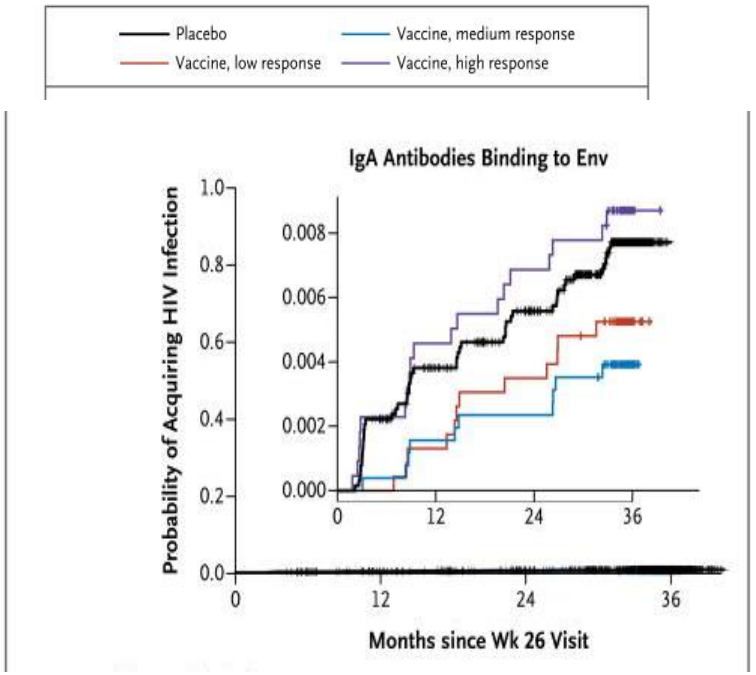
Inhibitory role of serum IgA upon Fc functions

Amy Chung

awchung@unimelb.edu.au

RV144 Vaccine Immune Correlates associated plasma gp120 IgA with reduced vaccine efficacy

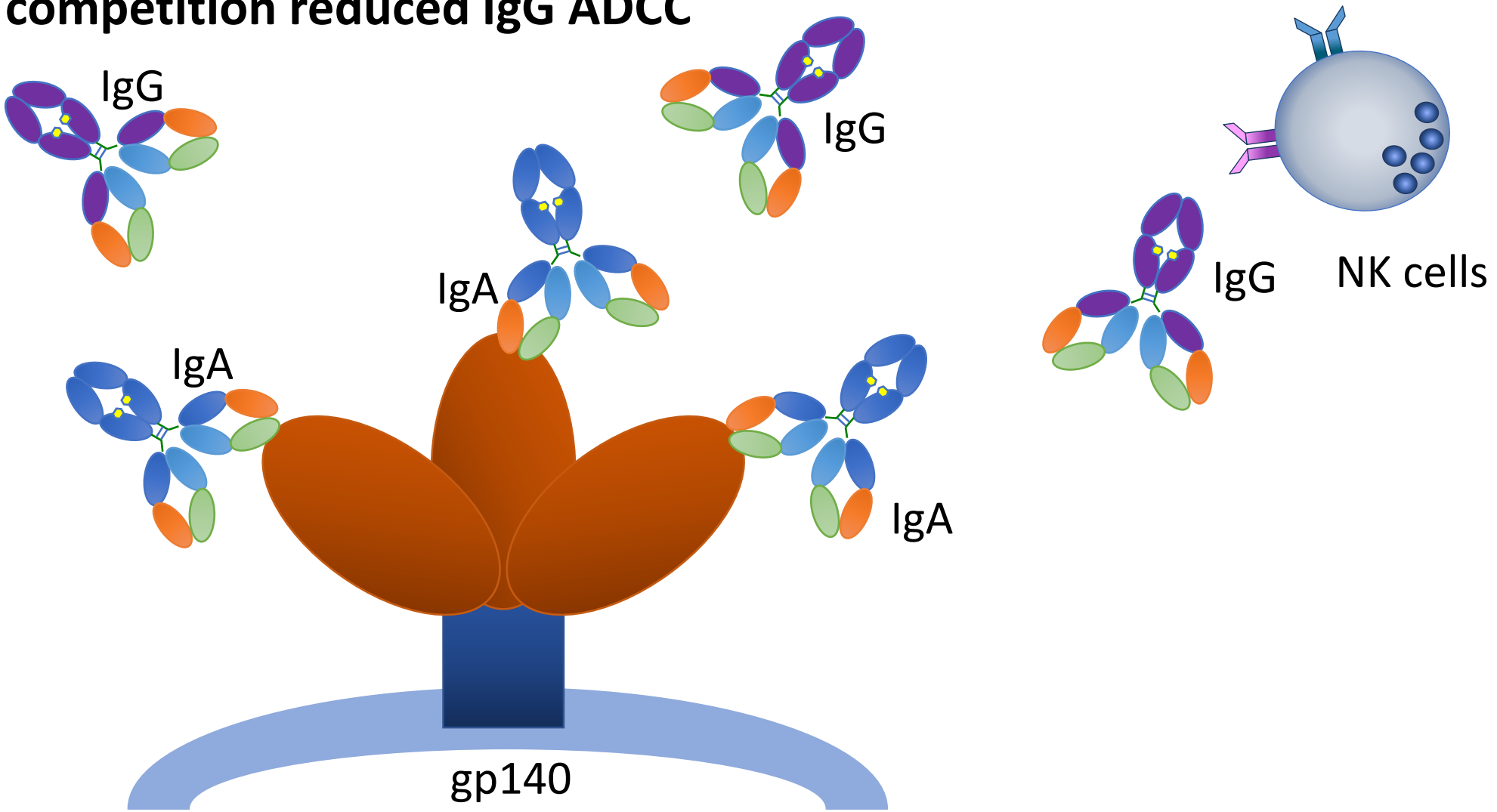


gp120 IgA in plasma- reduced vaccine efficacy

Haynes et al NEJM 2012

How did RV144 gp120-IgA reduce vaccine efficacy?

IgA epitope competition reduced IgG ADCC

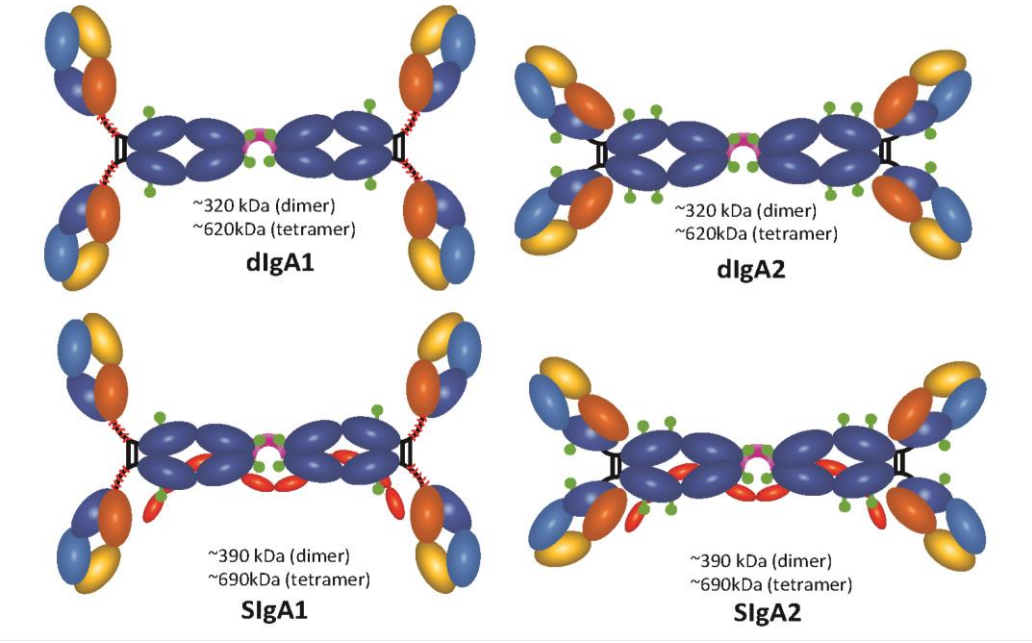


Tomaras et al. PNAS 2013

Role of IgA in HIV is complex

- **Protective Mucosal IgA:**
  - Passive transfer of **NAb of IgA** in NHP is protective *(Watkins AIDS 2013)*
  - Vaccination in NHP associated **mucosal IgA** with protection *(Bomsel Jimmuno 2011)*
  - **Mucosal ENV-IgA** in HESN associated with protection *(Tudor Mucosal Immuno 2009)*
  - **Dimeric/Polymeric IgA** is highly functional (*Wills Jimmuno 2018, Bakema mAbs 2011*)

