26th ADVAC
ADVANCED COURSE OF VACCINOLOGY

18th Stanley Plotkin Lecture: Advancing CMV Vaccine Strategies: Eliminating preventable life-long disabilities

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Nancy C Paduano Professor and Chair, Dept of Pediatrics
Weill Cornell Medicine

15 May, 2026

Les Pensières Center for Global Health, Veyrier du Lac, France

General objectives for the lecture :

- Review the historical landscape of CMV vaccine programs and trials
- Describe the immune correlates of protection against congenital CMV in human cohorts and non-human primate models
- Describe rationale design approaches for CMV vaccines

I am a consultant for Moderna, Dynavax, Kamada, Merck, and Pfizer CMV programs, and a CMV educator for Medscape

Weill Cornell Medicine
Pediatrics

NewYork-Presbyterian
Children's Hospital of New York

CMV Research Collaborators

Weill Cornell Medicine

Sallie Permar, Claire Otero, Chelsea Crooks, Erica Garcia, Krithika Karthegeyan, Hsuan-Yuan Wang, Carolyn Weinbaum, Husam Taher, Brittany Plummer + RARC!

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Cliburn Chan, Richard Barfield, Yishi Gong, Julian Sass, Sarah Valencia, Kevin Weihe, Brenna Hughes, Geeta Swamy

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***Amitinder (Miti) Kaur,** Matilda Mostrom, Margaret Gilbert, Lesli Sprehe, Elizabeth Scheef, Monica Shroyer, Joshua Taylor, Robert Blair

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NIH National Institute of Allergy and Infectious Diseases

***Special Thanks**

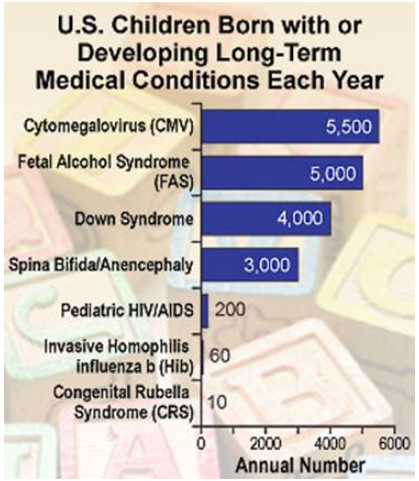
Chris Beisel and Rajeev Gautam, *Program Officers*, *Peter Barry, Scientific Advisory Board Members

NATIONAL CMV FOUNDATION

Congenital Cytomegalovirus (CMV)

- **Most common congenital infection, cause of birth defects and brain damage**
  - 1/200 (0.5%) live-born infants globally (~700,000 annually)
  - Up to 25% will have permanent disabilities (~175,000 annually)
  - Higher incidence in low SES and marginalized populations
- **Leading infectious cause of pediatric hearing loss**
  - Up to 25% of infant hearing loss due to cCMV
- **Associated with B-cell ALL risk**
  (Wiemels et al. 2019; Francis et al. 2017)
- **CMV associated with fatal pneumonia and atopy**
  (Mahtab et al, 2024; van Meel et al, 2020; Sbihi et al, 2022)
- **Associated with ADHD and autism**
  (Pesch et al. 2024; Lin et al, 2021; Topham et al 2019; Borbye-Lorenzen et al, 2025; Fang et al, 2024)

#1 priority vaccine >20 years (Natl Academy of Med)



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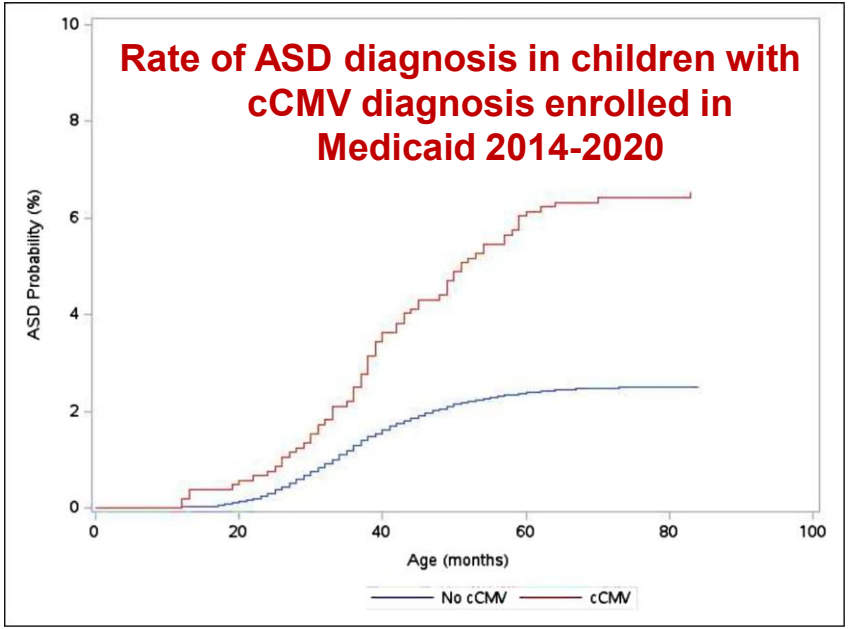
Congenital CMV and Autism

- **Congenital CMV infection is associated with risk of autism**
  - Autism 5–15× higher in cCMV

- **CMV infects the developing fetal brain and induces neuroinflammation, microglial activation, neuronal loss, and disrupted cortical organization during critical windows of development.**



Pesch et al. 2024

(Pesch et al. 2024; Lin et al, 2021; Topham et al 2019; Borbye- Lorenzen et al, 2025; Fang et al, 2024)

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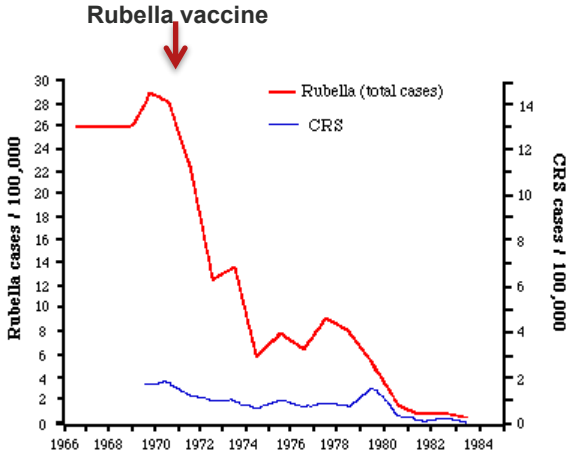
Dr. Megan Pesch

NewYork-Presbyterian Children's Hospital of New York

Impact of a CMV vaccine would mirror that of the rubella vaccine

Rubella vaccine eliminated congenital rubella syndrome in Americas



Dr. Stanley Plotkin,
Developer of rubella vaccine
Pediatrician-Scientist

"Introduction of the highly-effective rubella vaccine in 1969 led to the closure of a schools for the deaf and blind due to lack of children needing these services"

- Sam Katz, MD (Co-developer of measles vaccine, Pediatrician-Scientist)

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60+ years of CMV vaccine development, yet we still await an approved vaccine

Vaccine Platform	Phase	Efficacy
Live attenuated	Phase I,II	Reduction of disease in renal tx
Live viral vectors	Phase I	-
gB subunit	Phase I,II	**50%**
eVLP	Phase I	-
Single round DISC vectors	Phase I,II	**42%**
gB + PC subunit/MVA	Phase I	-
DNA	Phase I,II	ongoing
mRNA (gB + PC)	Phase I,II,III	**6-23%**

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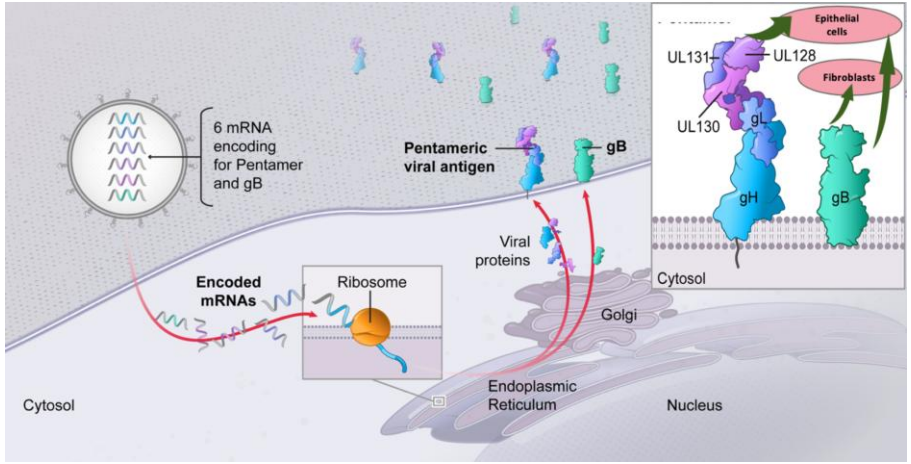
Modified from Schleiss et al, 2017

NewYork-Presbyterian Children's Hospital of New York

Phase III HCMV vaccine efficacy trial: mRNA-1647 HCMV glycoprotein B (gB) and pentameric complex (PC) antigens



moderna

CMVictory

- 8,000 seronegative women aged 16-40 enrolled in US and Europe
- No major safety events
- Final efficacy = 6-23%

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Gap in knowledge impeding development of a CMV vaccine:

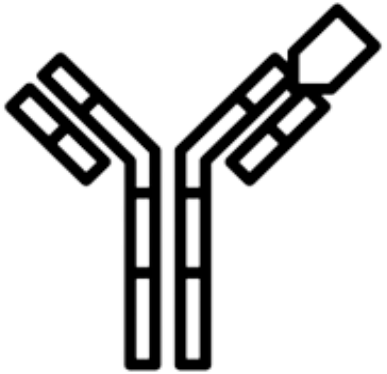
What maternal immune responses are protective against maternal acquisition and/or congenital CMV transmission?

