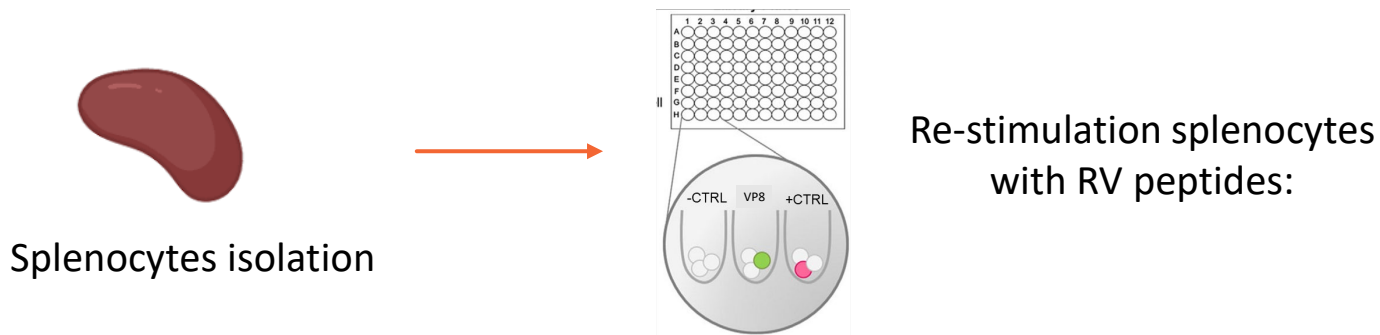
4 PL nonlinear regression analysis applied to raw data and QC criteria for assay acceptance in place

- Wa Tc-adapted **G1[P8]**
- Wi61 **G9[P8]**
- Hu/Australia/10-25-10/77 L **G2[P6]**
- DS-1 **G2[P4]**