Mucosal

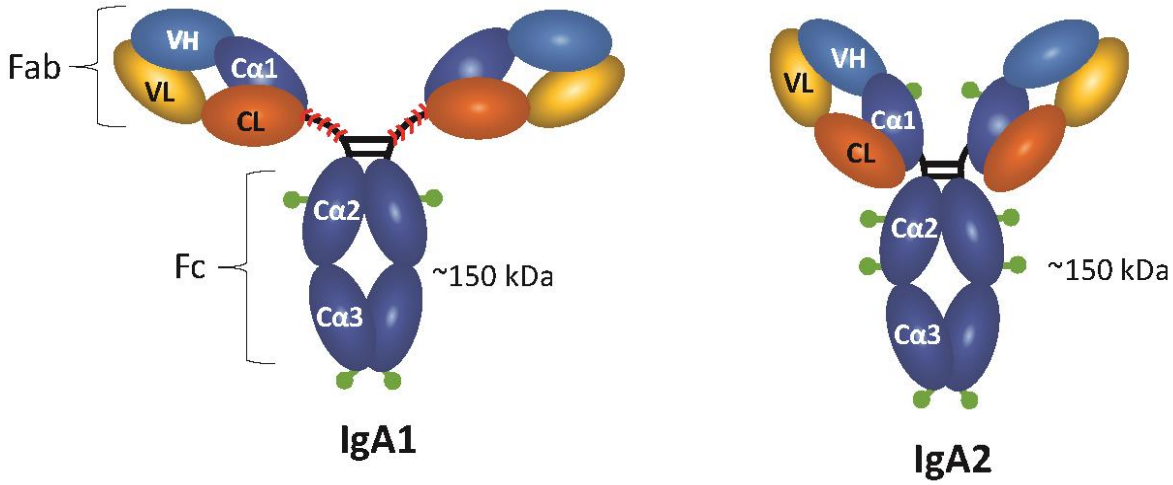


Lopez et al ARHR 2018

Role of IgA in HIV is complex

Plasma

- **<u>PLASMA</u> IgA: <u>Monomeric</u>**
  - **Plasma** gp120-IgA reduced RV144 vaccine efficacy (*Haynes NEJM 2012*)
  - **Plasma** gp120-IgA blocks IgG ADCC (*Tomaras PNAS 2013*)



Lopez et al ARHR 2018

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- **PLASMA IgA:**
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  - **Plasma** IgA associated with disease progression (*Fling J Allergy Clin Immuno 1988, Coates J Clin Epi 1992*)

Predictors of Progression to AIDS

Table 2. Univariate Cox relative risk regression models of enrolment values of various laboratory markers and one year lagged values in a cohort of male sexual contacts of men with HIV disease, Toronto, Ontario, Canada, 1984–1989

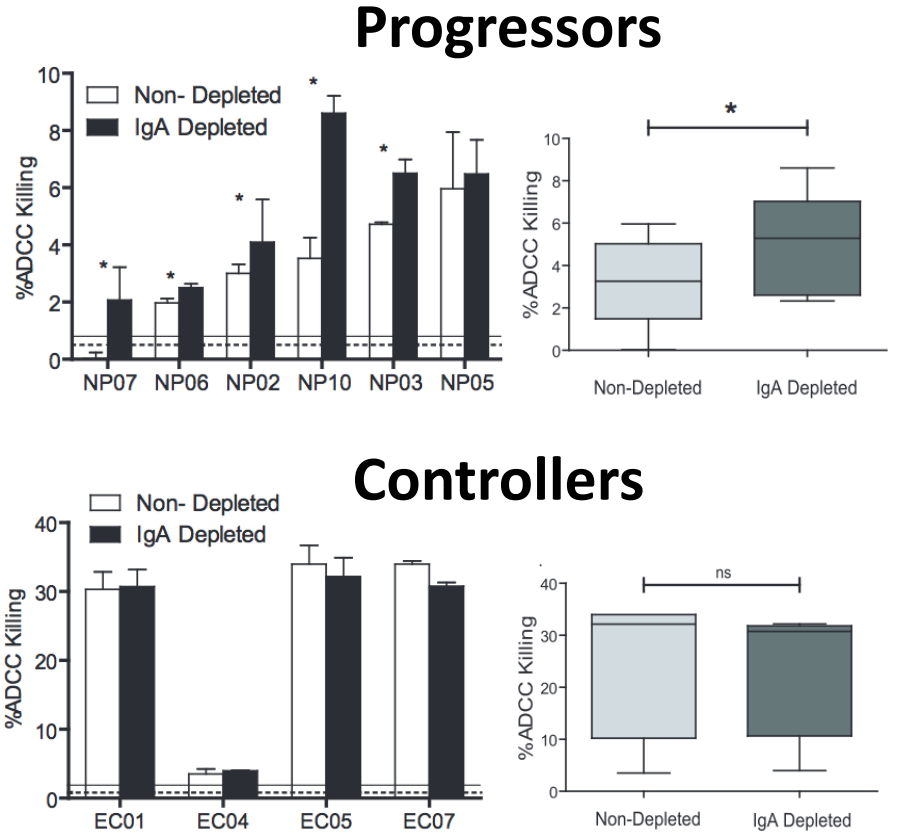
	Enrolment values of marker*			Values lagged one year†		
	Relative risk	95% CI	*p* Value	Relative risk	95% CI	*p* Value
T-cell markers						
T4 cell count (per 100 decline)	1.49	1.20–1.85	0.0004	1.67	1.34–2.08	<0.0001
T8 cell count (per 100 increase)	1.06	0.93–1.21	0.36	1.05	0.94–1.31	0.41
T4/T8 (per unit decline)	8.50	2.83–25.51	0.0002	74.44	13.53–409.45	<0.0001
Quantitative immunoglobulins						
IgA (per 100 μg/l increase)	1.30	1.01–1.66	0.04	1.57	1.25–1.94	<0.0001
IgM (per 100 μg/l increase)	1.27	0.90–1.80	0.16	1.19	0.93–1.50	0.16
IgG (per 100 μg/l increase)	1.48	0.78–2.80	0.24	1.39	0.75–2.56	0.30

Coates J Clin Epi 1992

plasma IgA equally predictive of progression to AIDS as low CD4 counts

Role of IgA in HIV is complex

- **<u>PLASMA</u> IgA:**
  - **Plasma** gp120-IgA reduced RV144 vaccine efficacy (*Haynes NEJM 2012*)
  - **Plasma** gp120-IgA blocks IgG ADCC (*Tomaras PNAS 2013*)
  - **Plasma** IgA associated with disease progression (*Fling J Allergy Clin Immuno 1988, Coates J Clin Epi 1992*)
  - **Plasma** IgA inhibits ADCC in HIV progressor subjects, but not Elite controllers *(Ruiz J Viro 2015)*



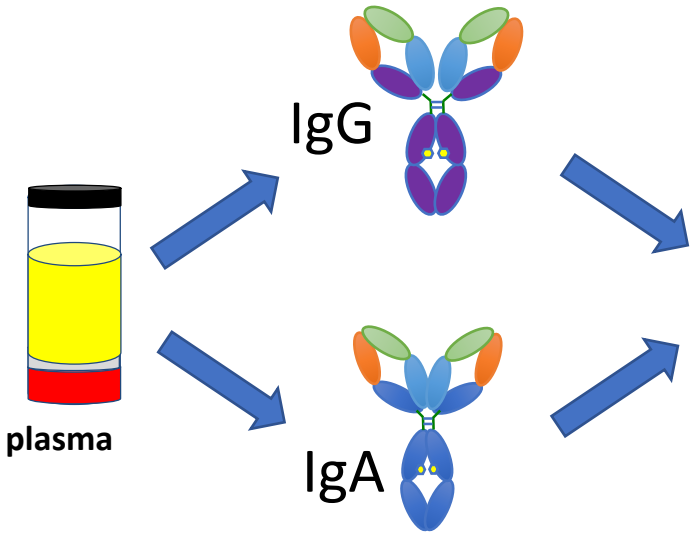
Ruiz et al J Virol 2015

Dissecting the role of plasma IgA in HIV infection using Systems Serology

Viremic Controller (VL<2000) vs Progressors
(Kelleher-Kirby Institute)

