The Immunomodulatory Role of IgA in HIV Infection

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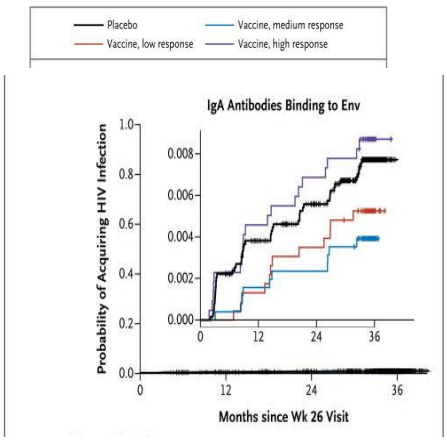
A joint venture between The University of Melbourne and The Royal Melbourne Hospital

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

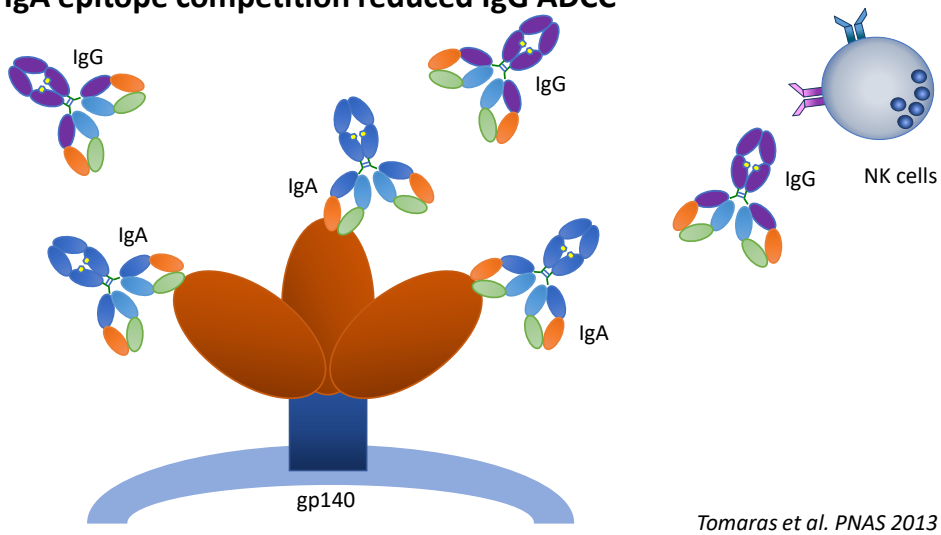


gp120 IgA in plasma- reduced vaccine efficacy

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

- **IgA is bad:**
  - Higher **plasma** IgA associated with disease progression (*Fling J Allergy Clin Immuno 1988, Coates J Clin Epi 1992*)
  - **Plasma** gp120-IgA reduced RV144 vaccine efficacy (*Haynes NEJM 2012*)
  - **Plasma** gp120-IgA blocks IgG ADCC (*Tomaras PNAS 2013*)
  - **Plasma** IgA inhibits ADCC in HIV subjects *(Ruiz J Viro 2015)*
- **IgA is good:**
  - 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)*

Serum total IgA is associated with HIV disease progression

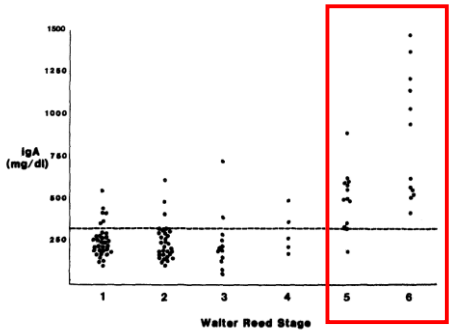


FIG. 3. Relationship of serum IgA concentrations to Walter Reed classification. Note that the serum IgA concentration increased significantly with increasing staging classification (analysis of variance $p = 0.0001$, Kruskal-Wallis $p = 0.0001$). *Dashed line* represents upper limits of normal.