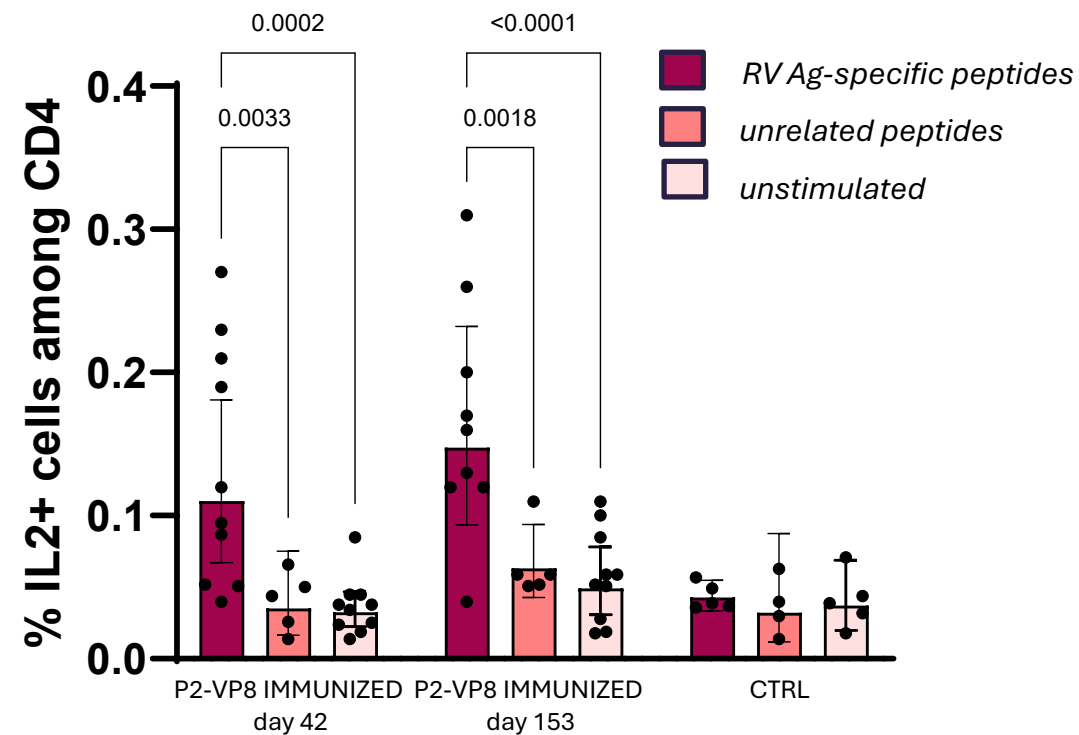
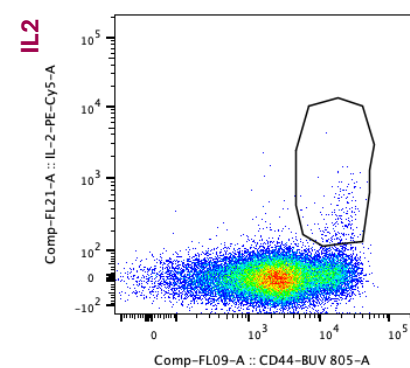
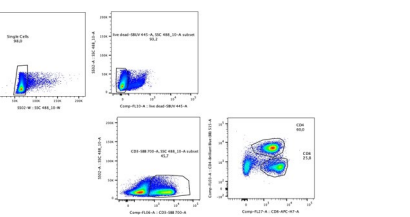
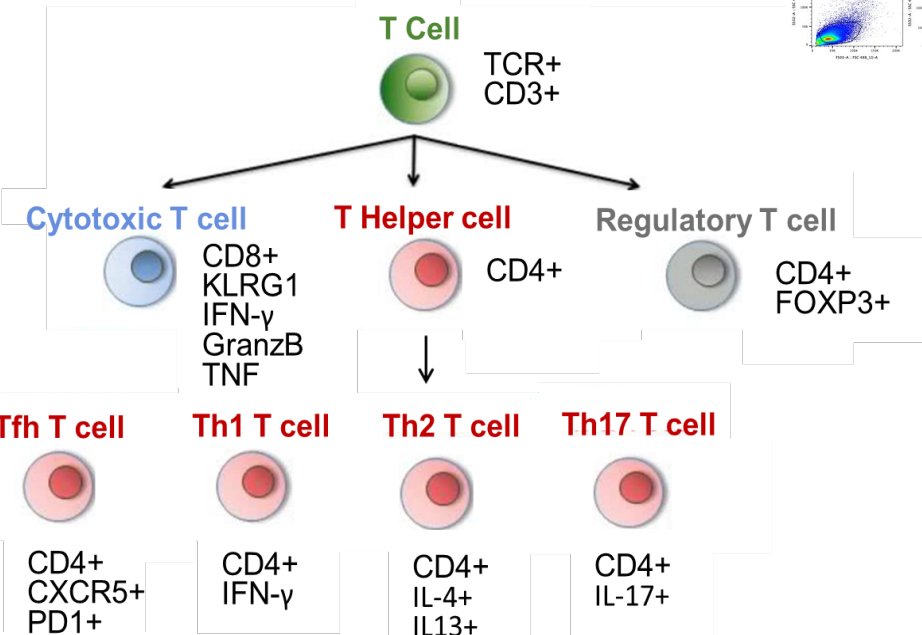