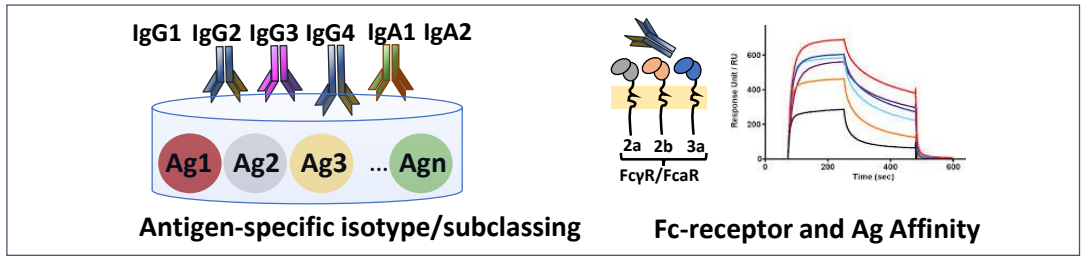
35 Controllers

40 Progressors

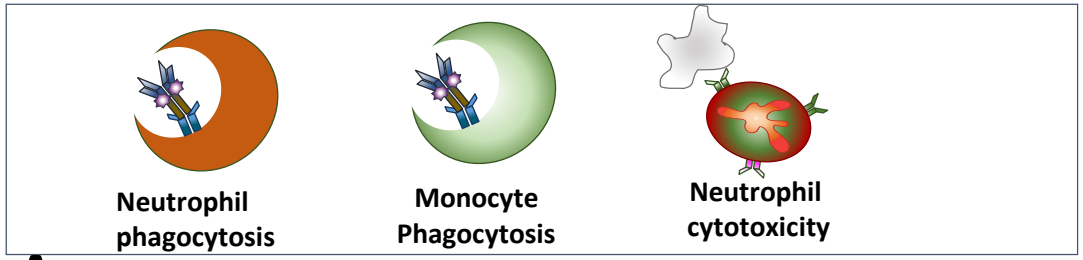


Purified the IgG and IgA

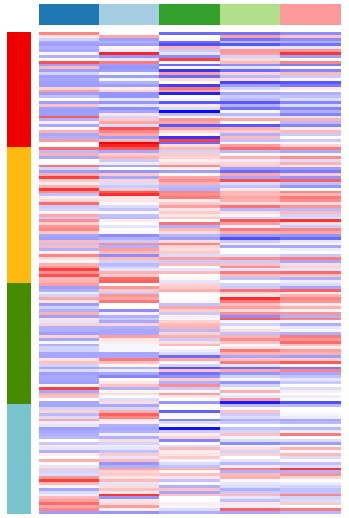
Biophysical Profiling



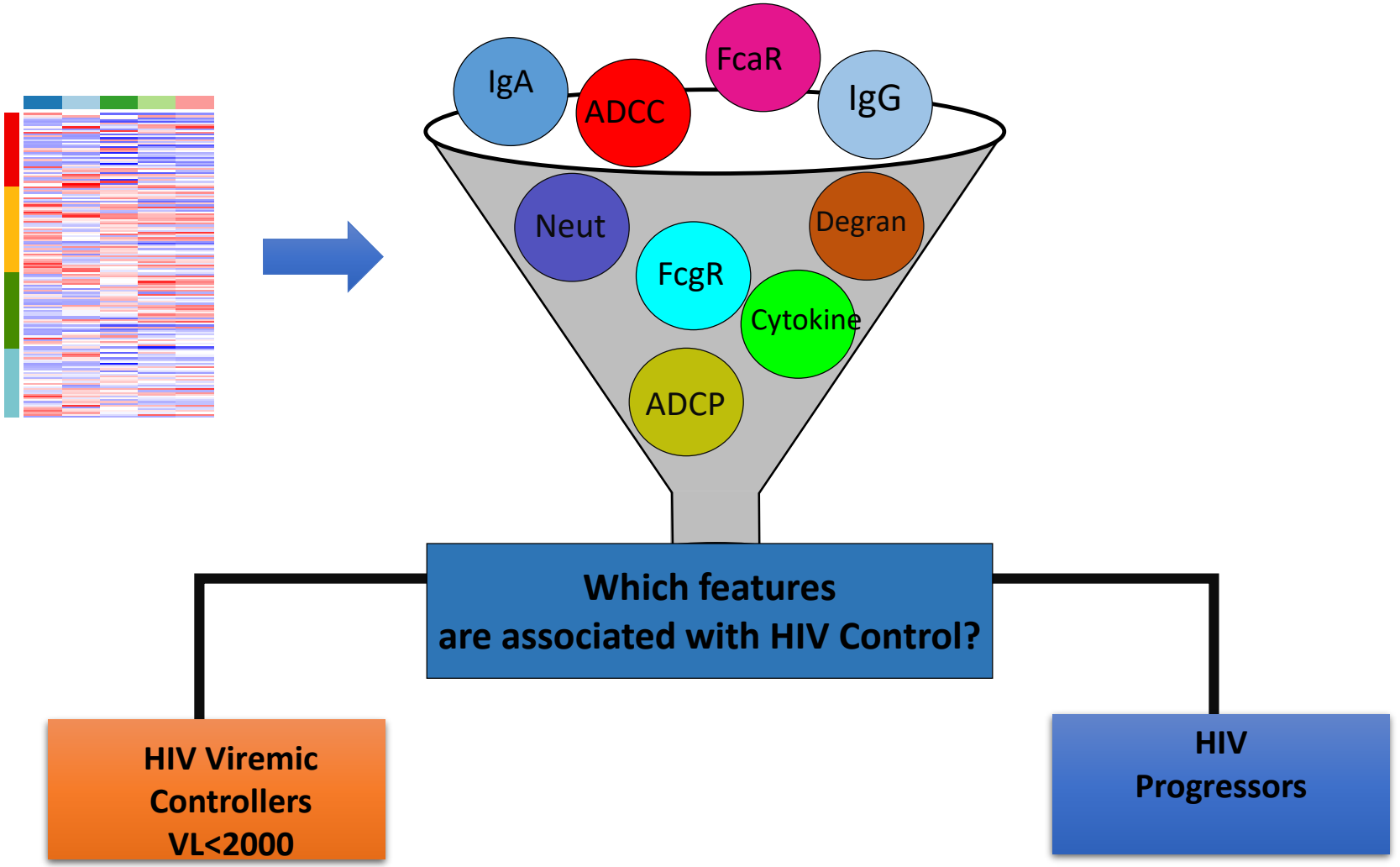
Functional Profiling



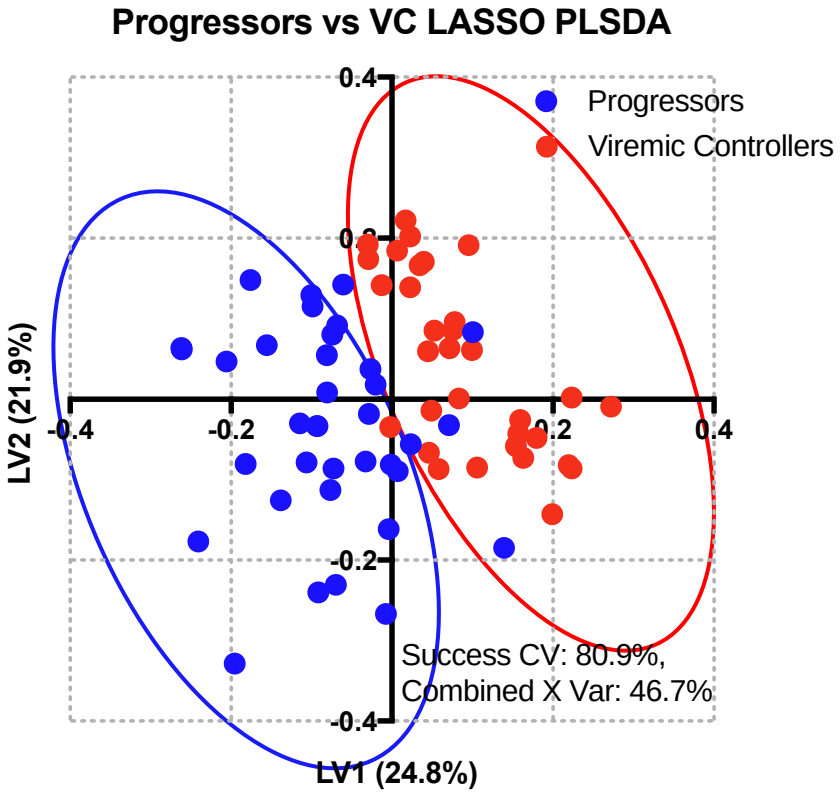
Computational Analysis "humoral signatures"