Fling J Allergy Clin Immuno 1988

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

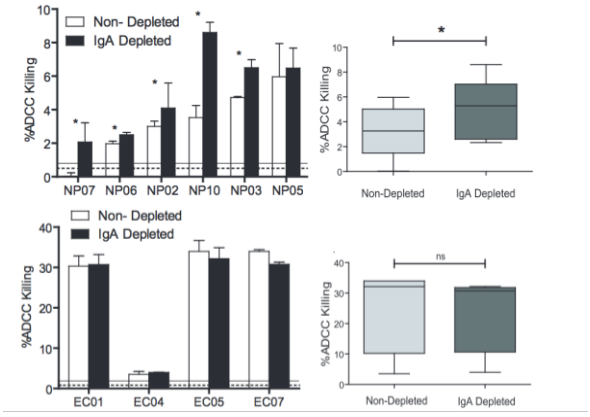
	Enrolment values of marker*			Values lagged one year†		
	Relative risk	95% CI	*p* Value	Relative risk	95% CI	*p* Value
T-cell markers						
T4 cell count (per 100 decline)	1.49	1.20–1.85	0.0004	1.67	1.34–2.08	<0.0001
T8 cell count (per 100 increase)	1.06	0.93–1.21	0.36	1.03	0.94–1.31	0.41
T4/T8 (per 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

WHY?

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

Coates J Clin Epi 1992

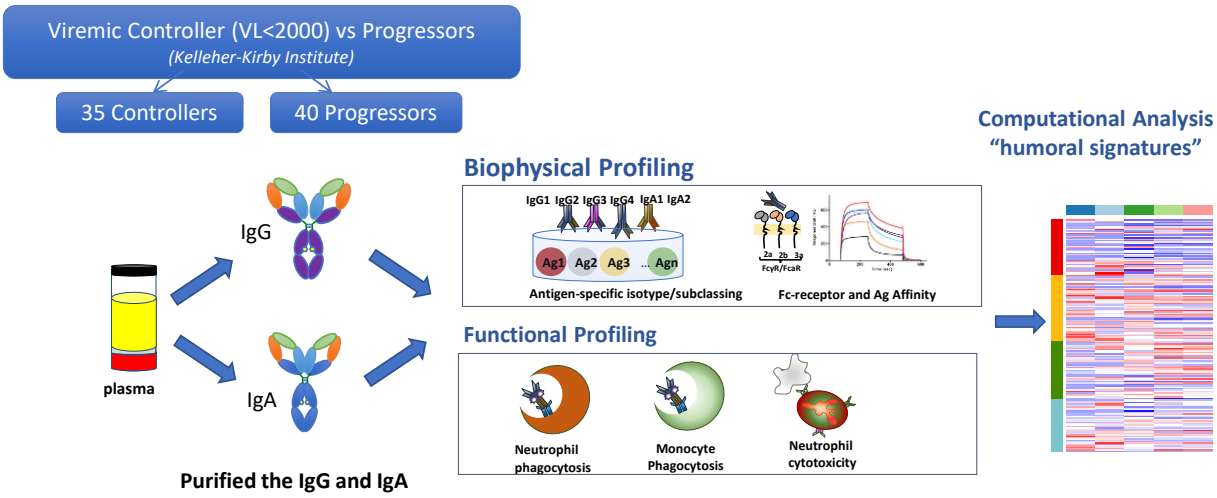
Plasma IgA selectively inhibits ADCC in HIV Progressors



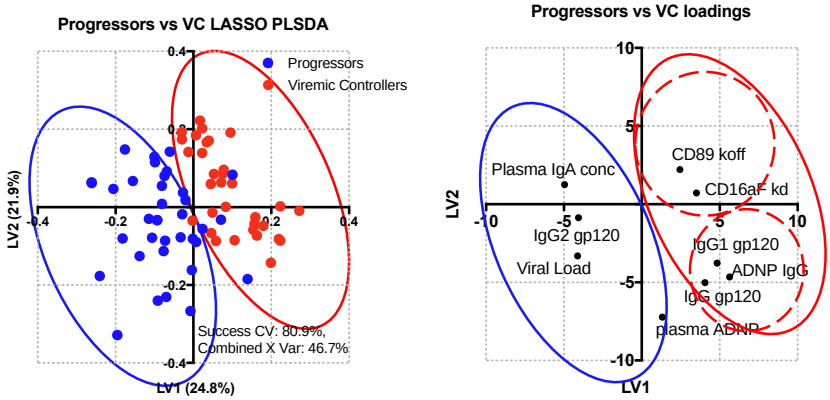
Ruiz et al J Virol 2015

- Progressors: Depletion of IgA improved ADCC
- Elite Controllers: Depletion of IgA had **no effect upon ADCC**?!
- **Plasma IgA is different in spontaneous controllers of HIV?**
- **What is the plasma IgA doing?**