Sera from RV-immunized mice neutralize various RV strains with different IC_{50}

Evaluation of antigen-specific T cell response

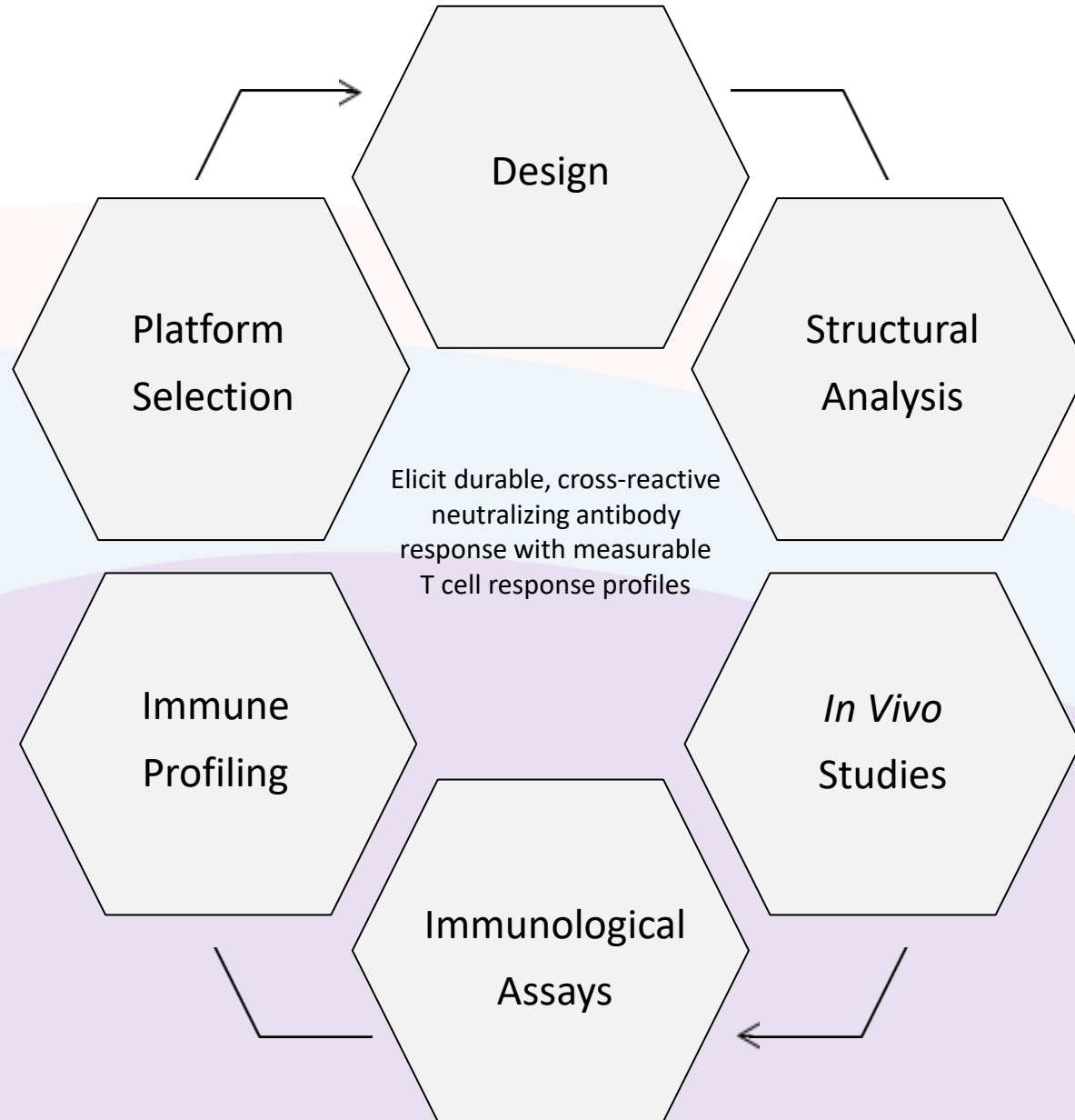


Flow cytometry

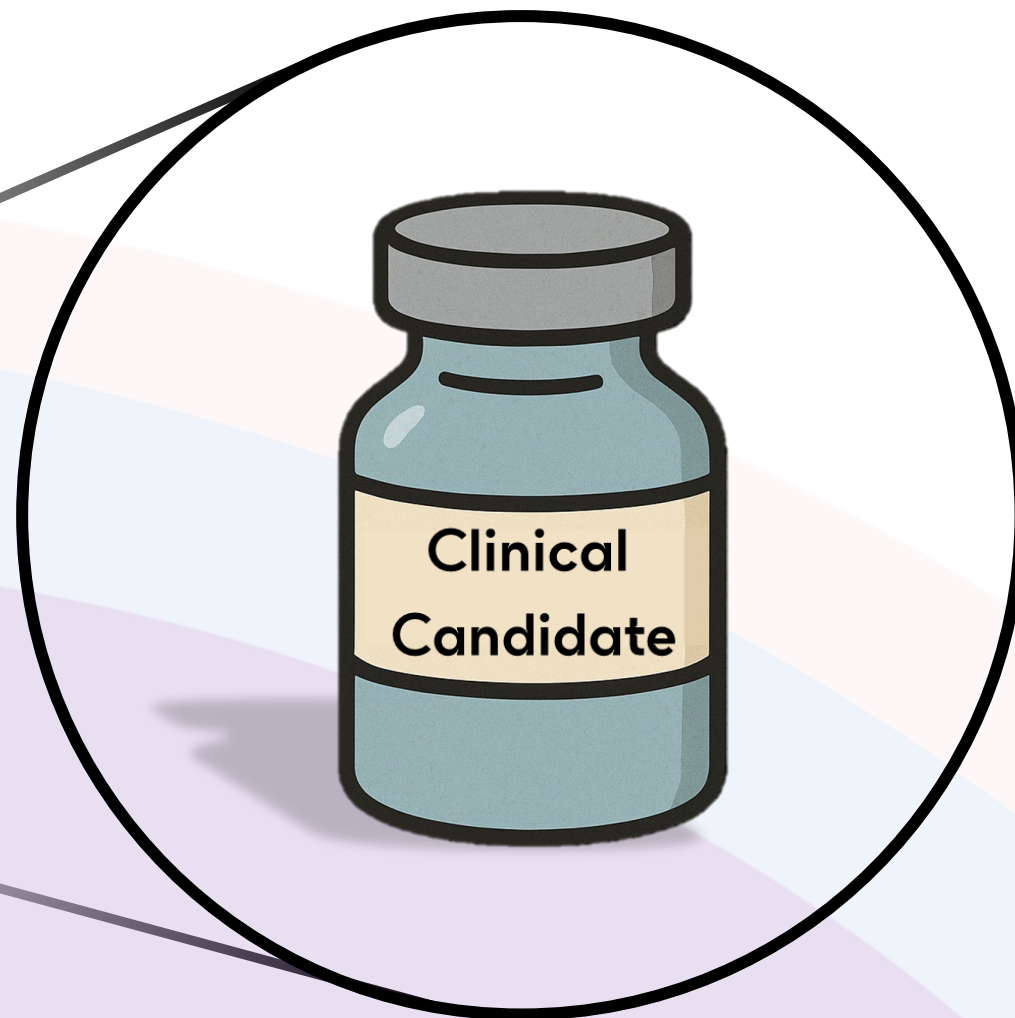


RV-immunization induces Ag-specific activation of T cells

Next generation Rotavirus vaccine design: from structure to clinical candidate



Next generation Rotavirus vaccine design: from structure to clinical candidate



Acknowledgements

GVGH



Vanessa Arato

Patrick Byrne

Melania Della Peruta

Francesca Mancini

Luisa Massai

Elena Morandi

10/27/2025

Lais Nascimento Alves

Davide Oldrini

Teresa Anne Clarisse Reyes

Mirko Scordio

Giacomo Vezzani

Nezha Darghamouni

Omar Rossi

Makrina Totsika

Umber Saeed

Miren Iturriza-Gomara

Francesco Berlanda Scorza

Rebecca Loomis

GSK Vaccines

Gianmarco Gasperini

Maria Scarselli

Paolo Cinelli

Javier Caceres

Chelsy Chesterman

Linda Feng

Bruno Galletti

Andrea Palladino

Vanessa Bol

Simona Tavarini

Stefano Tozzi

Michela Brazzoli

Animal Facility

