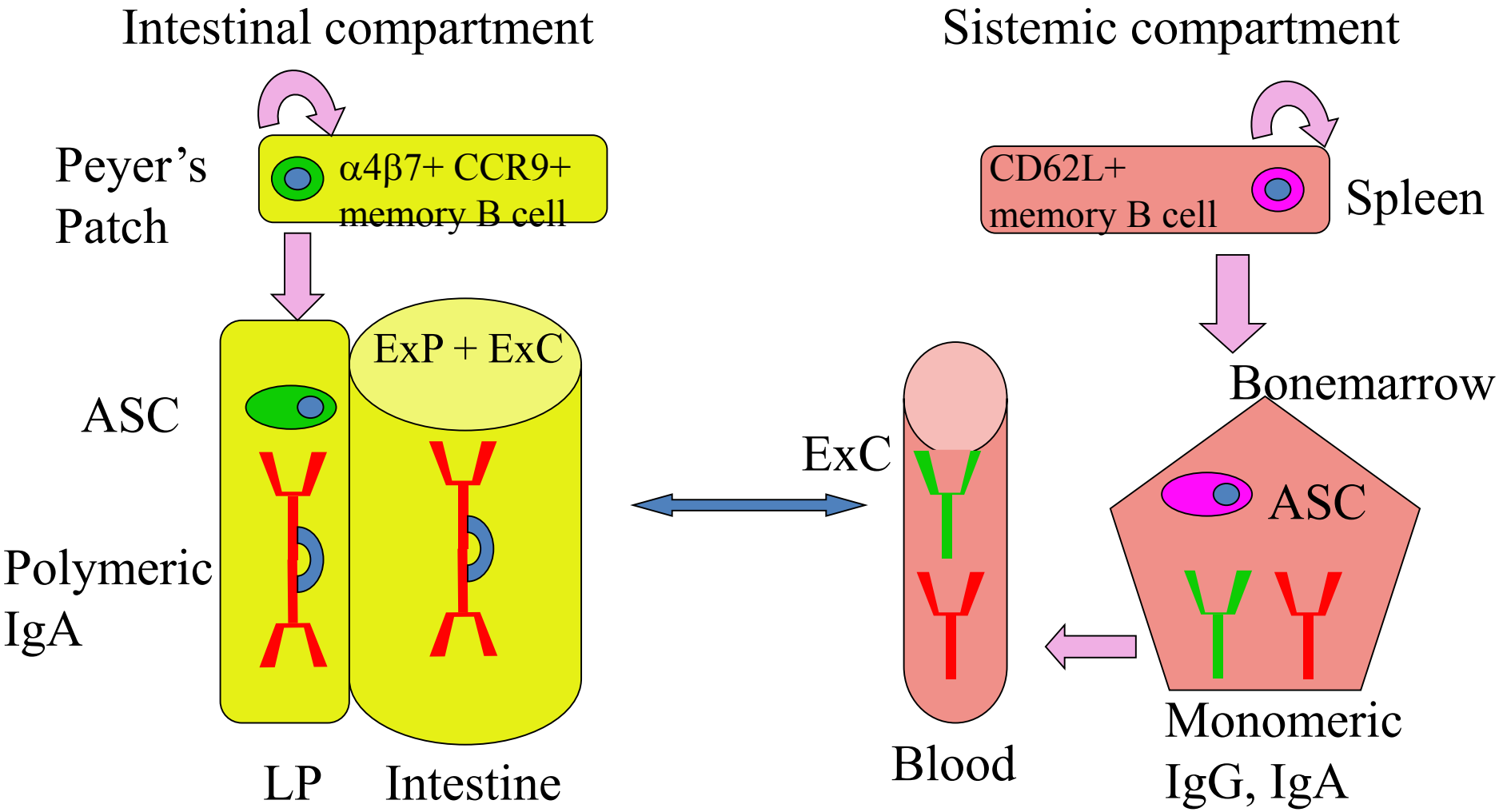
Rotavirus immune responses and correlates of protection (CoP)