Mother-infant cohort studies

Nonhuman primate model

Vaccine immune correlates

Reverse vaccinology



What are the immune correlates of protection against HCMV acquisition in partially-protective vaccine trials?

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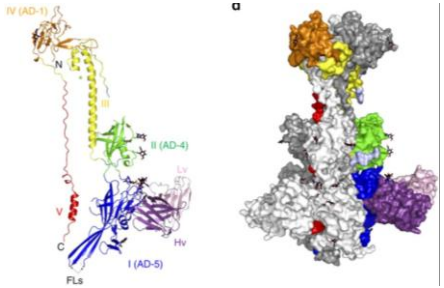
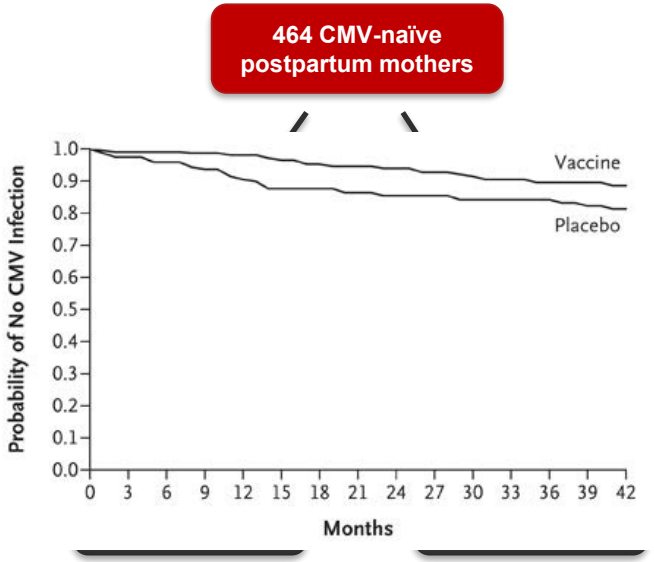
HCMV gB/MF59 vaccine was 50% protective against maternal CMV acquisition in 2 Phase 2B trials

- Most efficacious CMV vaccine to-date
- 2 phase IIb trials: seronegative, postpartum and adolescent women
- Immunized with gB (Sanofi) (20µg) + MF59 squalene adjuvant (Novartis) at 0, 1, 6 mos
- Primary Endpoint: Time to HCMV acquisition

Postfusion gB



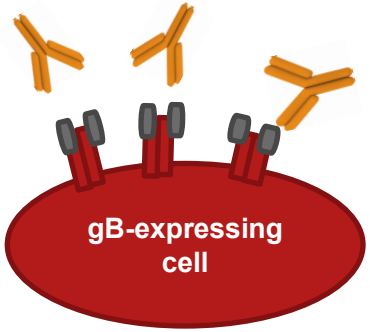


→50% Efficacy in preventing maternal primary infection (p = 0.02)

→45% Efficacy in prevention of adolescent infection (p = 0.08)

(Bernstein, *et al.* Vaccine, 2016, Pass, *et al.* NEMJ, 2009)

Combined gB/MF59 vaccine trial immune correlate: binding to native-like gB

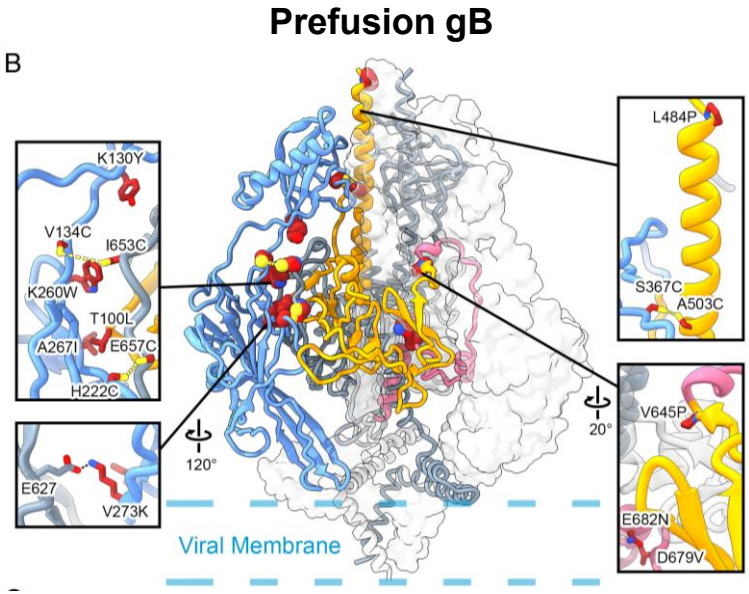


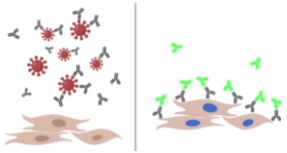
	Assay	p	FDR
1	**gB-transfected cell IgG binding (% binding)**	**0.008**	**0.190**
2	Full-length gB IgG binding (LogMFI)	0.04	0.307
3	gB Domains I+II IgG binding (LogMFI)	0.04	0.307
4	gB ectodomain IgG binding (LogMFI)	0.058	0.334
5	ADCP of AD169r-GFP (% phagocytosis)	0.115	0.385
6	ADCP of TB40/E (% phagocytosis)	0.122	0.385
7	gB Domain II IgG binding (LogMFI)	0.135	0.385
8	gB IgG binding (Log AUC)	0.146	0.385
9	gB-specific IgG1 subclass (LogMFI)	0.151	0.385
10	gB Domain I IgG binding (LogMFI)	0.169	0.389
11	Whole virion (TB40/E) IgG Avidity (RAI)	0.205	0.395
12	FcγR3a V158 binding to gB-specific IgG (LogMFI)	0.206	0.395
13	FcγR1a binding to gB-specific IgG (LogMFI)	0.294	0.507
14	FcγR2b binding to gB-specific IgG (LogMFI)	0.309	0.507
15	Whole virion (TB40/E) IgG binding (LogAUC)	0.354	0.513
16	FcγR2a H131 binding to gB-specific IgG (LogMFI)	0.357	0.513
17	gB IgG Avidity (RAI)	0.451	0.610
18	gB AD-1 IgG binding (LogMFI)	0.529	0.677
19	gB-specific IgG3 subclass (LogMFI)	0.559	0.677
20	Neutralization of Towne virus on MRC5 ($LogID_{50}$)	0.728	0.837
21	gB-specific IgG2 subclass (LogMFI)	0.809	0.887
22	gB-specific IgG4 subclass (LogMFI)	0.93	0.948
23	gB AD-2 Site 1 IgG binding (LogMFI)	0.948	0.948

Jenny Jenks, MD, PhD

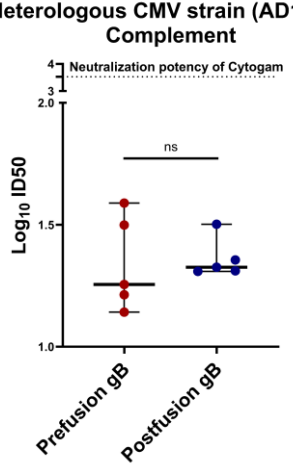
Jenks, Chan, Permar et al, Sci Transl Med 2020

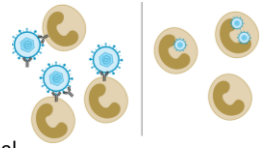
Pre-fusion gB as vaccine immunogen did not elicit superior anti-viral humoral immunity