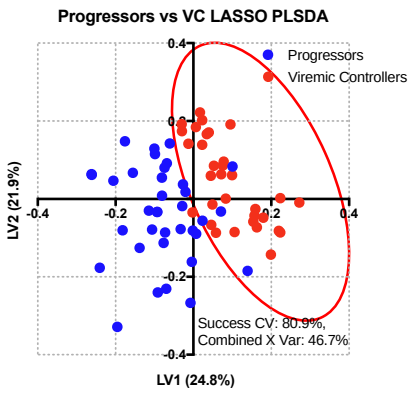
Dissecting the role of serum IgA in HIV infection using Systems Serology

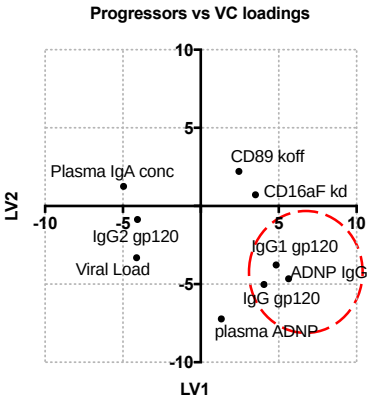


Viremic controllers (VC) and Progressors have very different Ab profiles



Neutrophil IgG mediated Fc effector functions are enhanced in Viremic Controllers





IgG Fc effector functions

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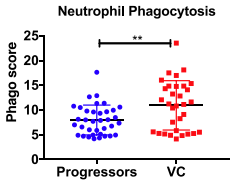
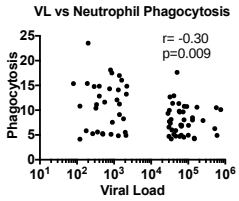
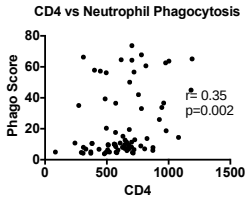
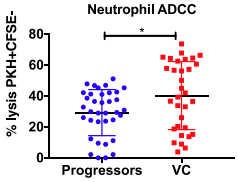
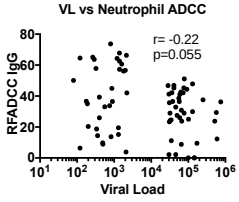
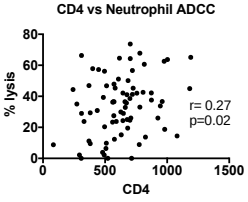






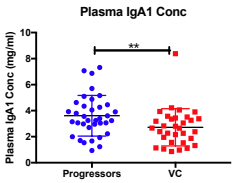


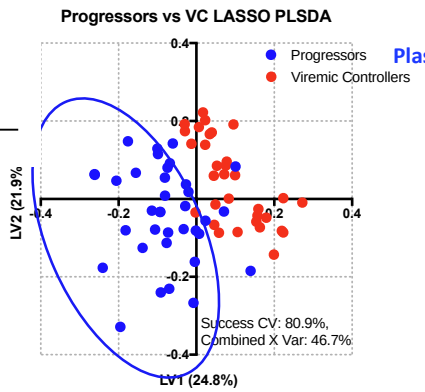


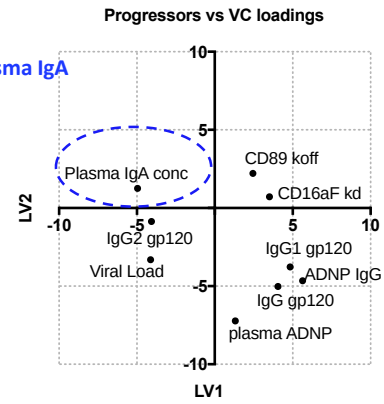


Neutrophil IgG mediated Fc effector functions correlate with delayed disease progression

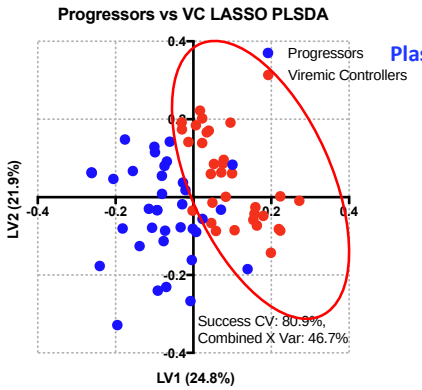
Plasma IgA markers differentiate Viremic controllers (VC) from Progressors