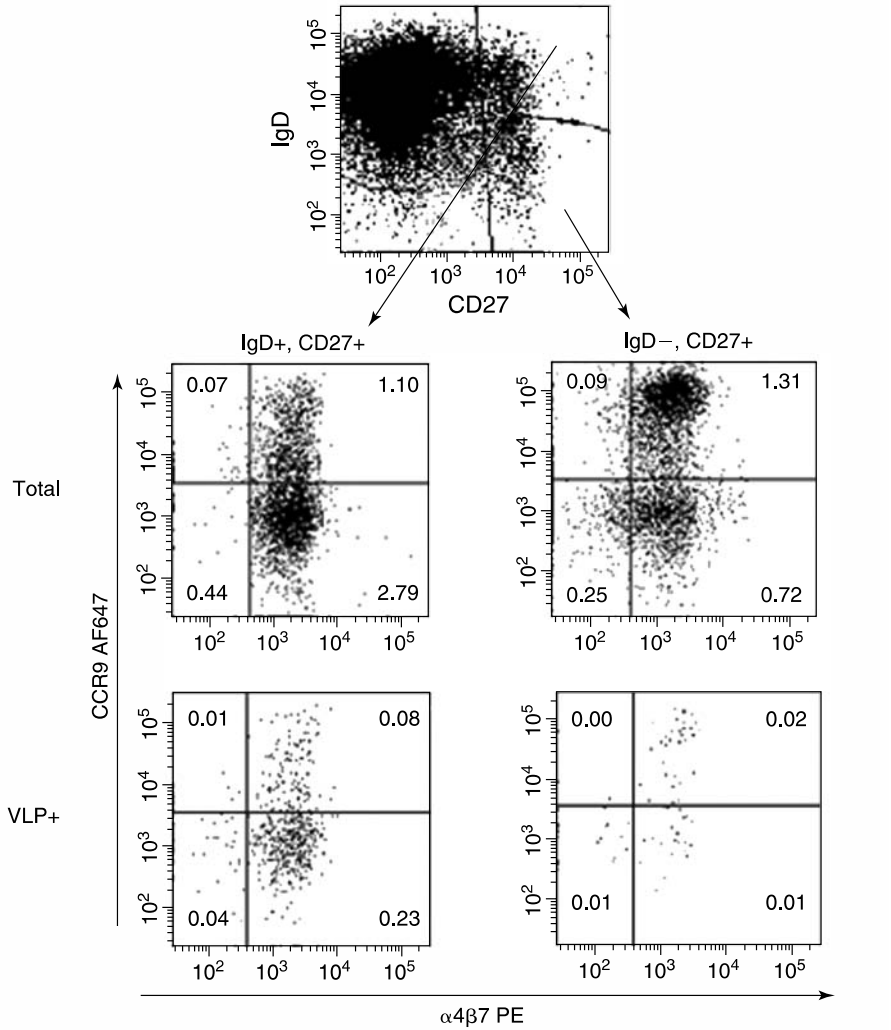
Juana Angel, Manuel Franco

Compartmentalization of the immune system



Vaccine 24 (2006) 2718–2731

RV-memory B cells with an intestinal homing phenotype in vaccinees



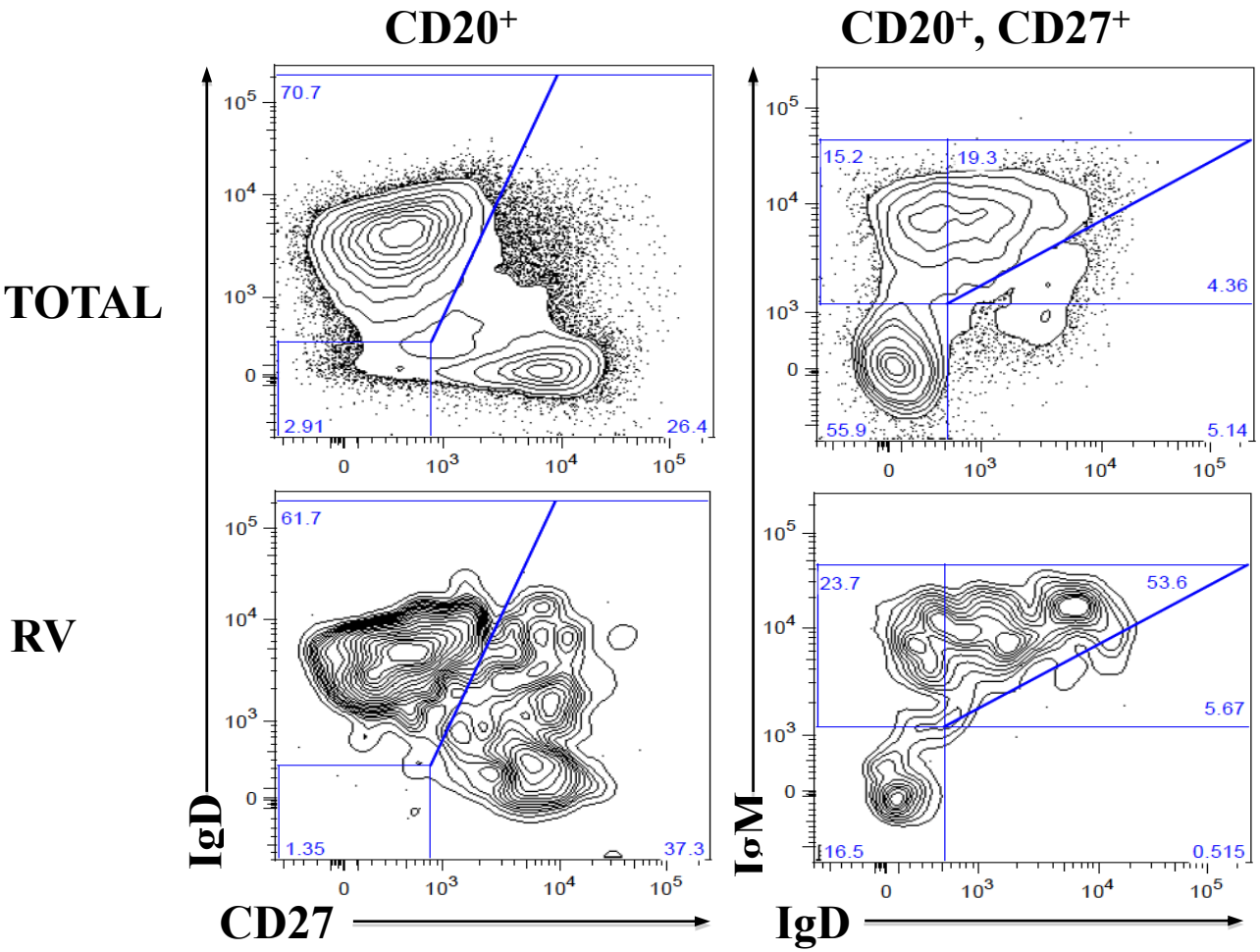
Serum RV-IgA and RV-specific IgD-, α4β7+, CCR9+ mBc correlate weakly (rho< 0.2) with protection after D2 when vaccinees and placebo recipients are considered together

Rojas OL, et al. Viral Immunol. 2007;20(2):300-11.