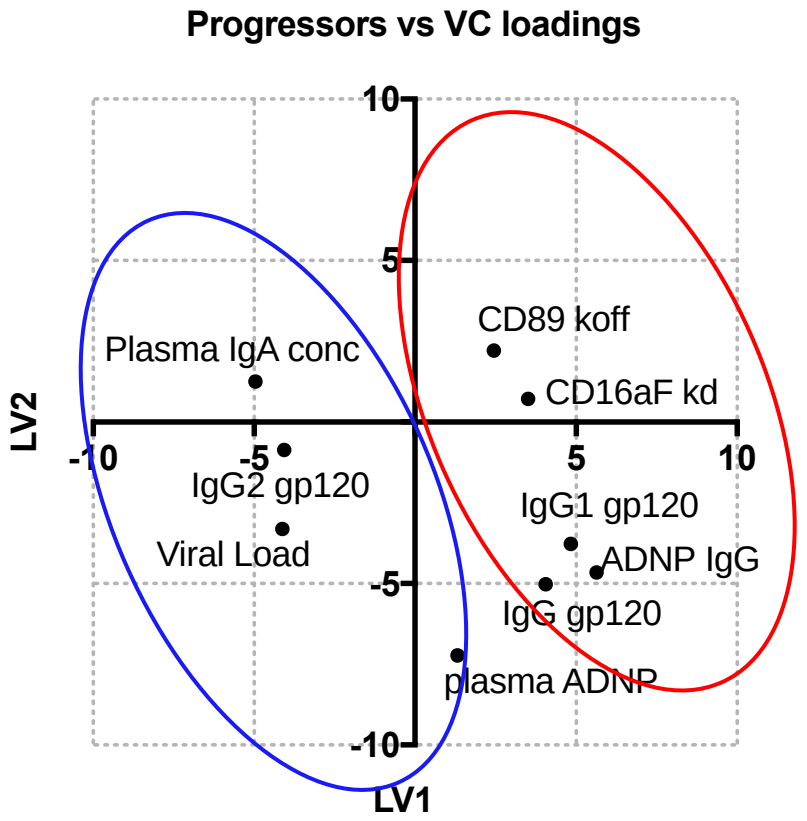


Identifying IgG and IgA humoral signatures associated with HIV viral control

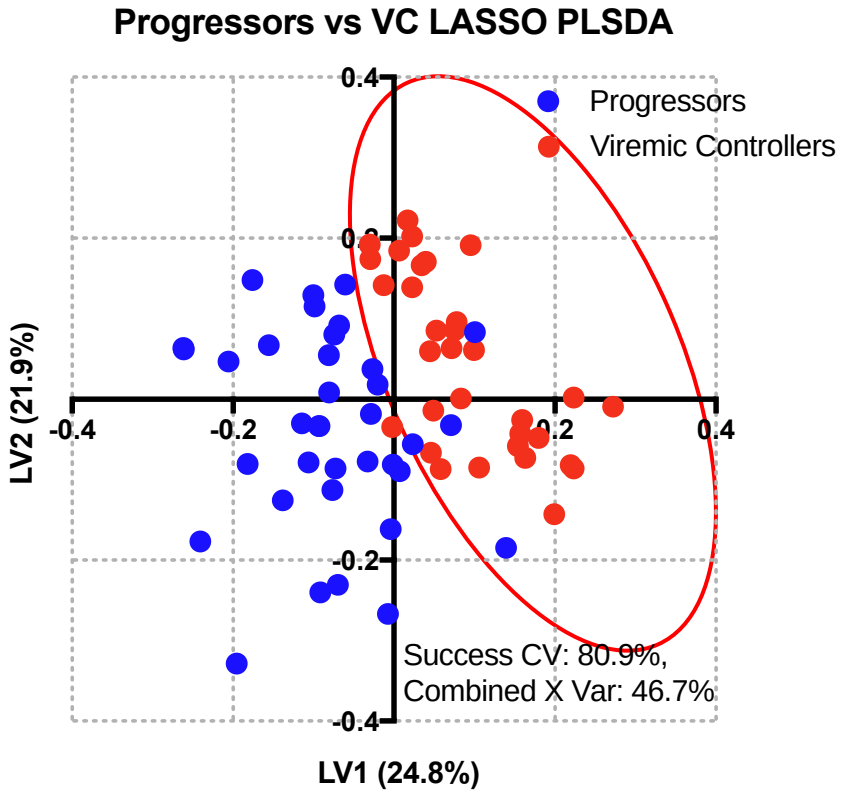


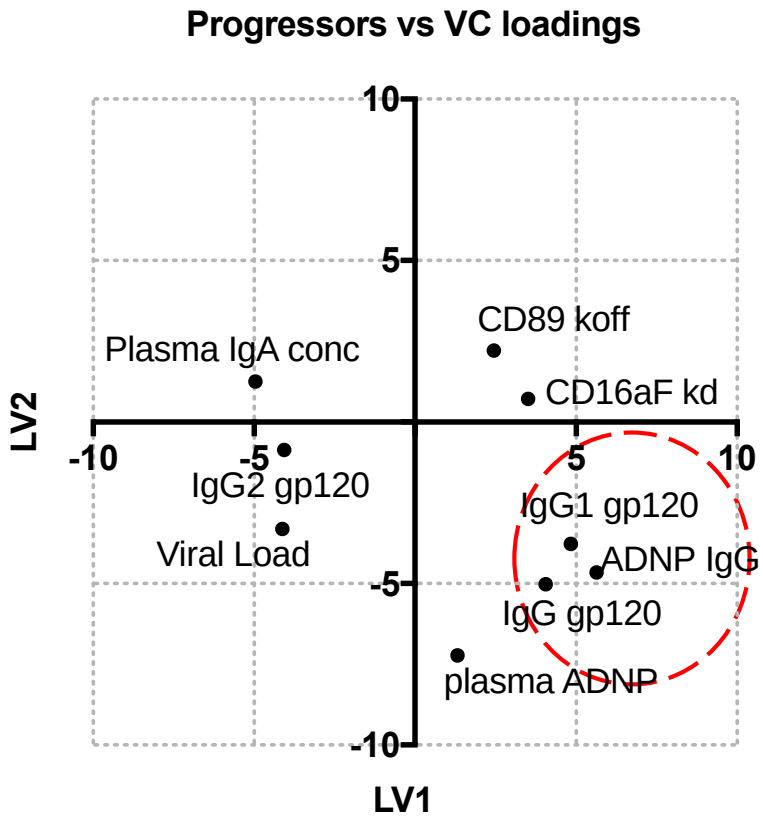
Viremic controllers (VC) and Progressors have very different Ab profiles





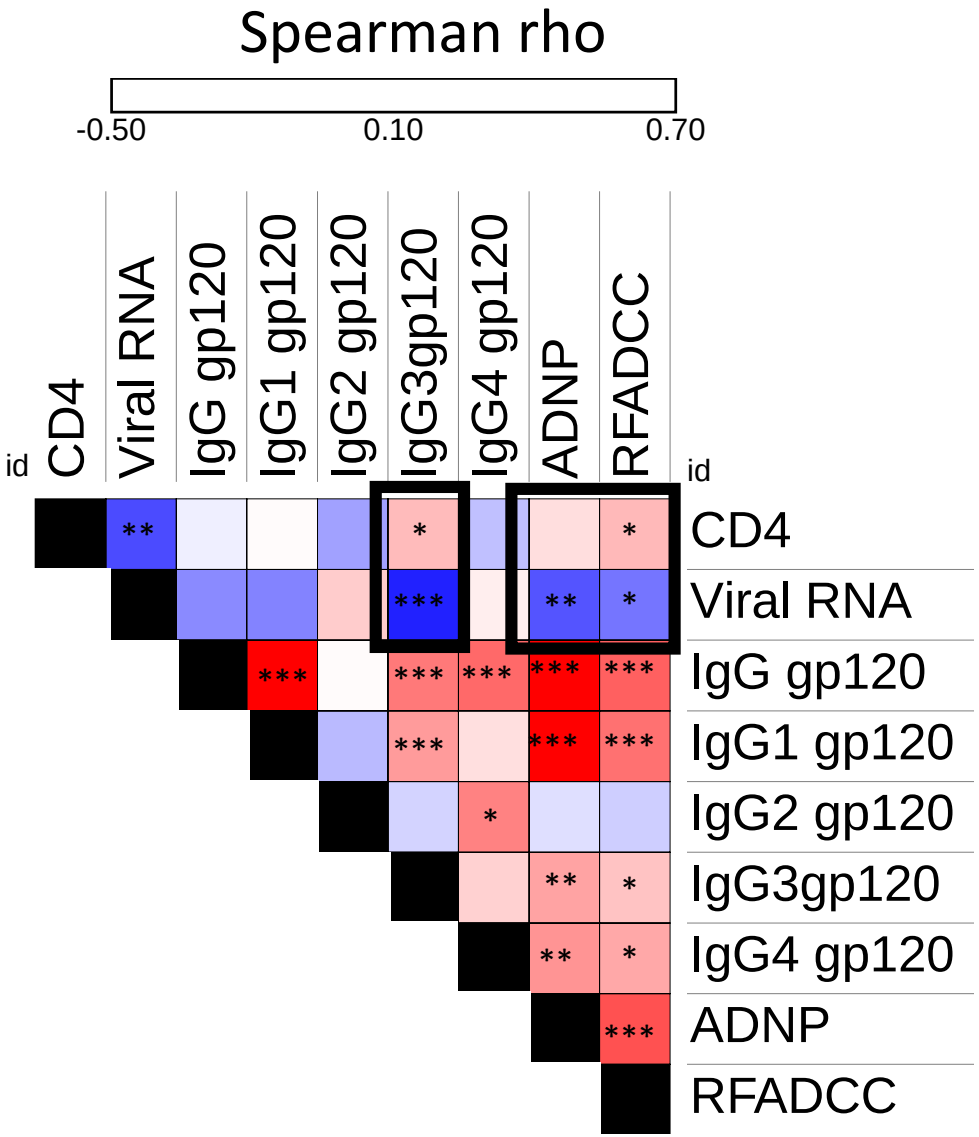
IgG mediated Fc effector functions are enhanced in Viremic Controllers