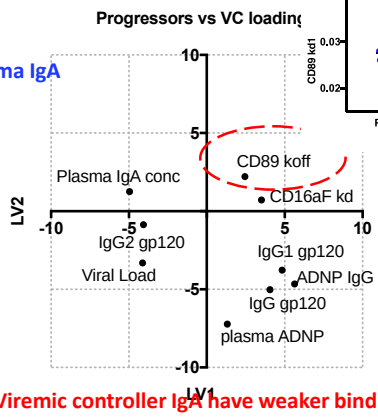


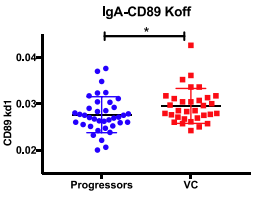




Plasma IgA and CD89 (FcaR) engagement differentiate Viremic controllers (VC) from Progressors







weaker affinity

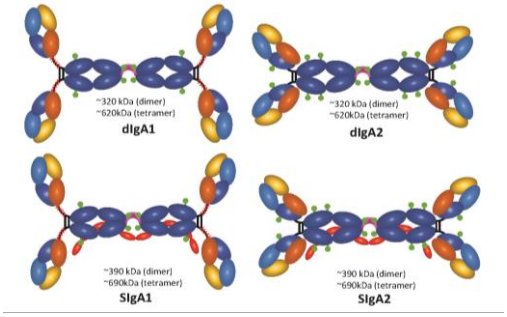
Progressor total plasma (monomeric) IgA1 bind with higher affinity to FcaR

Viremic controller IgA have weaker binding to FcaR

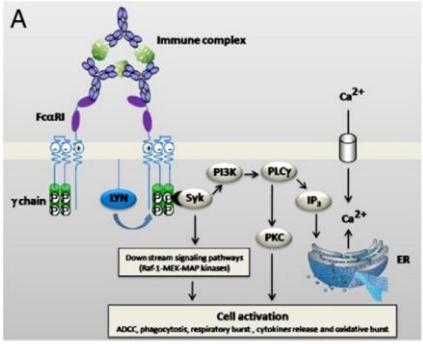
What does this mean?!

Different Forms of IgA: Dimeric IgA

Mucosal



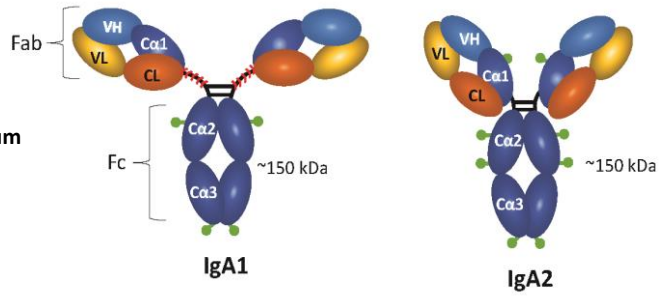
Dimeric IgA
-crosslink FcAR
-Fc activation (ITAM)
-ADCC
-Phagocytosis
-activating cytokines



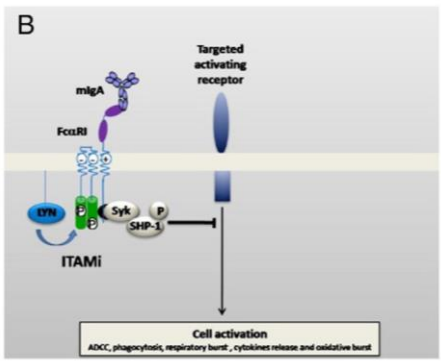
Ben Mkaddem Autoimmunity Reviews 2013

Different Forms of IgA: monomeric IgA

Serum



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



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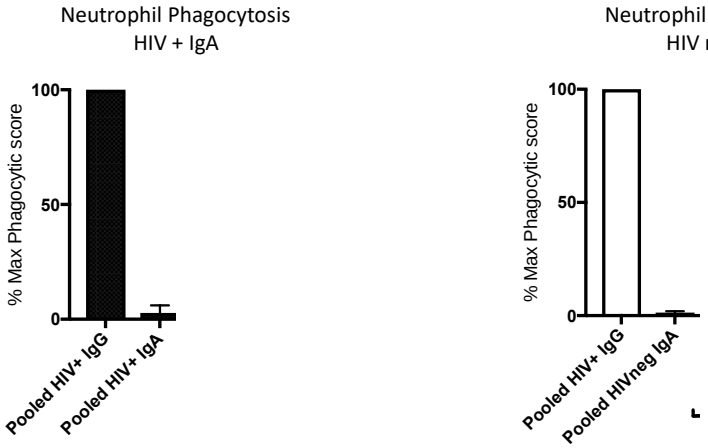
Plasma IgA can inhibit IgG Fc effector functions – via FcAR inhibitory signaling