Two problems

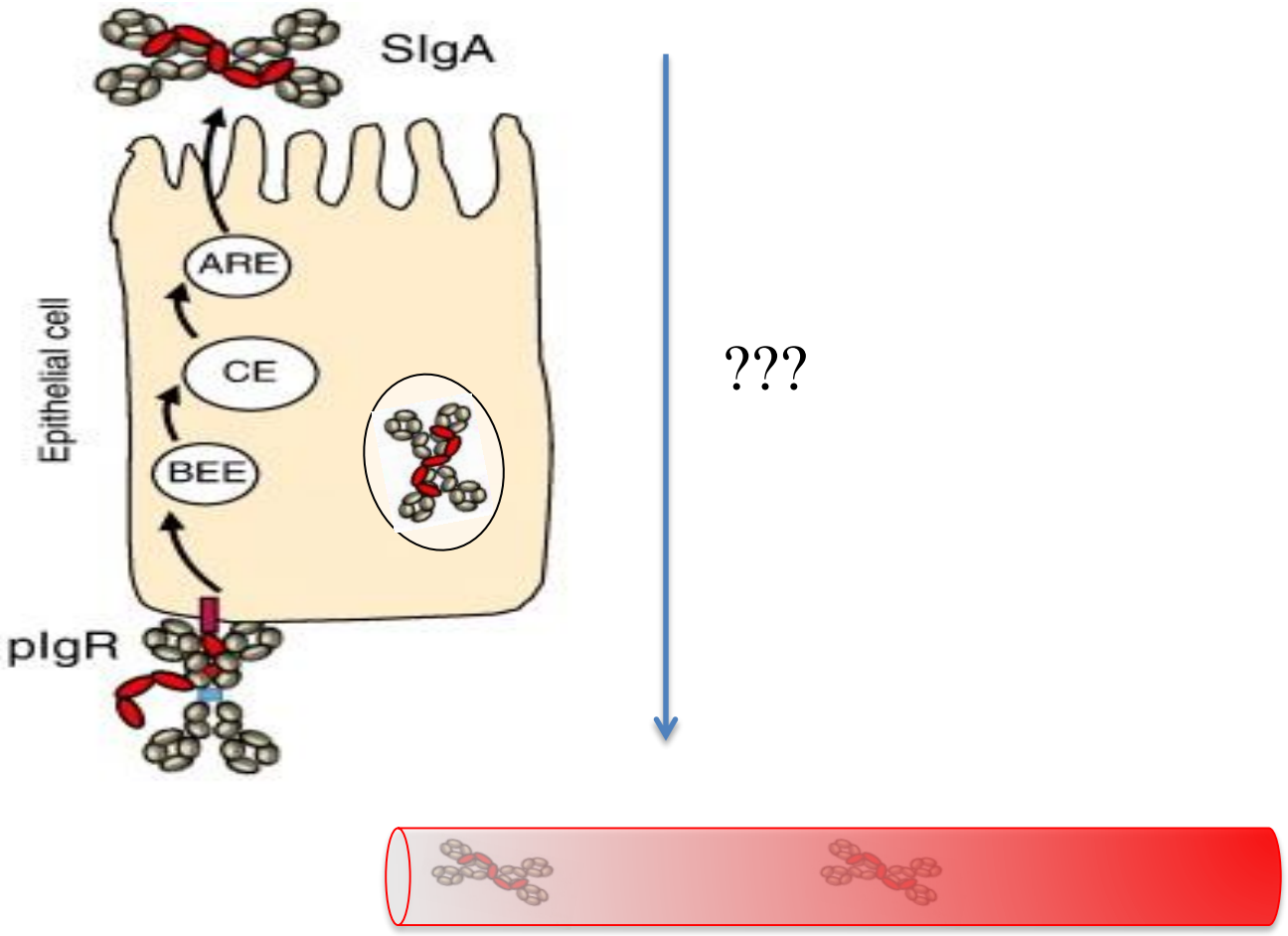
- Frequencies of RV-specific mBc are not different between vaccinees and placebo recipients and do not correlate well with protection.
- Are we measuring the relevant cells?
- Protection is higher than frequency of children that have RV-IgA.
- Can we indirectly measure the “missing” intestinal antibodies?