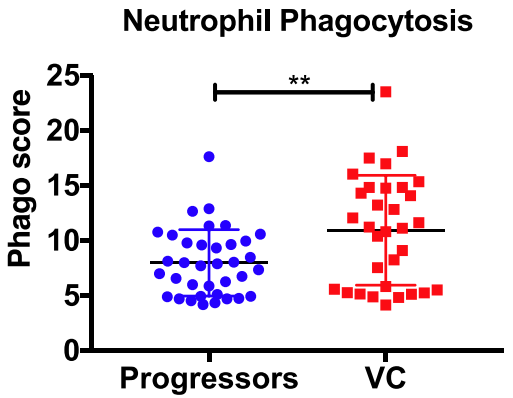


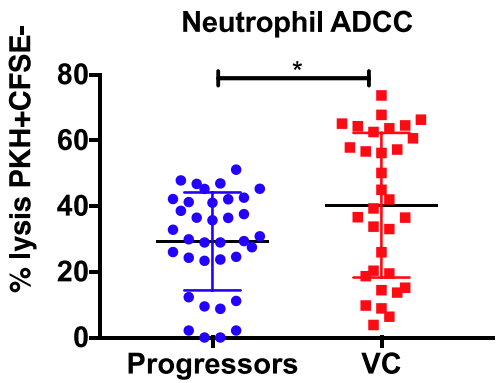


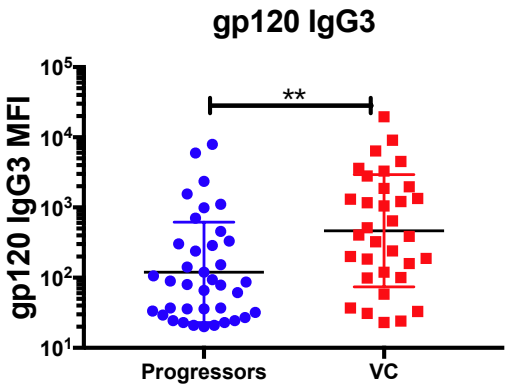
Enhanced IgG Fc functions

Viremic Controllers have enhanced Fc effector functions

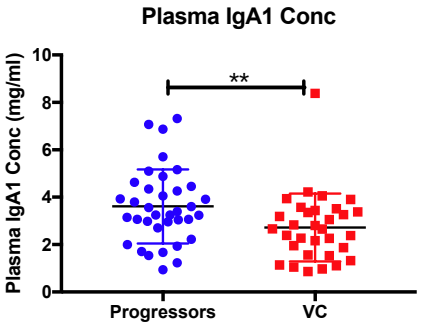


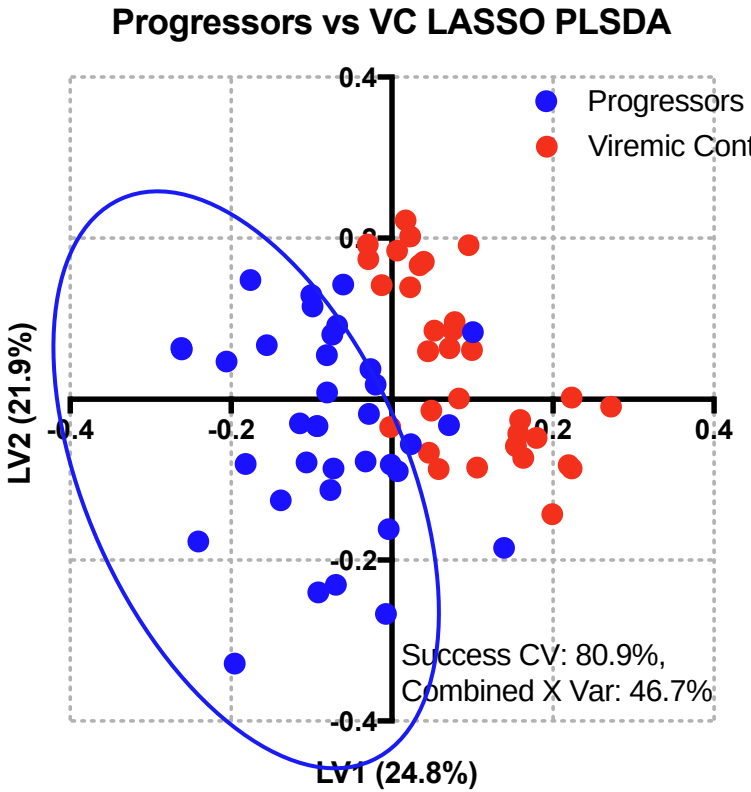




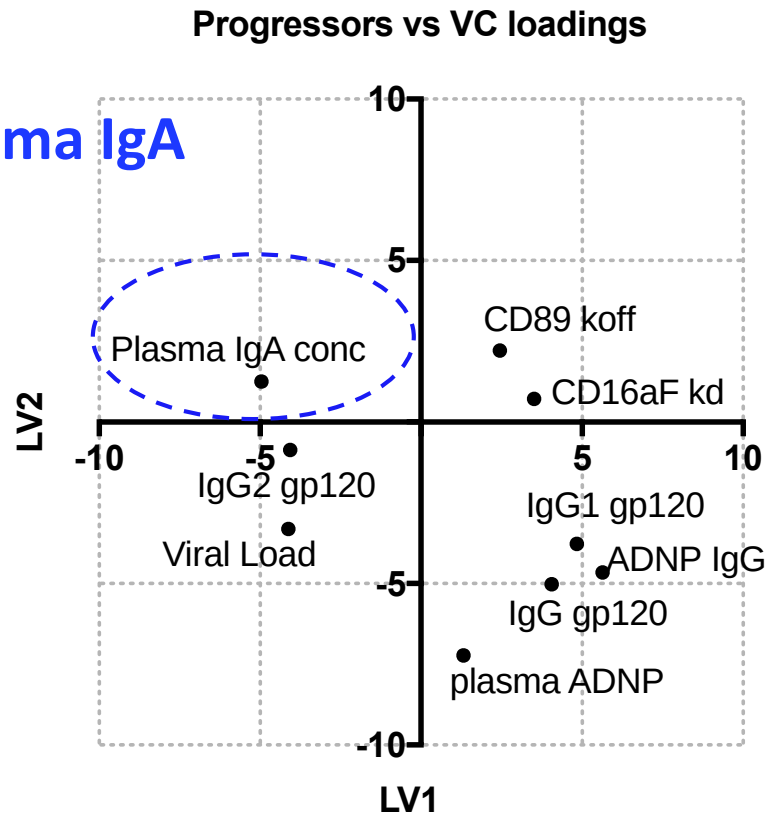


Plasma IgA markers differentiate Viremic controllers (VC) from Progressors