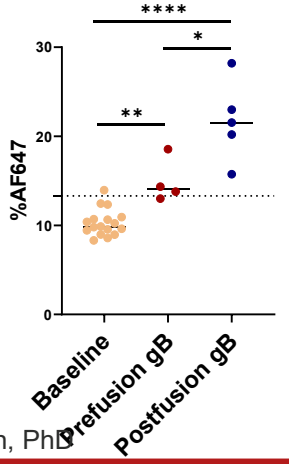


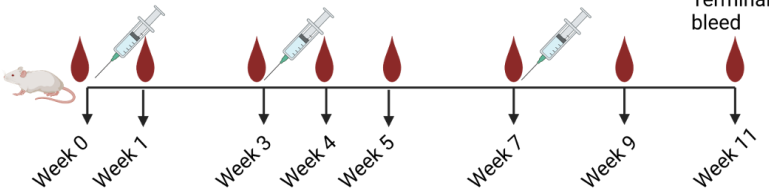
Neutralization (fibroblast, in the presence of complement)





ADCP

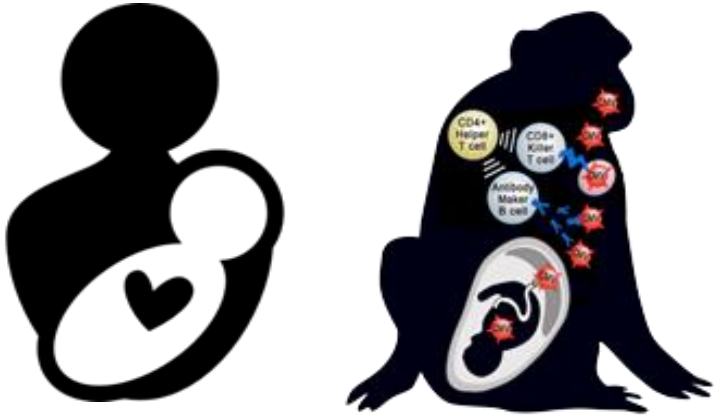




Sponholtz, McLellan et al, PNAS, 2024

Krithika Karthegeyan, PhD

What immune responses are required to protect against congential CMV?



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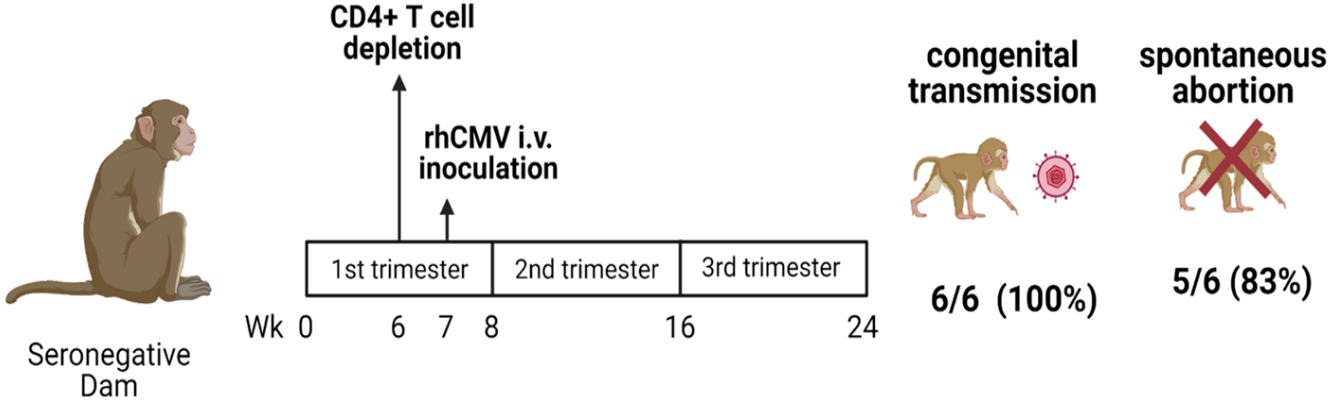
Pre-existing maternal IgG responses protective against cCMV in a high-risk preclinical NHP model



Seropositive Dams	**1/6 (20%) (0%)**	**0/6**
Seronegative Dams + IgG	**2/6 (33%) (0%)**	**0/6**

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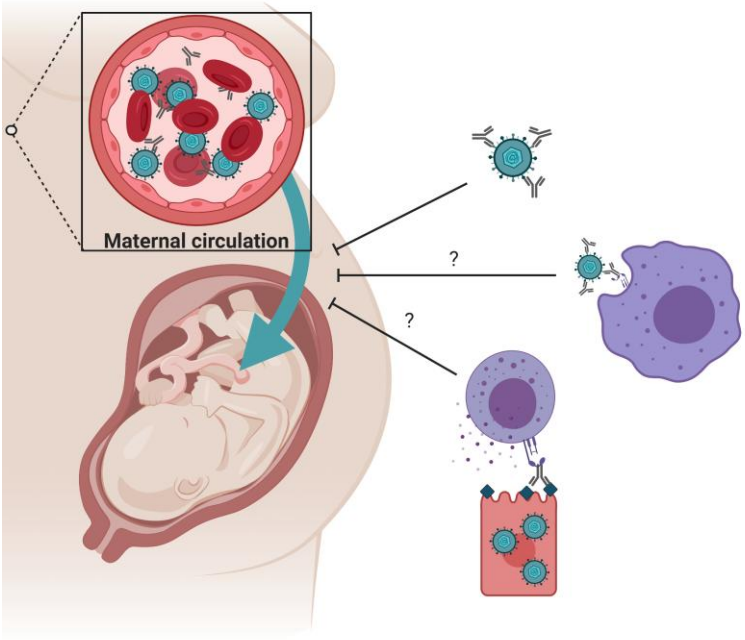
Mostrom, Kaur et al, Plos Path, 2023
Nelson, Kaur, Permar, JCI-Insight 2017
Bialas, Kaur, Permar, PNAS 2015

Graph created with *Biorender.com*

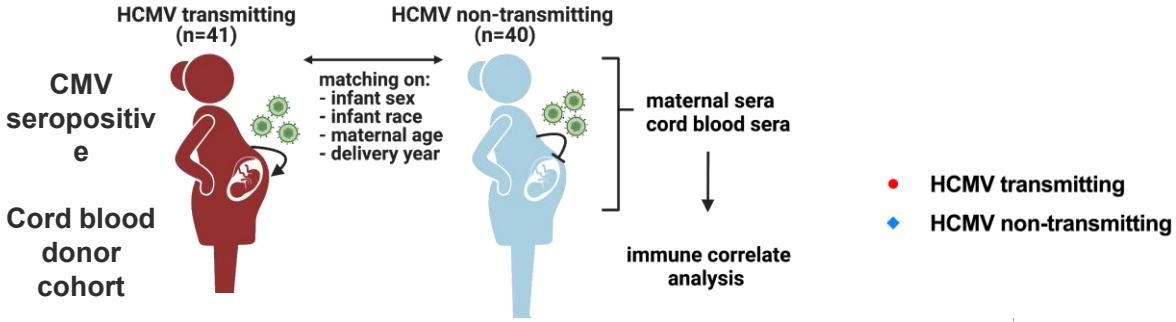
NewYork-Presbyterian Children's Hospital of New York

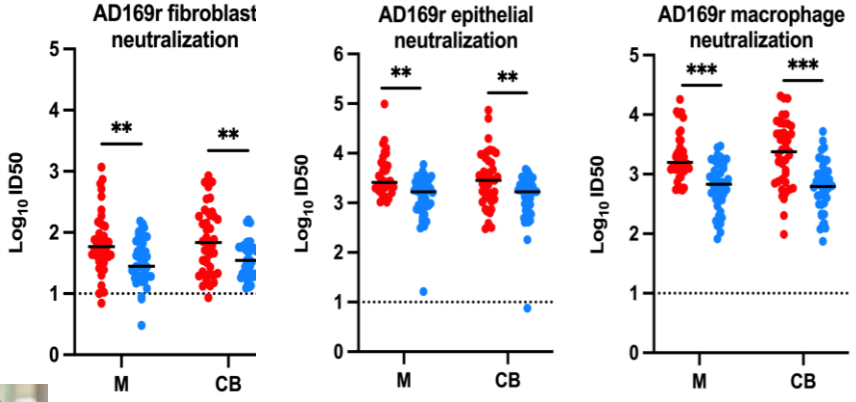
What antibody functions associate with protection from fetal CMV infection?