RV-specific mBc are enriched in the IgM^{hi}, IgD^{low} subset



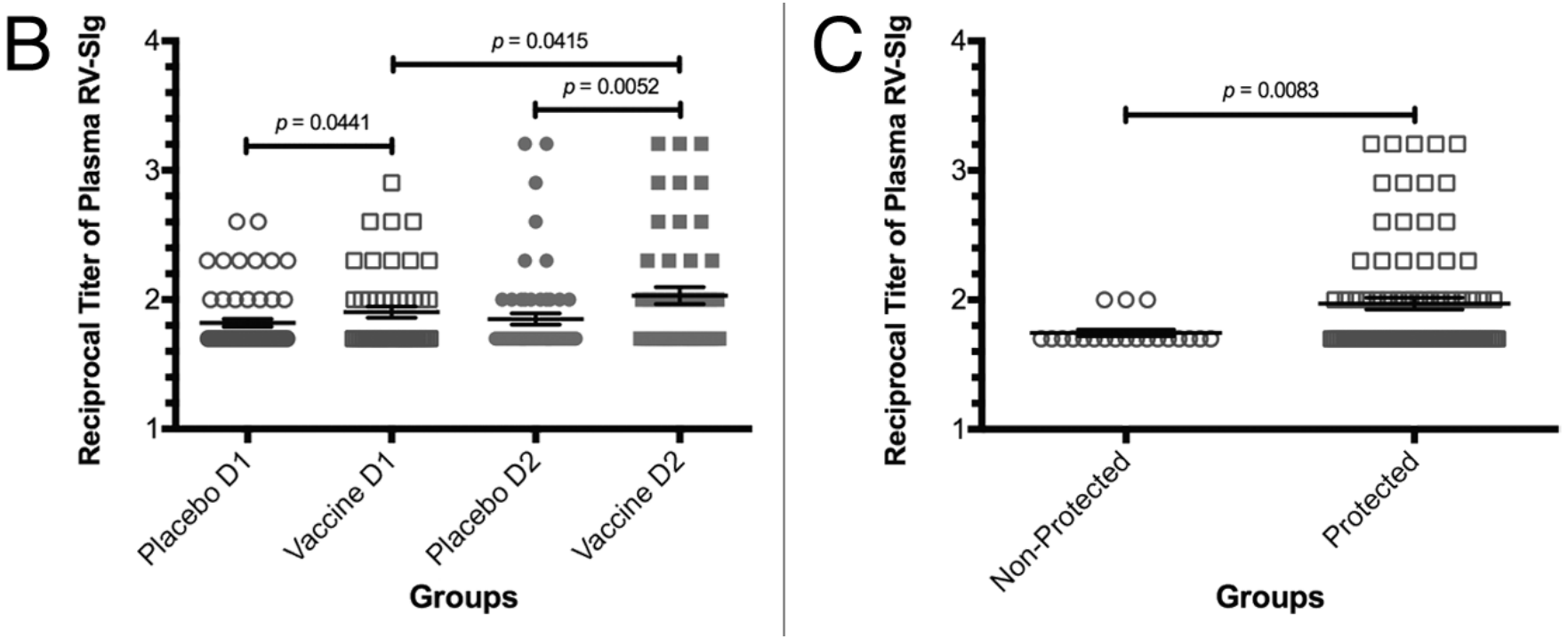
J Virol. 2012 Vol 86 p.10829-40. PLOS ONE 2014 Vol 9, 5 e97087

Can we quantify RV-specific intestinal antibodies in blood?



Corthesy B. Autoimmun Rev 2013, 12(6): 661-665.

RV-specific SIg titers in plasma of vaccinees and placebo recipients after D1 or D2 and in protected and non protected individuals



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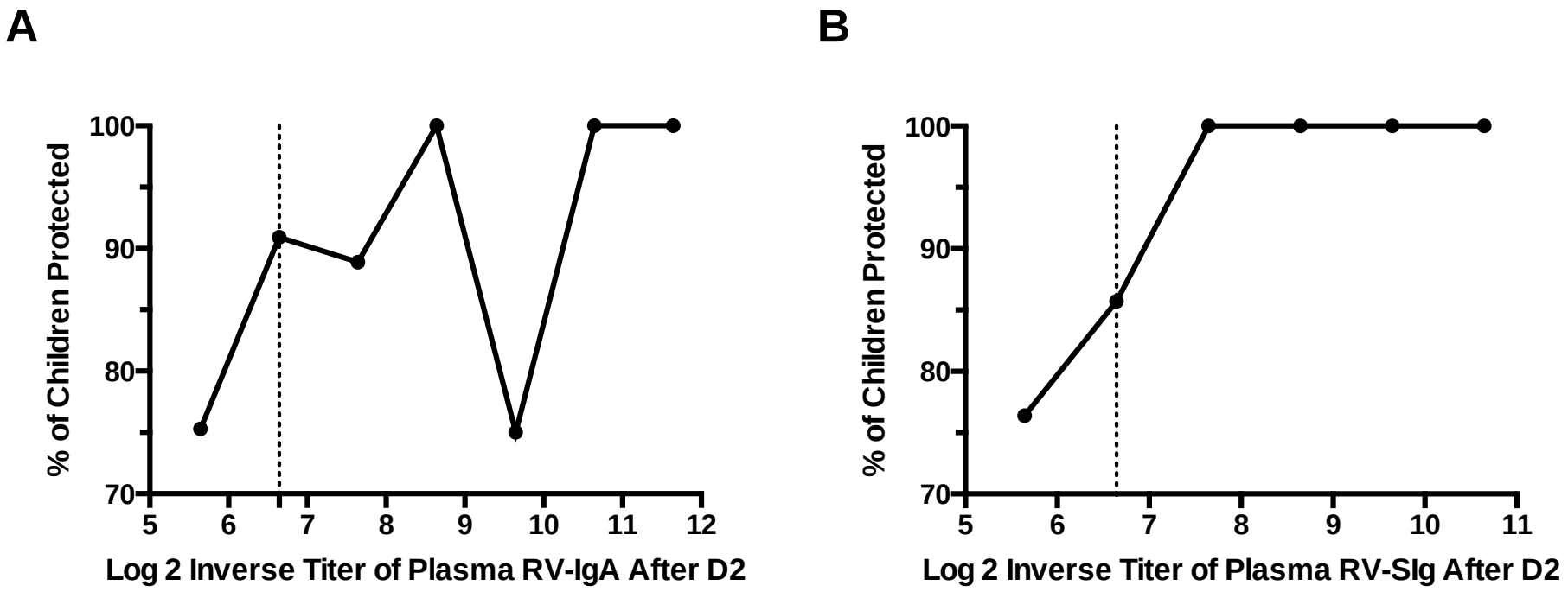
Comparison of RV-IgA and RV-Sig as CoP