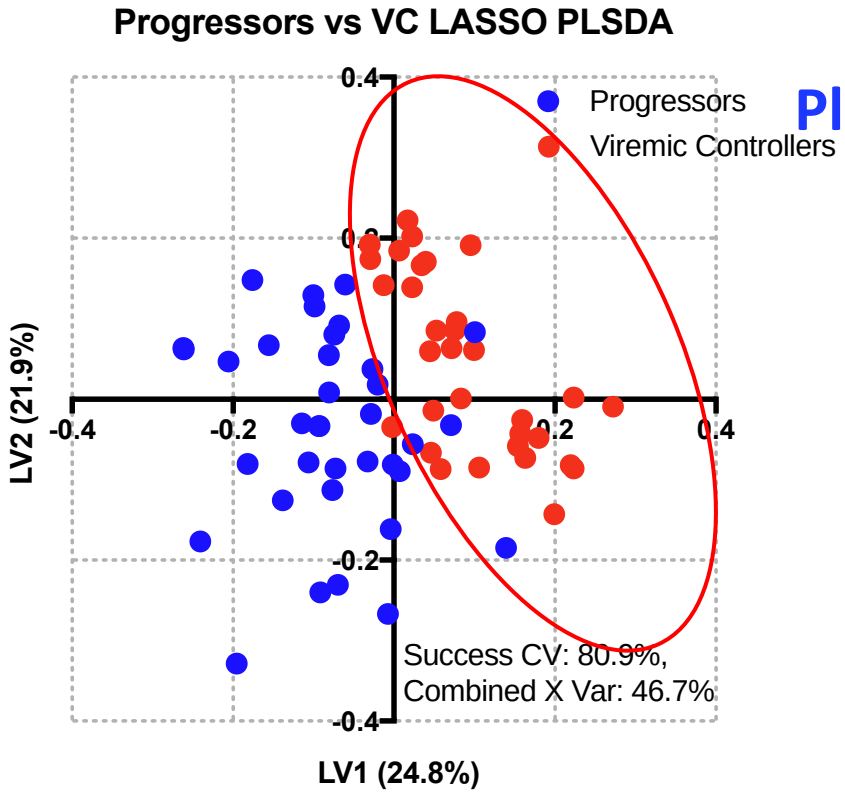




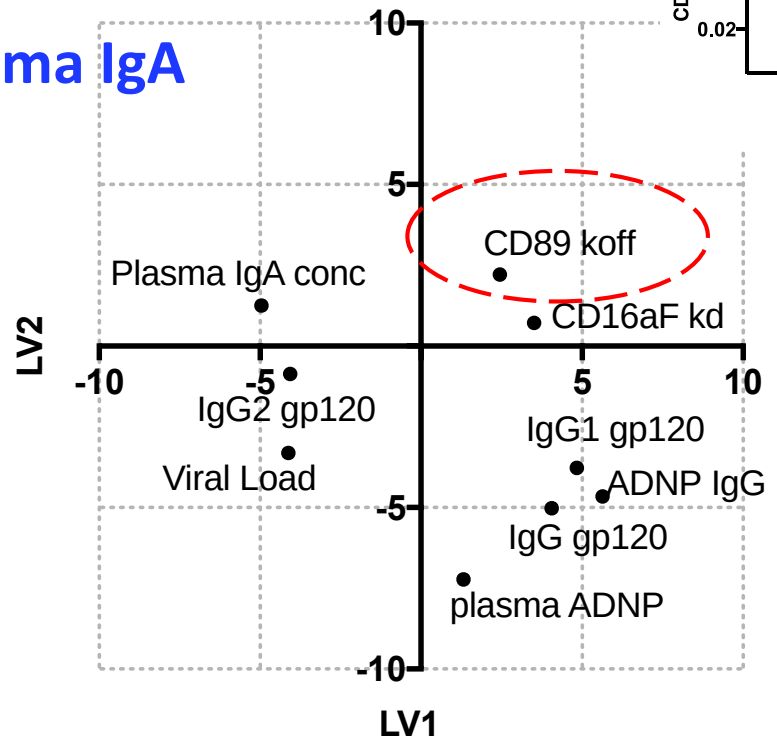
Plasma IgA

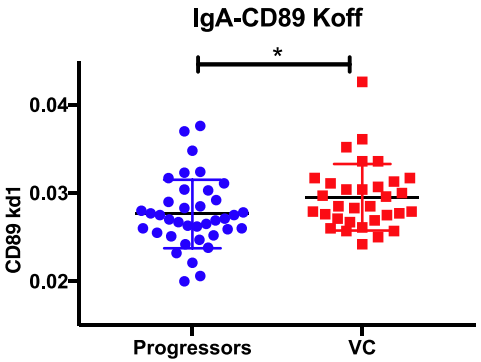


Plasma IgA and CD89 (FcaR) engagement differentiate Viremic controllers (VC) from Progress(



Plasma IgA





CD89 (FcaR) Binding

↑ koff = weaker affinity

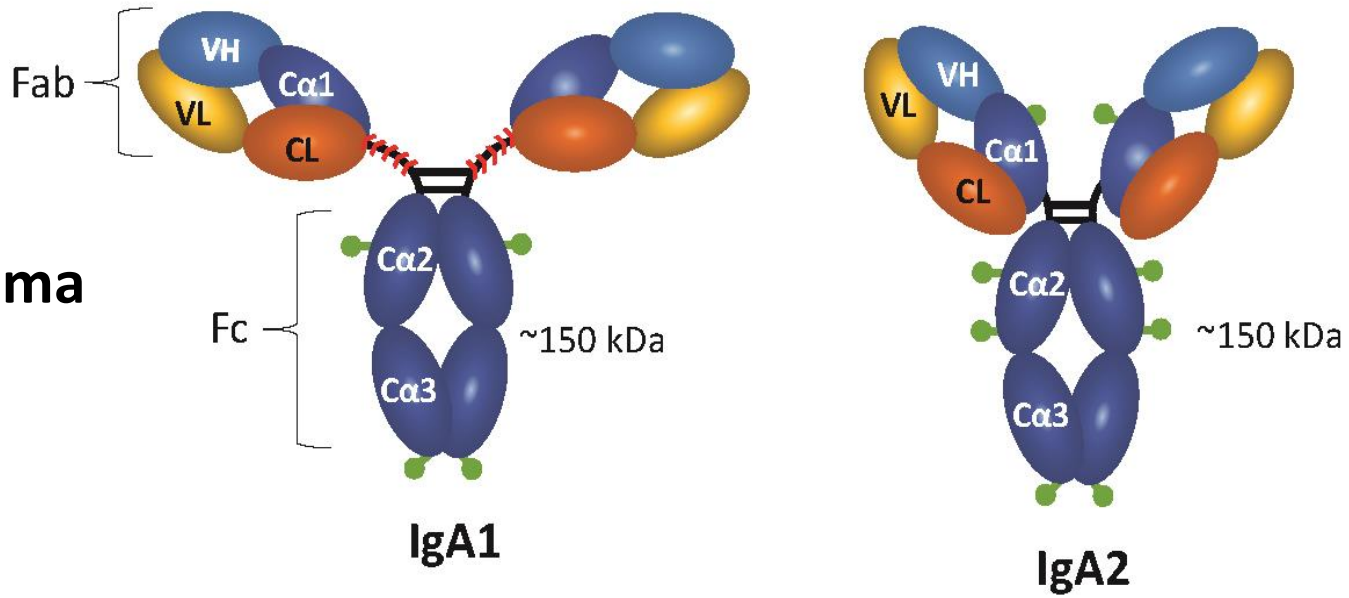
Progressor total plasma (monomeric) IgA1 bind with higher affinity to FcaR