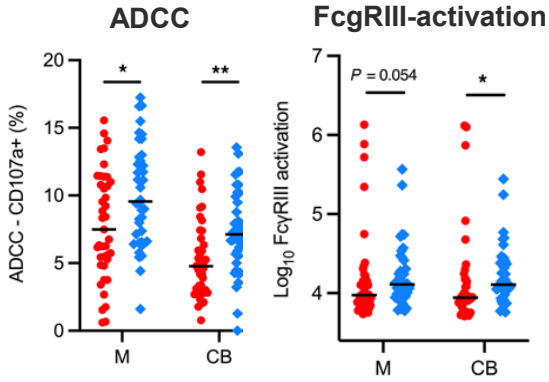


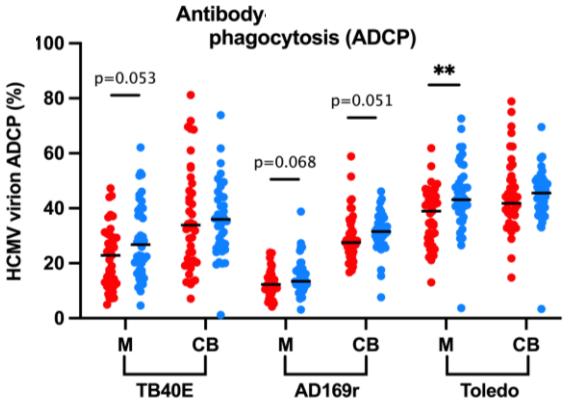
- Antigen binding
- Neutralization
- Antibody dependent cellular phagocytosis (ADCP)
- Antibody dependent cellular cytotoxicity (ADCC)

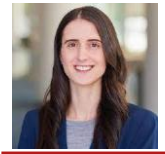
Maternal Fc-mediated non-neutralizing antibody responses correlate with protection against congenital CMV infection











Eleanor Semmes, MD, PhD

Semmes, Permar et al. JCI, 2022

M = maternal sera

CB = cord blood sera

Defining immune correlates of protection against cCMV and disease
MFMU HIG Clinical Trial

Chelsea M. Crooks, PhD

>200,000 pregnancies screened for CMV

713 participants with acute, primary CMV[1]

No acute CMV detected

399 participants 1:1 randomized into trial

Samples for immune analysis collected prior to treatment

Placebo

CMV Hyperimmune Globulin Treatment

Trial stopped early due to futility of response

399 participants

78 transmission events[2]

321 no evidence of transmission

B cell

T cell

NK cell

Define humoral & cellular immune response

Hughes et. al. *NEJM.* 2021

[1]**Primary CMV Infection:** positive IgM with low avidity IgG or evidence of maternal IgG seroconversion
[2]**Transmission:** fetal loss with pathologic evidence of CMV infection or detection in amniotic fluid and/or infant urine or saliva prior to 21 days of life

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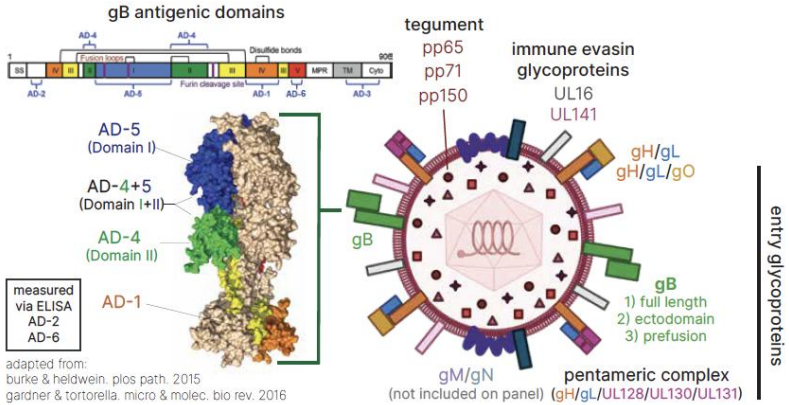
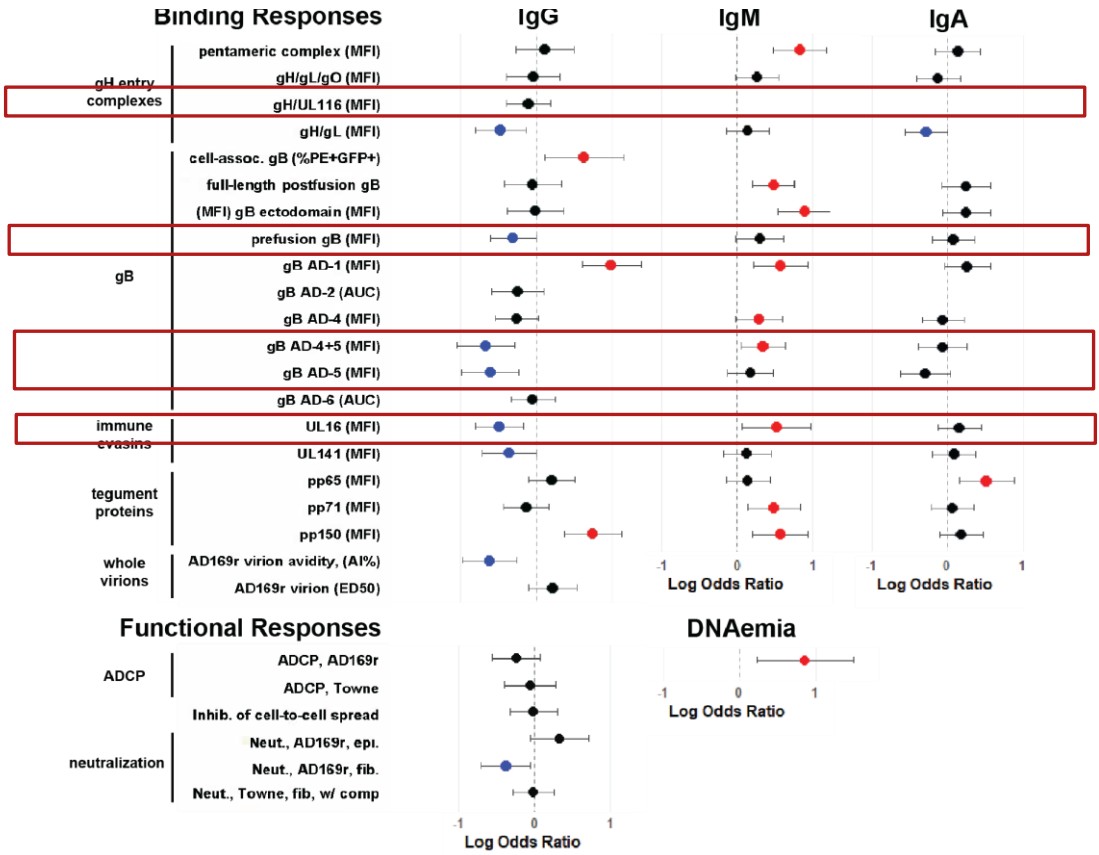
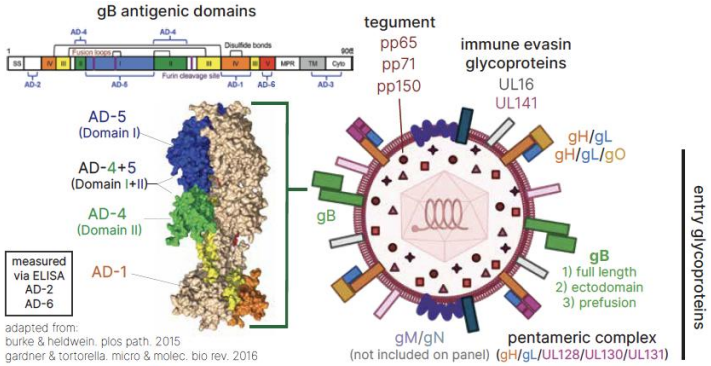
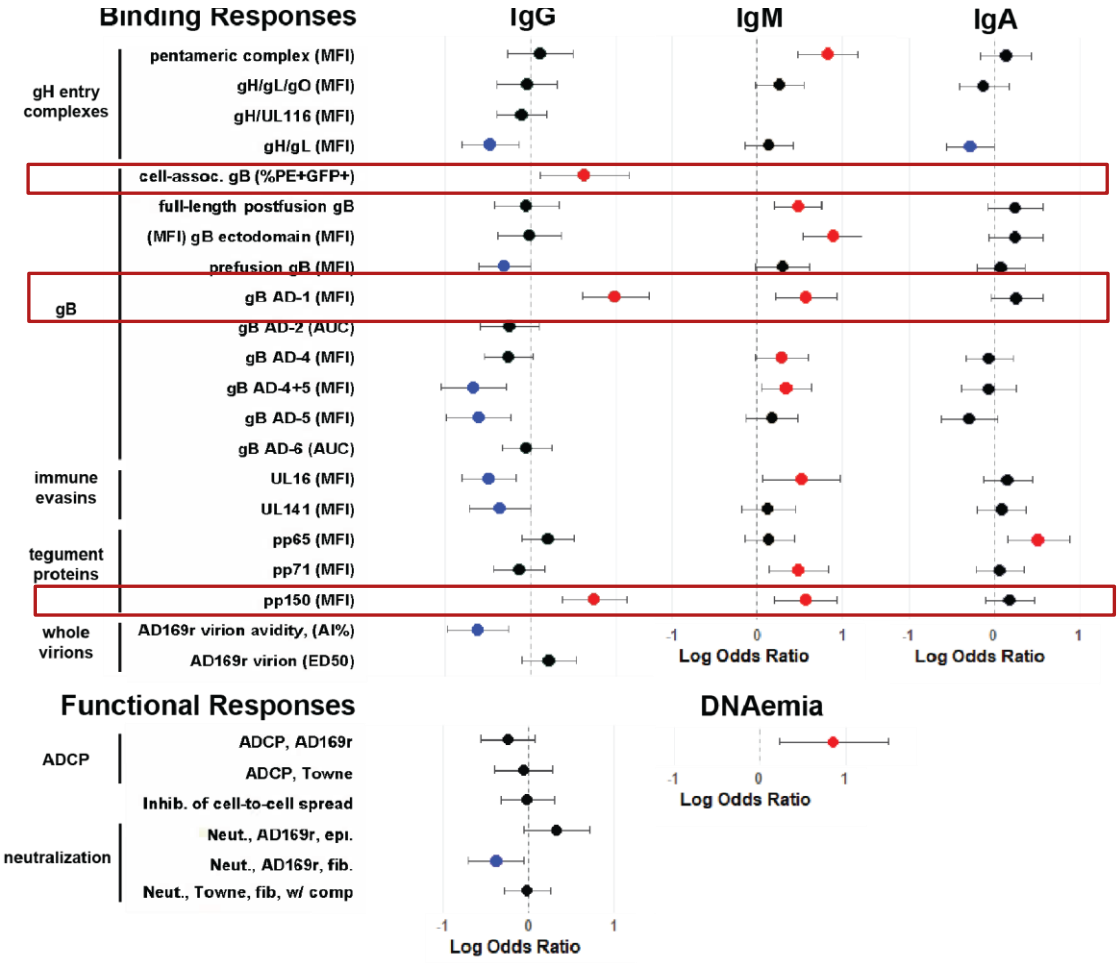
Humoral immune correlates of cCMV transmission following acute infection