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Comparison between RV-SIg and RV-IgA

	RV-SIg	RV-IgA
Specificity vaccination after dose 2	74%	92%
Sensitivity vaccination after dose 2	48%	50%
Differences between titers of vaccinees and placebo recipients	Yes	No
Higher frequencies of **protected** vaccinees than placebo recipients without the marker	No	Yes
Specificity protection after dose 2	85%	88%
Sensitivity protection after dose 2	40%	28%
Differences in titers between protected and non protected children	Yes	No
Correlation with protection (vaccinees/placebo)	After Dose 2	After Dose 2

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Conclusions

- IgM RV-Bc are probably composed of both antigen experienced and non experienced cells.
- “Antigen experienced” IgM and switched RV-mBc that express intestinal homing receptors may be good correlates of protection.
- RV-SIg includes RV-IgM and seems more sensitive, but less specific in detecting protection.
- RV-SIg can be complementary to RV-IgA as a correlate of protection in vaccine trials.

In favor of Serum RV-IgA as a correlate of protection

- Reflects duodenal RV-IgA levels 4 months after RV natural infection.
- Correlates with protection after natural infections in children.
- Follows Prentice's first condition as a CoP for RV1 as it correlates with the true clinical endpoint in an individual trial.
- Using meta-analysis it correlates with protection in different vaccine settings for both RV1 and RV5.

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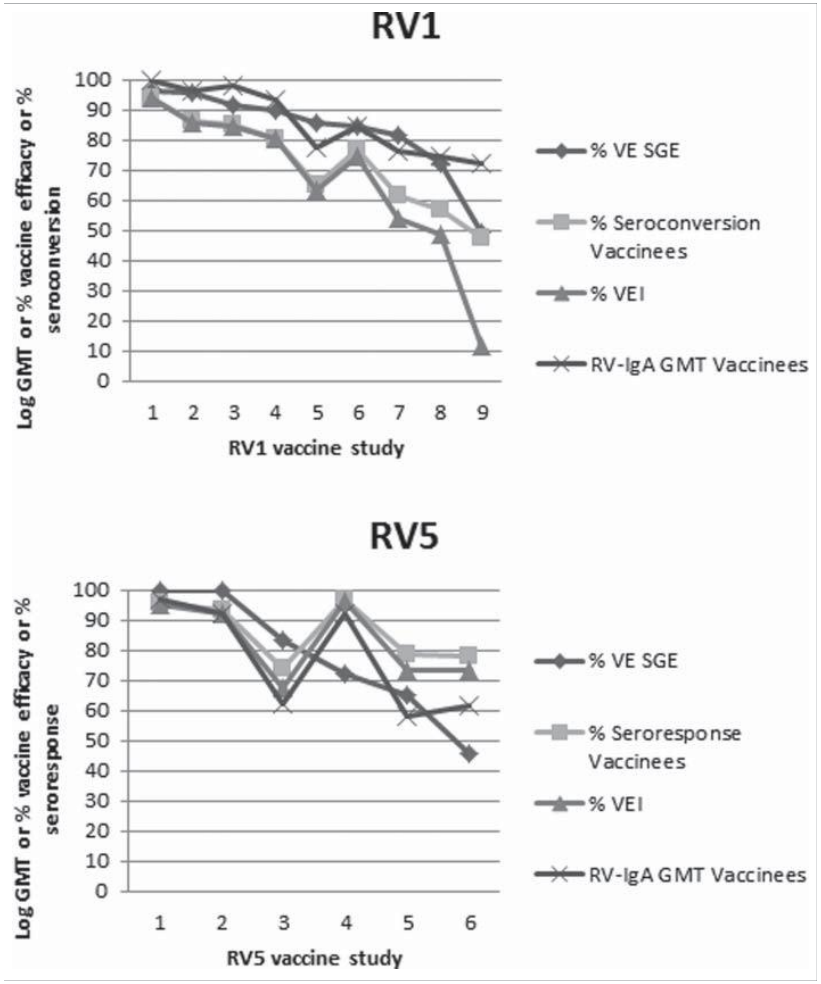
Correlation between RV-IgA and protection may vary for each type of vaccine