Viremic controller IgA have weaker binding to FcaR

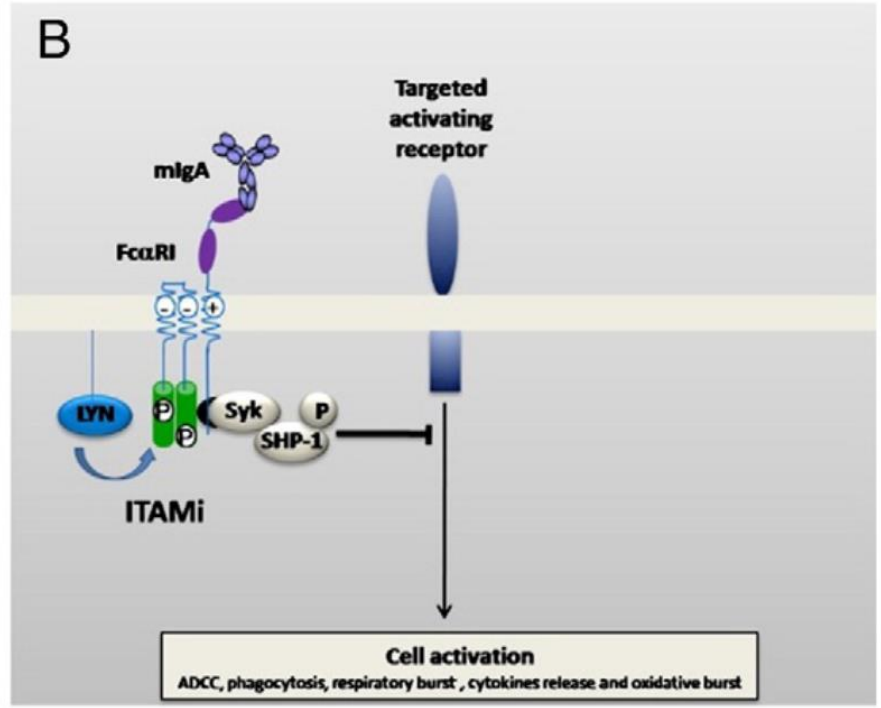
What does this mean?!

Different Forms of IgA: monomeric IgA

Plasma



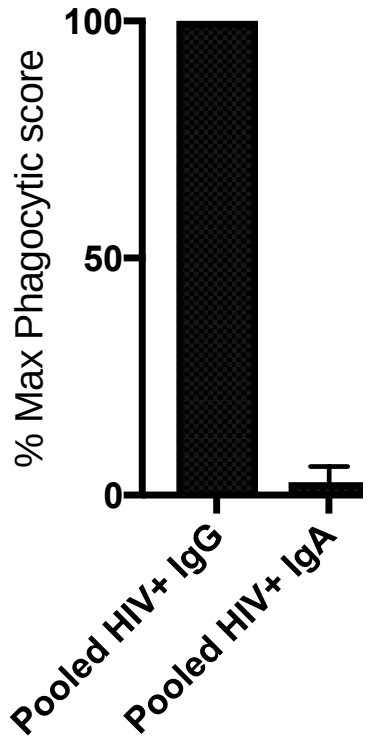
monomeric IgA
-bind FcAR-lower affinity
-Fc inhibition (ITAMi)
-inhibits ADCC and Fc functions
-secrets inhibitory cytokines
(Pasquier Immunity 2005)



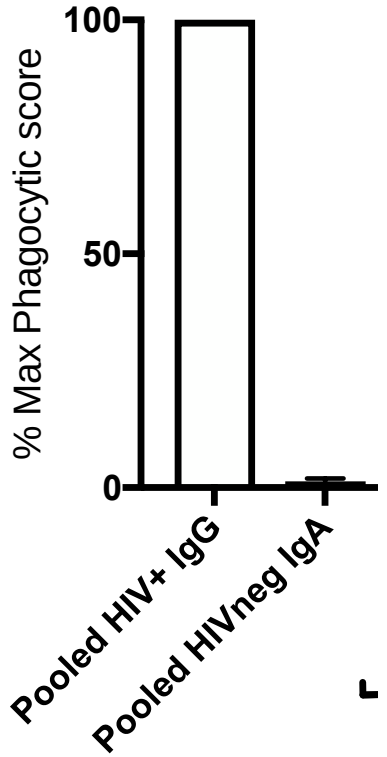
Lopez et al ARHR 2018
Ben Mkaddem Autoimmunity Reviews 2013

Plasma IgA can inhibit IgG Fc effector functions – via FcAR inhibitory signaling

Neutrophil Phagocytosis
HIV + IgA

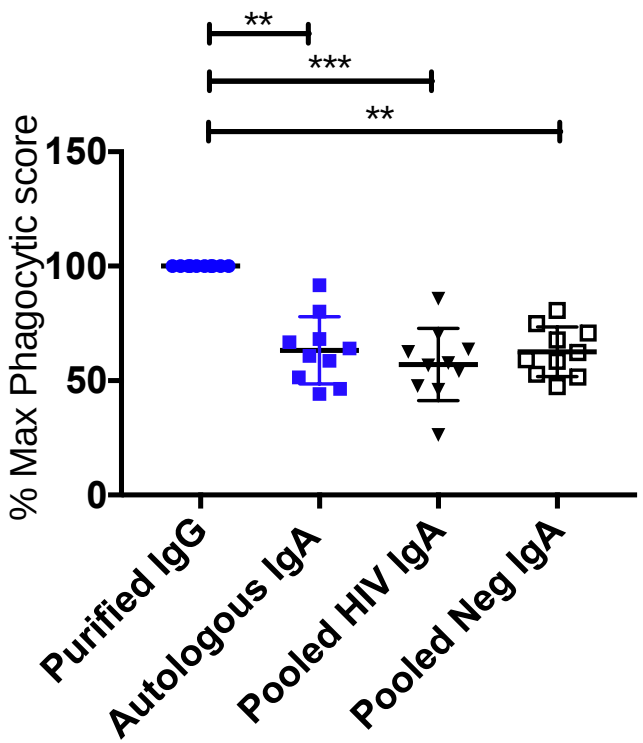


Neutrophil Phagocytosis
HIV neg IgA

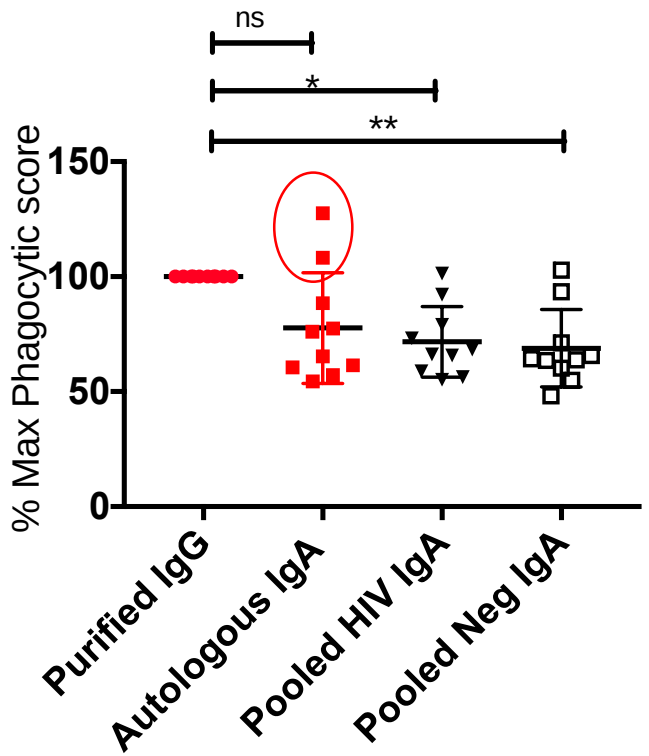


Plasma IgA can inhibit IgG Fc effector functions via FcaR (CD89) inhibitory signaling

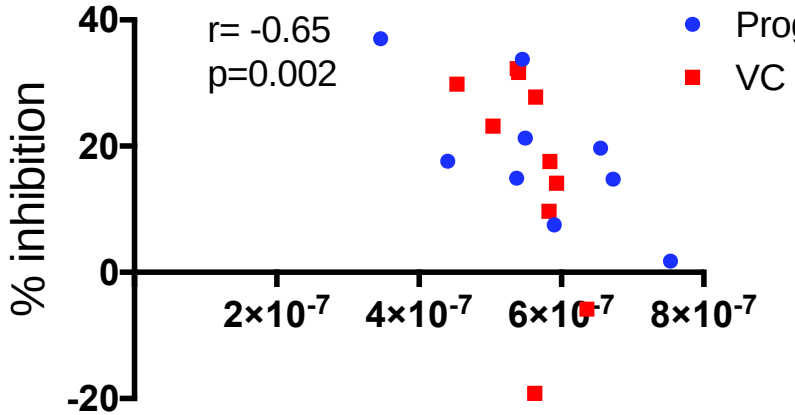
Progressor plasma IgA inhibits Fc functions