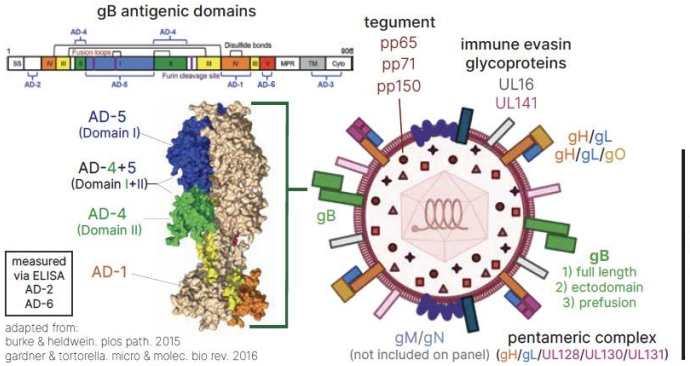


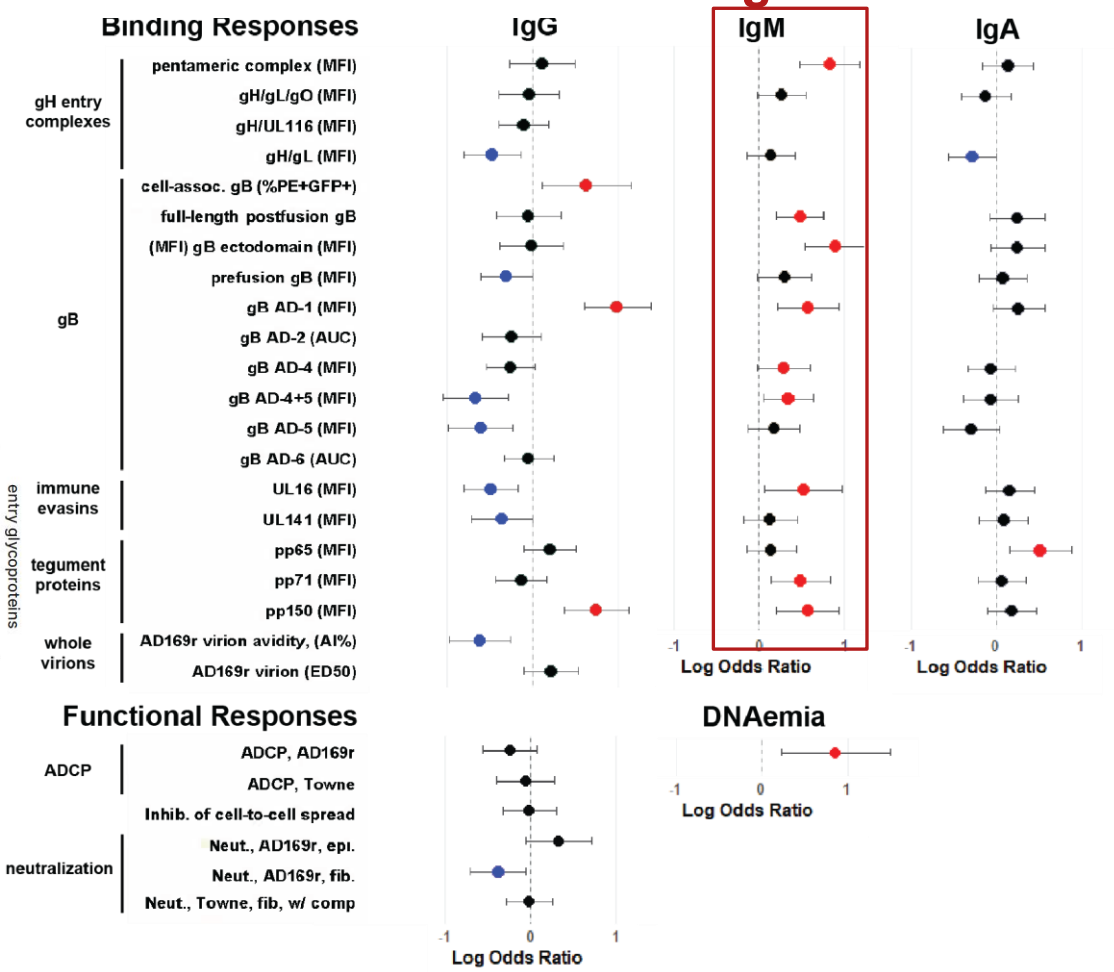
Humoral immune correlates of cCMV transmission following acute infection