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Against Serum RV-IgA as a correlate of protection

- It fails to fulfill Prentice's second condition for a surrogate endpoint, as it does not "fully capture the treatment's "net effect "on the true clinical endpoint." But it is "reasonably likely to predict clinical benefit", so it is a level 3 endpoint surrogate of protection.
- It is a "non-mechanistic" CoP, hence, any vaccine change affecting this biomarker may or may not affect the clinical endpoint.
- A dose effect (likelihood of not having a RV associated-GE with each 1 log increase in RV-IgA titer) has not been observed.
- Vaccinees without serum RV-IgA have significantly less RV GE than placebo recipients, suggesting that factors other than serum RV-IgA play a role in protection.

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Proposals to validate RV-IgA as a level 2 endpoint surrogate marker

- For new human attenuated vaccines: evaluate Vaccine Efficacy with a clinical endpoint (with delayed OPV), assessing serum RV-IgA with a standardized protocol and testing in "parallel" RV1. If the correlation between RV-IgA and protection induced by new RV vaccines is similar to the one observed for RV1, serum RV-IgA could be considered a practical "validated" level 2 surrogate endpoint for this type of vaccine.
- For new heterologuos vaccines: Determine if RV-IgA correlates with protection after RV5 in an individual trial. And repeat with RV5 as for RV1 above.

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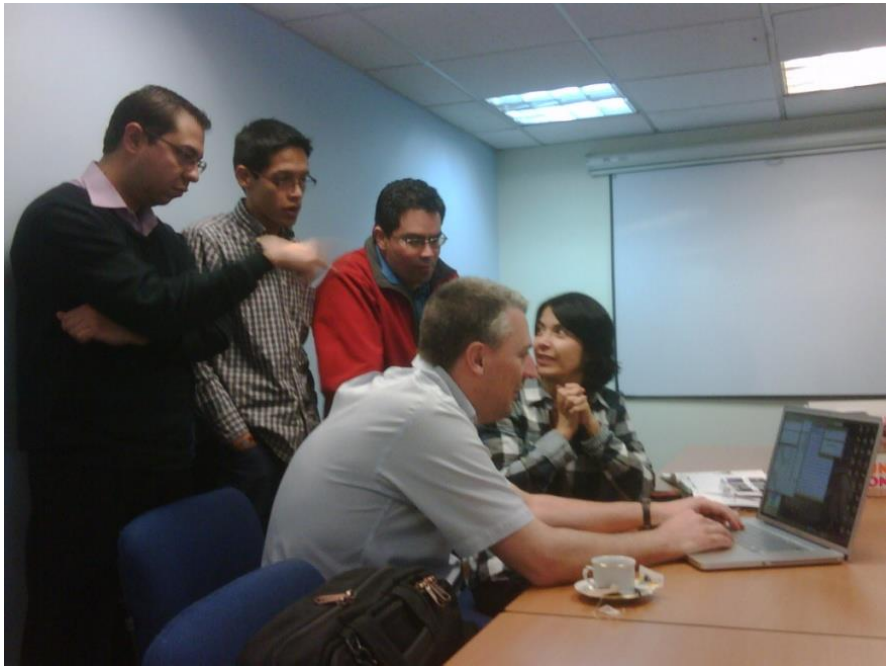
Prioritization of blood assays as RV correlates of protection against GE