VC total IgA weakly inhibits Fc functions



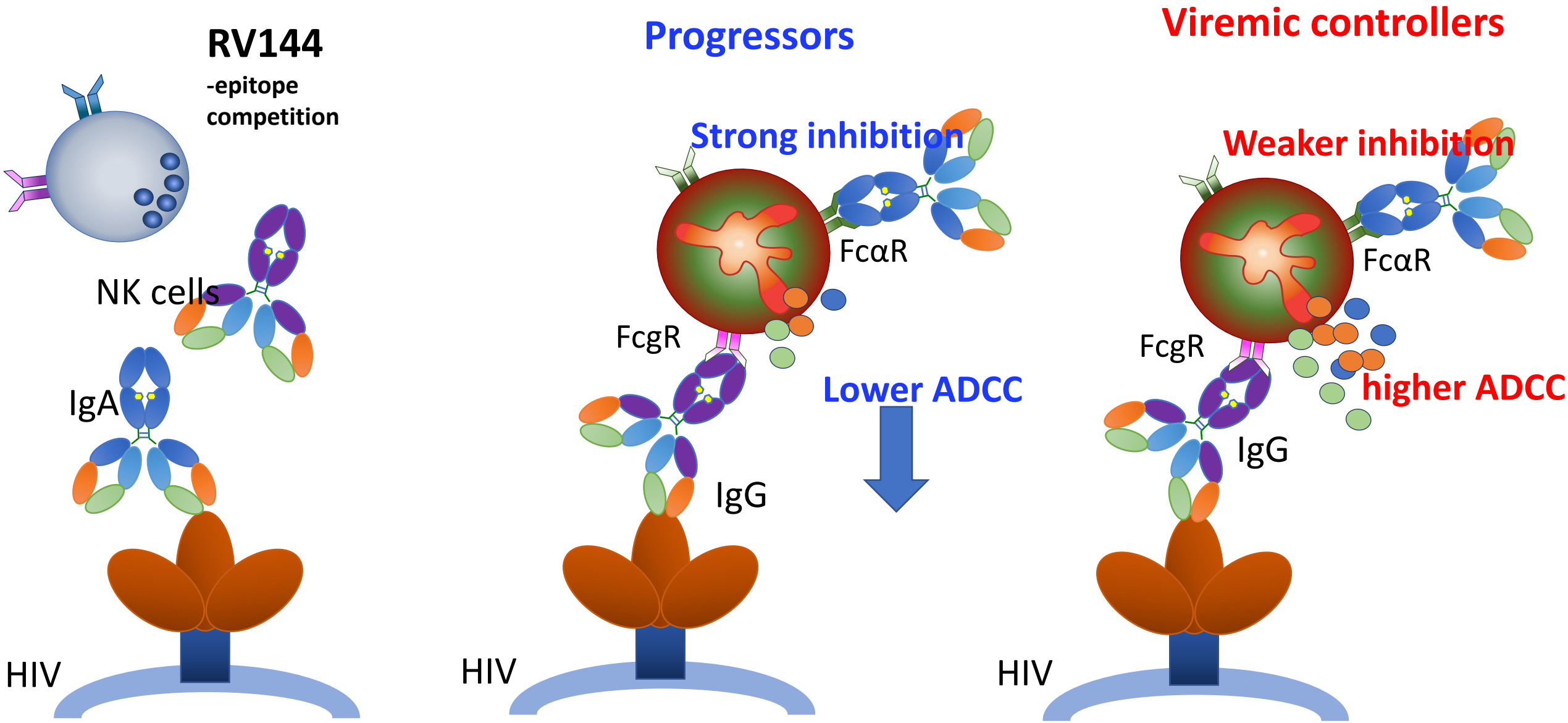
% inhibition vs IgA-CD89 affinity



IgA - CD89 KD

Matthew Worley
Ester Lopez

Multiple mechanisms of IgA inhibition in HIV infection



Fc effector functions may be important for enhancing broadly neutralizing Abs

Vol 449|6 September 2007|doi:10.1038/nature06106

Fc receptor but not … in antibody protecti…

Ann J. Hessell[1]*, Lars Hangartner[1]*, Meredi…
Caroline M. S. Lanigan[1], Gary Landucci[4], D…
& Dennis R. Burton[1]

ARTICLE

Corrected: Publisher Correction

https://doi.org/10.1038/s41586-018-0600-6

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

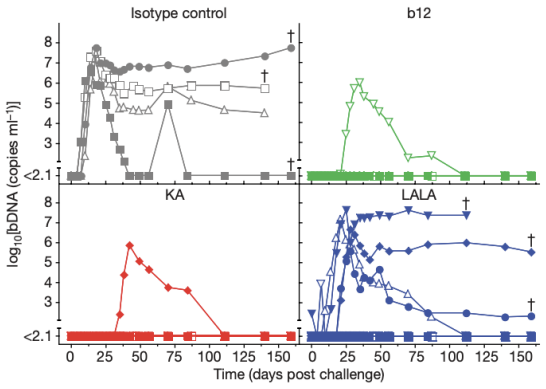
Erica N. Borducchi[1,6], Jinyan Liu[1,6], Joseph P. Nkolola[1,6], Anthony M. Cadena[1,6], Wen-Han Yu[2], Stephanie Fischinger[2], Thomas Broge[2], Peter Abbink[1], Noe B. Mercado[1], Abishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[3], Joseph Hesselgesser[3], Wenjun Li[4], Mark G. Lewis[5], Galit Alter[2], Romas Geleziunas[3] & Dan H. Barouch[1,2]*

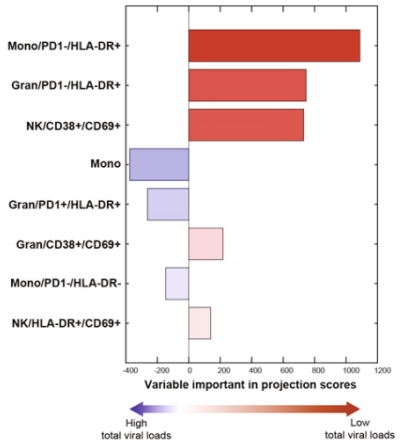
The Journal of Clinical Investigation

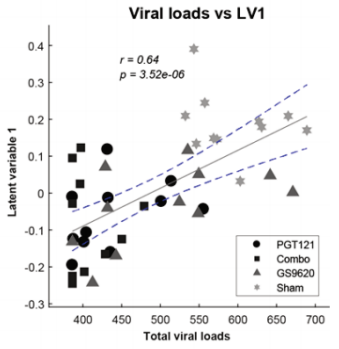
…ctions are redundant to efficacy …dy PGT121 in macaques

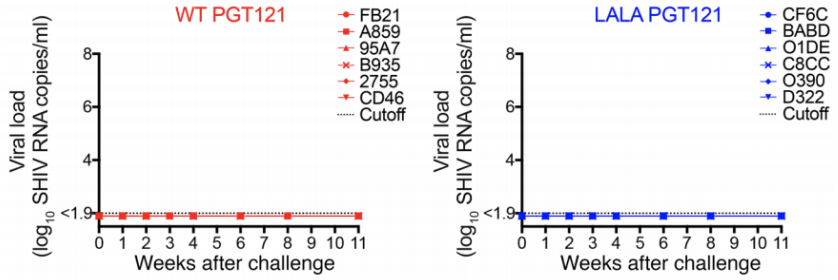
B. Kristensen,[1] Thakshila Amarasena,[1] Georges Khoury,[1] Adam K. Wheatley,[1,2] …k Hogarth,[4] Miles P. Davenport,[3] and Stephen J. Kent[1,2,5]

…itute for Infection and Immunity, and [2]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, The University of …of New South Wales, Sydney, New South Wales, Australia. [4]Centre for Biomedical Research, Burnet Institute, Melbourne, Victoria, …ectious Diseases, Alfred Health, Central Clinical School, Monash University, Melbourne, Victoria, Australia.









Summary

- Multiple mechanisms by which IgA can inhibit Fc Functions
  - Epitope competition
  - IgA-FcaR inhibitory signaling
- HIV progressors have enhanced IgA-FcaR inhibition
- Viremic Controllers may have enhanced IgA
- IgA can also reduce Fc functional capacity of bNAb responses *in vitro*

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- Sandy Vassan

RV144

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- Sorachai Nitayaphan

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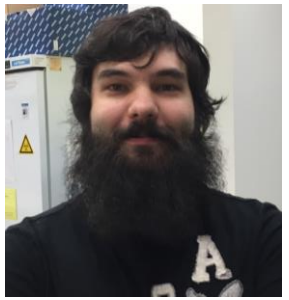
- amfAR

Volunteers!!!!!

Ester Lopez



Matthew Worley

Doherty Institute

THE UNIVERSITY OF MELBOURNE

amfAR MAKING AIDS HISTORY

Australian Government
National Health and Medical Research Council