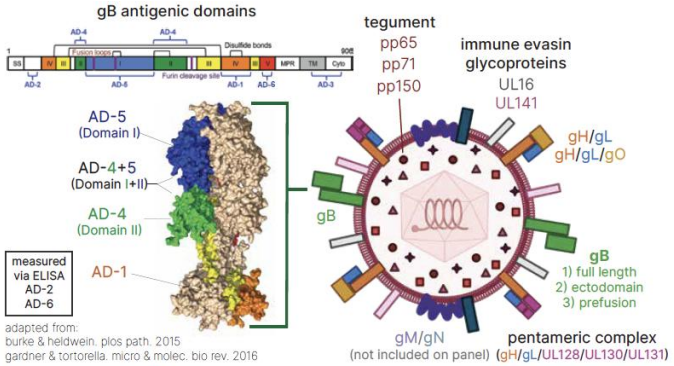


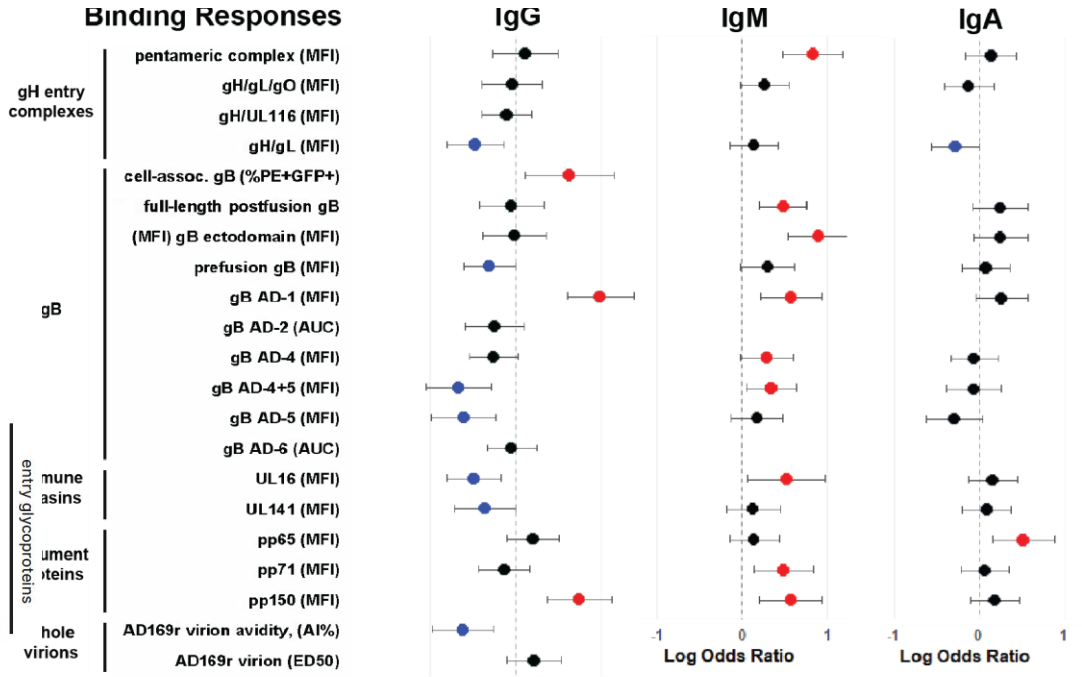
Humoral immune correlates of cCMV transmission following acute infection



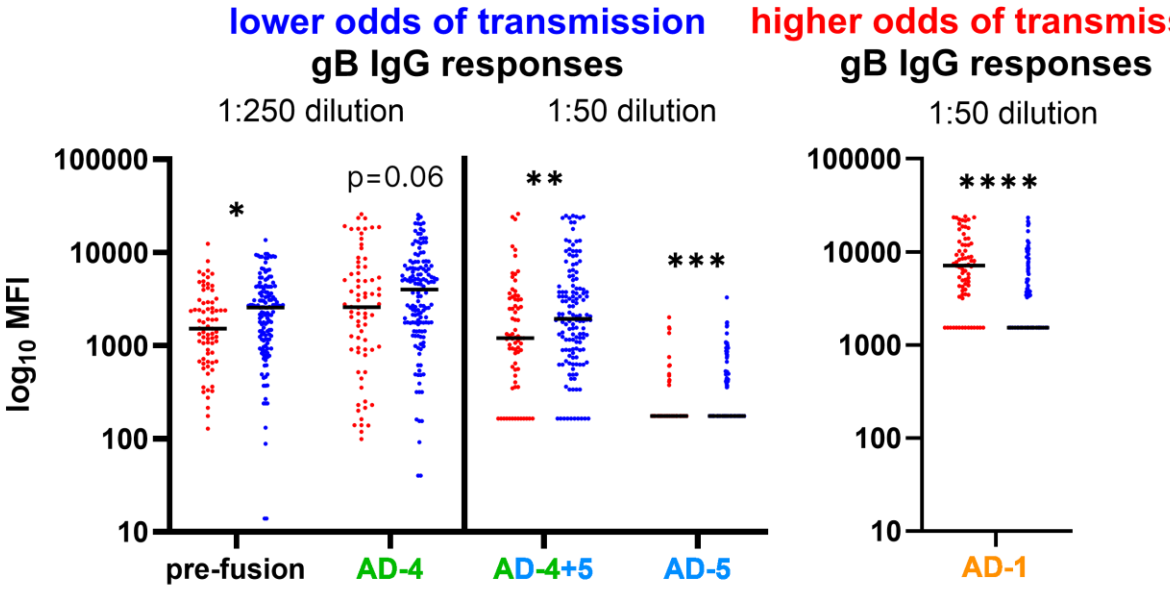


Humoral immune correlates of cCMV transmission following acute infection





Design gB antigens that enhance IgG response to domains associated with decreased risk of placental transmission



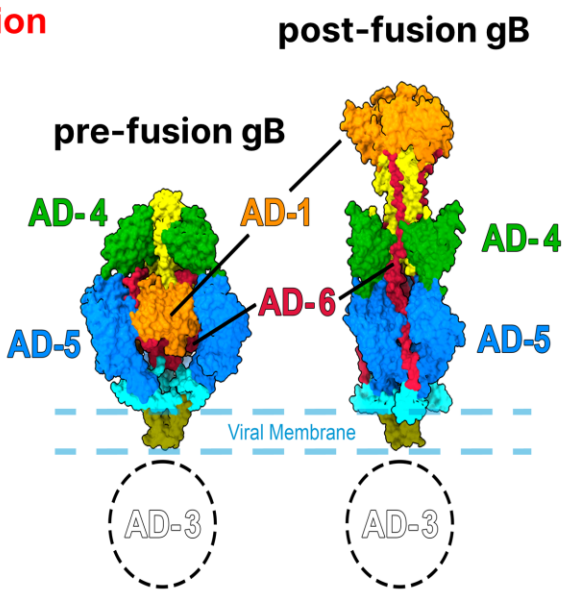
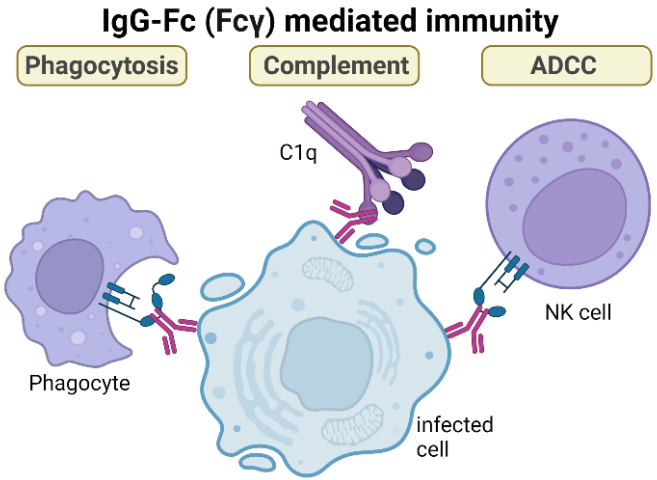


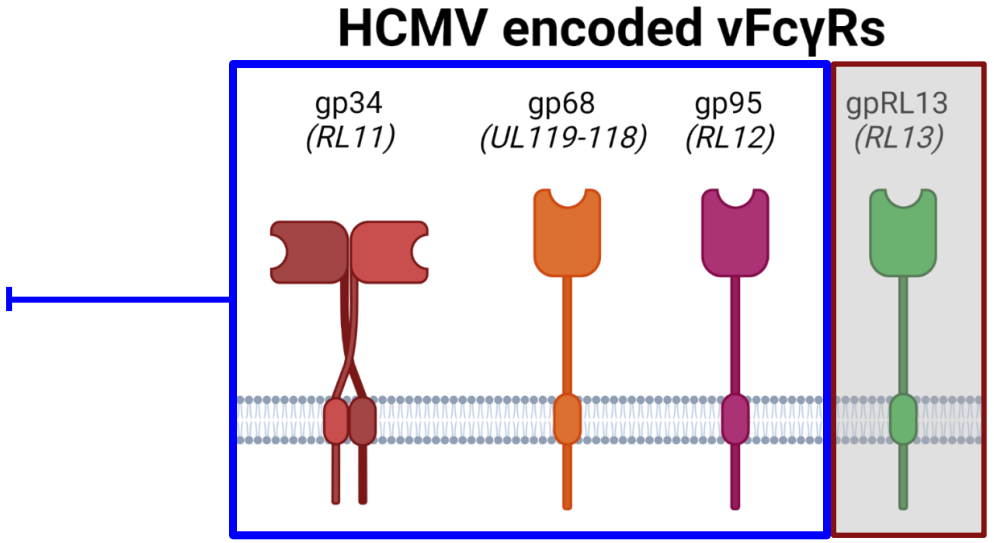
figure generated by Madeline Sponholtz
Karthigeyan et al. *JVI* 2025.

data generated by Adelaide Fuller
conditional logistic, likelihood ratio test, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

How can anti-HCMV immunity be rationally enhanced, to be >50% protective?