	IgA	SIg	Conform VP4/7 SIg/IgA	Gut homing mBc	Antibody Lymph Sup	Gut homing T cells	Neutralize Ab	IgG
Not present in "naïve" children	+++	++	++	+++	+++	+++	-	-
Mechanistic	+	++	+++	++	++	+	++	-
Practical to measure	+++	+++	+	+	++	+	+++	+++
Reflects intestinal immunity	+	+++	+++	+++	++	+++	+	-
Reflects long lasting protection	++	+	++	+++	++	+++	+	+

Acknowledgements



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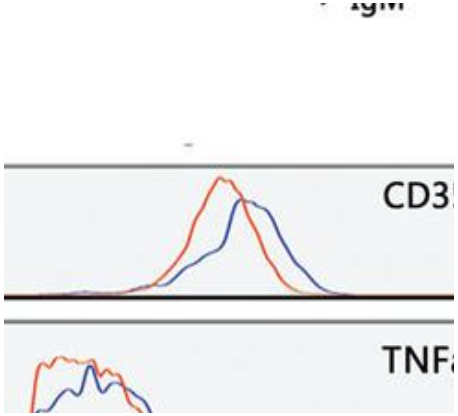
Daniel Herrera Miguel Parra, Alfonso Barreto

IgM^{hi}, IgD^{low} subsets have different phenotypes



ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *B-1 Cell Development and Function*

Age-related aspects of human IgM^+ B cell heterogeneity

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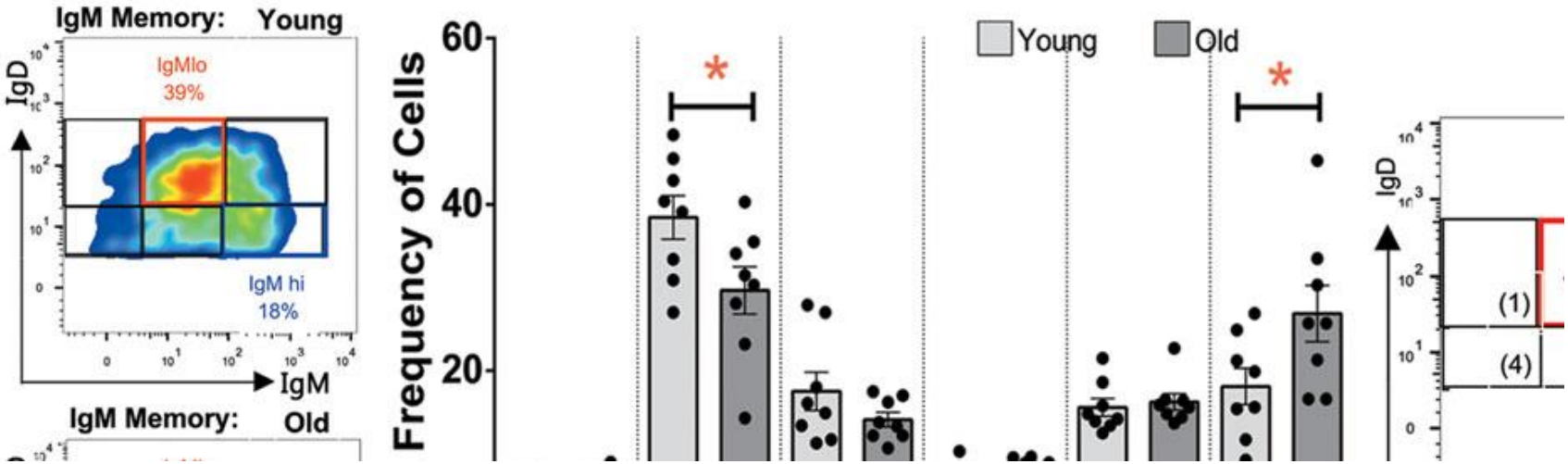

RV-specific IgA bound to secretory component (SIgA) in serum and secretions

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