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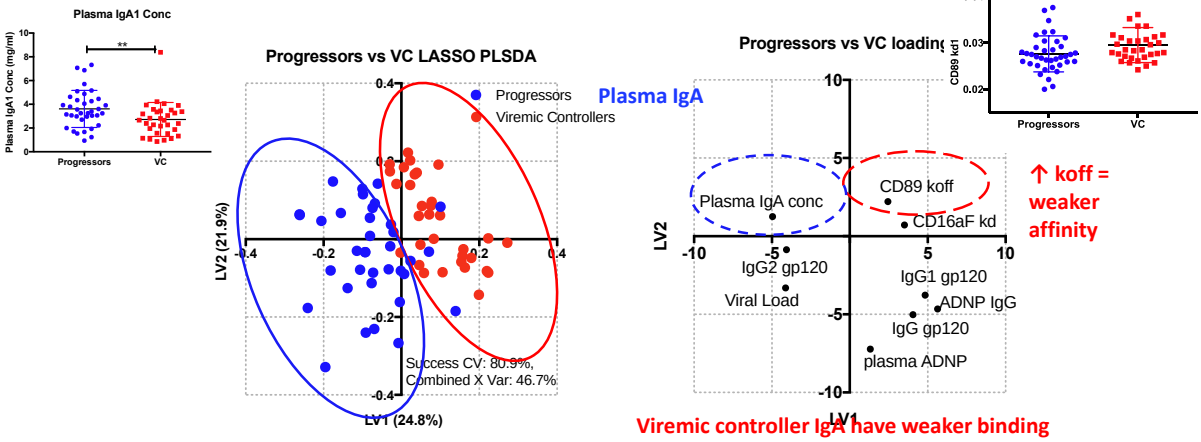
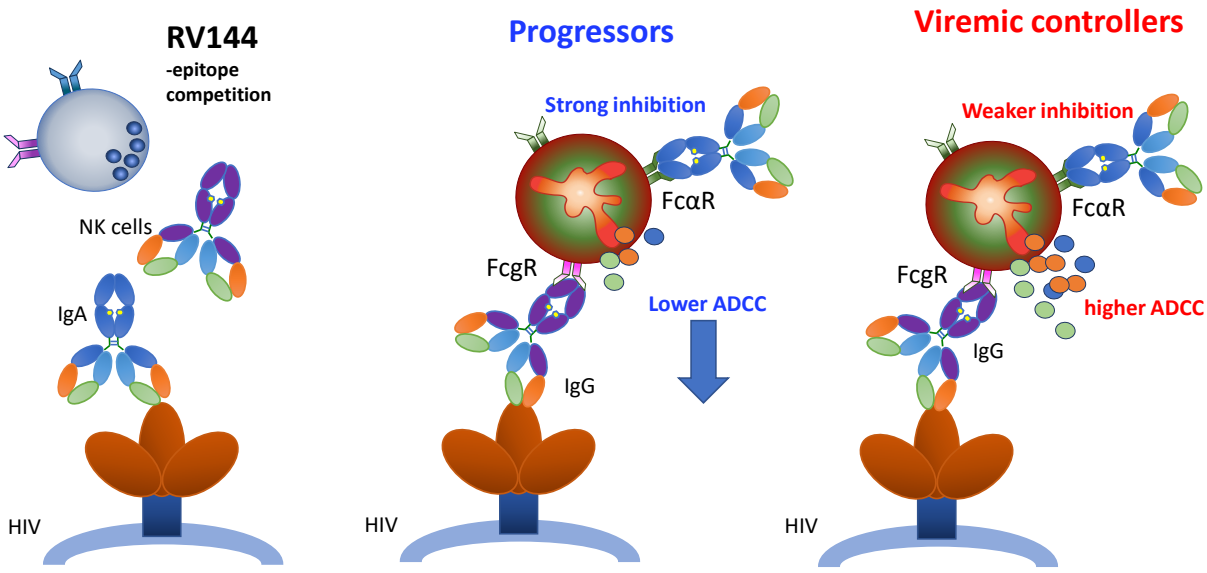


Progressor total plasma (monomeric) IgA1 bind with higher affinity to FcaR

Viremic controller IgA have weaker binding to FcaR

What does this mean?!

Multiple mechanisms of IgA inhibition in HIV infection



Future directions:

- What is so unique about IgA in controllers?
- Why do controllers have less inhibitory IgA?
  - Why do a subset of controllers have IgA that work in combination with IgG?
- Did IgA-FcaR inhibition of Fc effector responses contribute to RV144?

Acknowledgments

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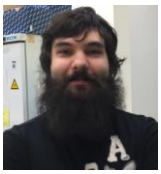
Volunteers!



Matthew Worley

Ester Lopez