HCMV encodes IgG Fc-binding glycoproteins that interfere with IgG function





adapted from Corrales-aguilar et al. Semin Immunopathol 2014

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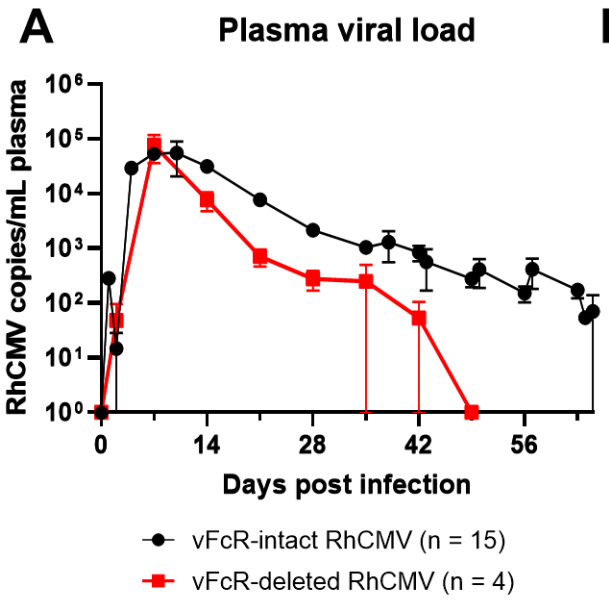
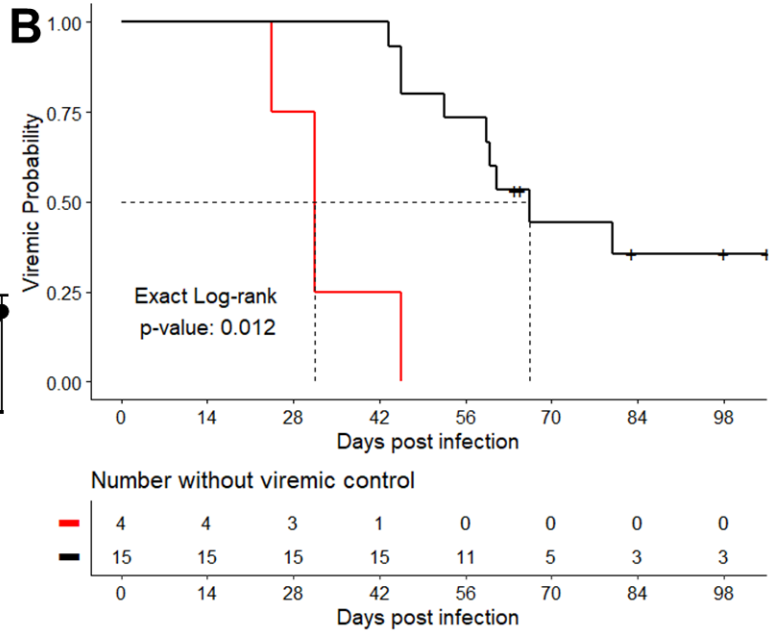
26

vFcγR-deleted RhCMV is rapidly contained following primary infection

RhCMV negative macaques (i.v. infection)

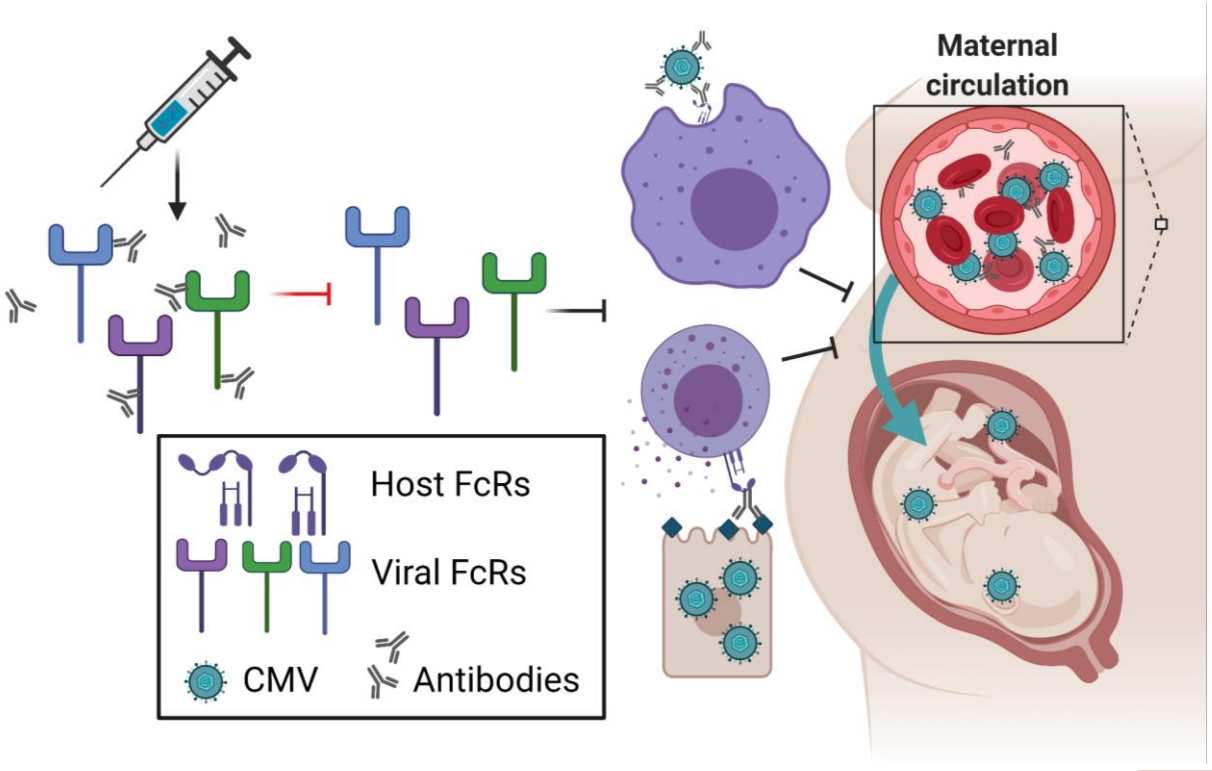




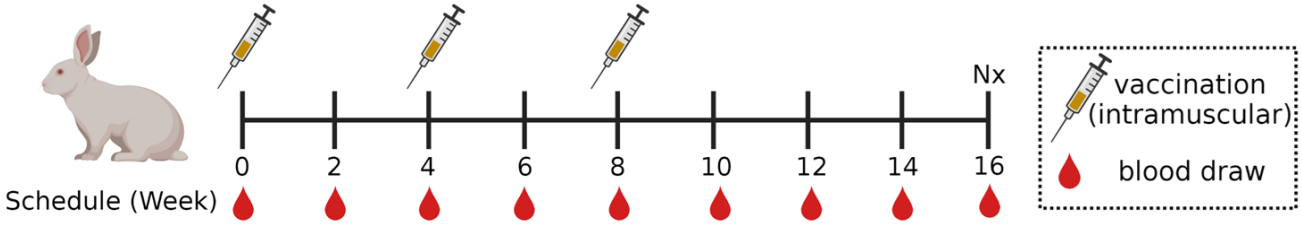
Otero, Petkova, Hengel, Kaur, Permar, Fruh, Malouli, Kolb et al, Nature Communications

Can Fc mediated immunity be improved by targeting vFcγRs through vaccination?

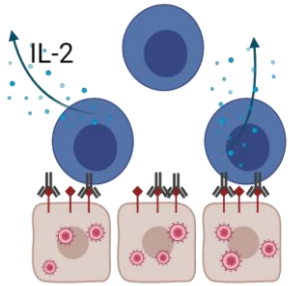
Goal: Exceeding natural immunity

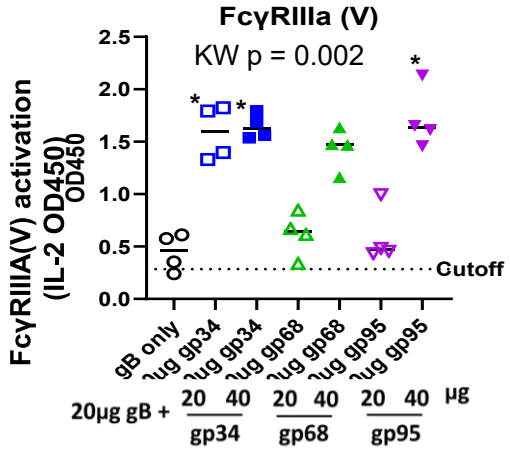


Host FcR activation enhanced by inclusion of vFcγRs in a rabbit immunogenicity model



Project led by Claire Otero, PhD
Diagrams created using Biorender
Assay described in Corrales-Aguilar, et al. Journal of Immunological Methods, 2013





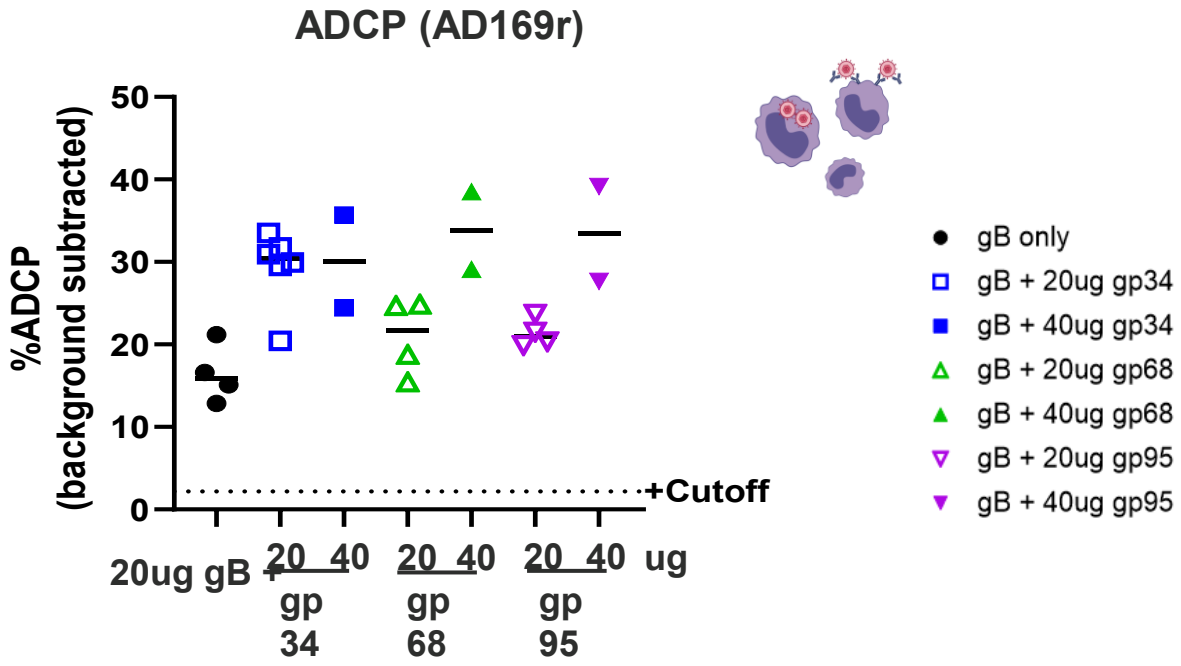
Week 10 post prime (peak immunogenicity)

Cutoff = AVG + 3SD of wk 0

Weill Cornell Medicine Pediatrics

NewYork-Presbyterian Children's Hospital of New York

Anti-CMV ADCP improved with addition of vFcRs to gB vaccination



Weill Cornell Medicine Pediatrics

NewYork-Presbyterian Children's Hospital of New York

Next generation CMV vaccine design: Achieving >50% efficacy

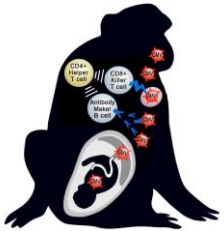
- **Antibody-based vaccines can be effective**
  - Fc-mediated effector function responses required
  - Use immune correlates of the endpoint that matters: cCMV

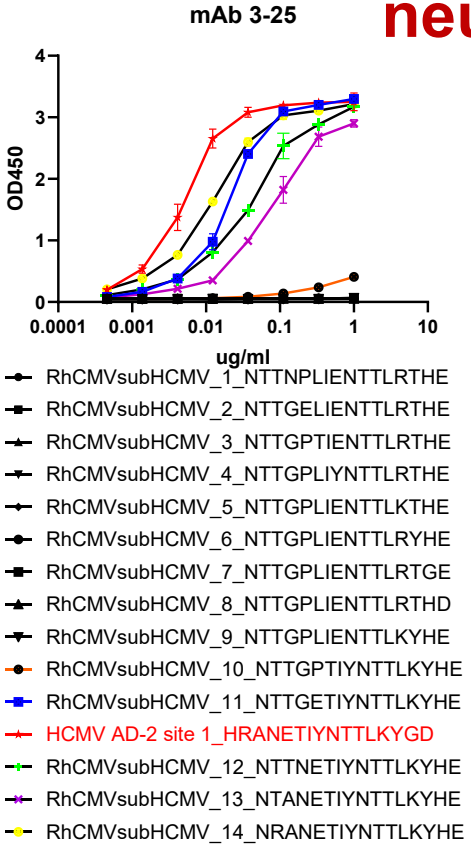
- **Optimize conformation of structure glycoproteins**
  - Prefusion and antigenic domain-based structural design of glycoproteins
  - Epitope display, based on immune correlate studies

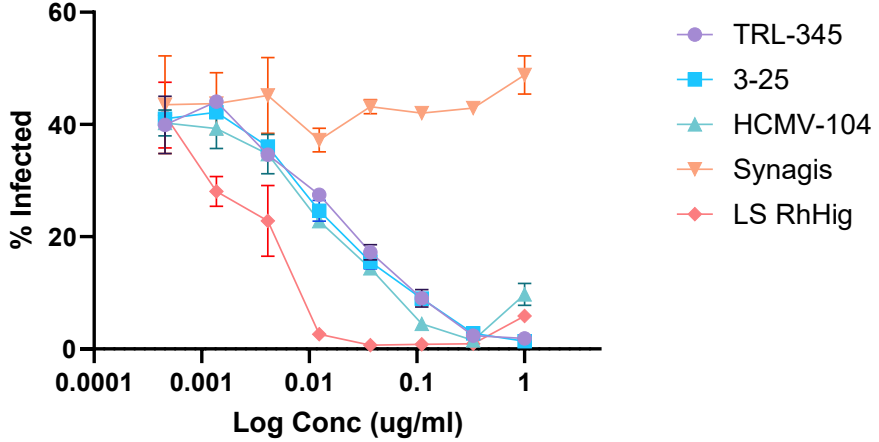
- **Target the virus' immune evasion strategies**
  - vFcRs to improve Fc-mediated immunity

- **Use tractable animal models of CMV acquisition and placental transmission to derisk clinical vaccine trials**

Nonhuman primate model of anti-HCMV immunotherapy: RhCMV-HCMV chimeric viruses susceptible to anti-HCMV gB neutralizing mAbs

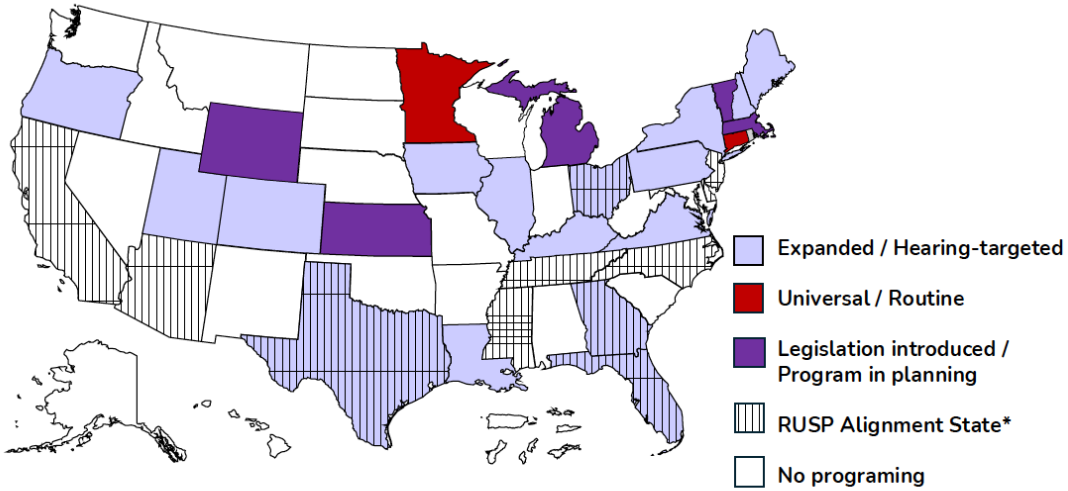






Daniel Malouli, Libby Mitchell, Sherry Wang

Advocacy for universal newborn cCMV testing in US



Lisa Saunders, cCMV mom and advocate
Daughter Elizabeth

1. **Assembly Bill A3956**: "Requires cytomegalovirus screening for every newborn..."

2. **Assembly Bill A3074**: "Requires reporting of positive cytomegalovirus results." Newborns "Shall be referred to a Pediatric Infectious Disease Specialist and hearing/eye exam before 4 weeks of age"

NY Assembly member
Linda Rosenthal
District 67

Actress Carrie Coon
cCMV mom

Dr. Mark Schleiss
Champion of MN Universal CMV testing

Advocacy Matters for Them

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Weill Cornell Medicine
Pediatrics

NewYork-Presbyterian
Children's Hospital of New York

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