Highly Sensitized Transplant Candidate

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FDA WORKSHOP:
ANTIBODY MEDIATED REJECTION
IN KIDNEY TRANSPLANTATION

April 12-13, 2017

Disclosure

- Funding:
  - BMS- *Investigator Initiated Trial*
  - Takeda Millennium- *Investigator Initiated Trial*
  - NIDDK- *R01*

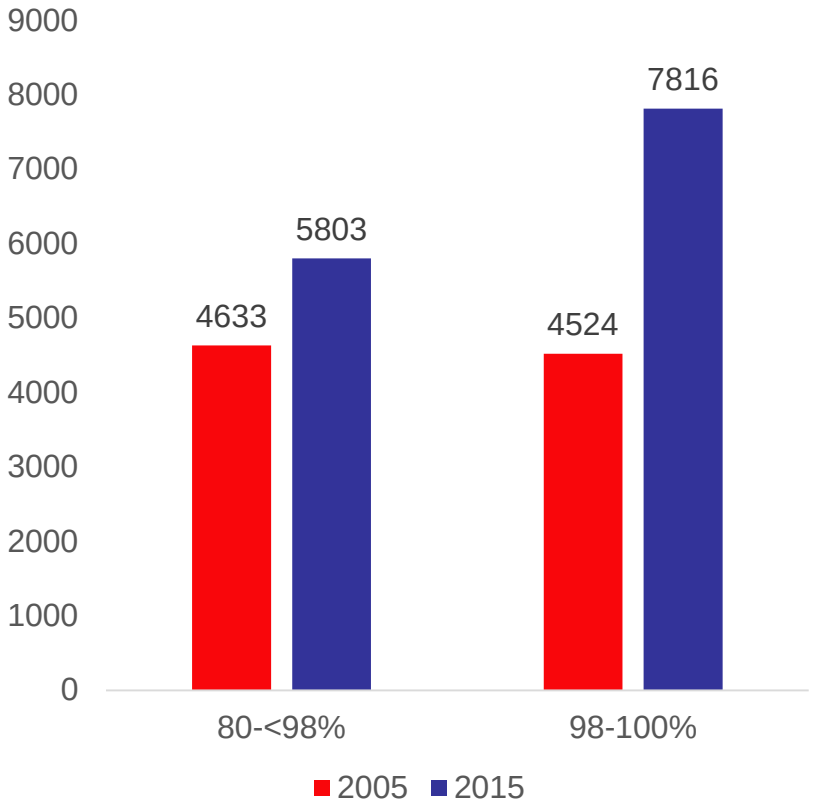
- Off label drug use
  - The of material in this presentation WILL include discussion of unapproved or investigational uses of products.

Highly Sensitized Transplant Candidate

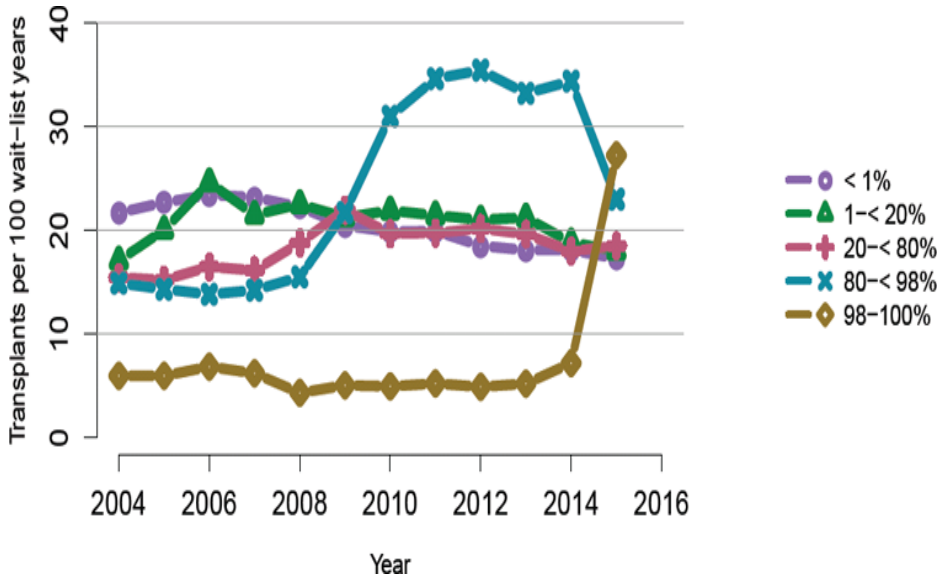
- Background
- Clinical Studies
- Outcomes
- Limitations
- Future Directions

Growing numbers: ~ **14,000** patients in 2015
Modest impact of new KAS on total rate of transplant

Accumulation of highly sensitized transplant candidates on the waitlist

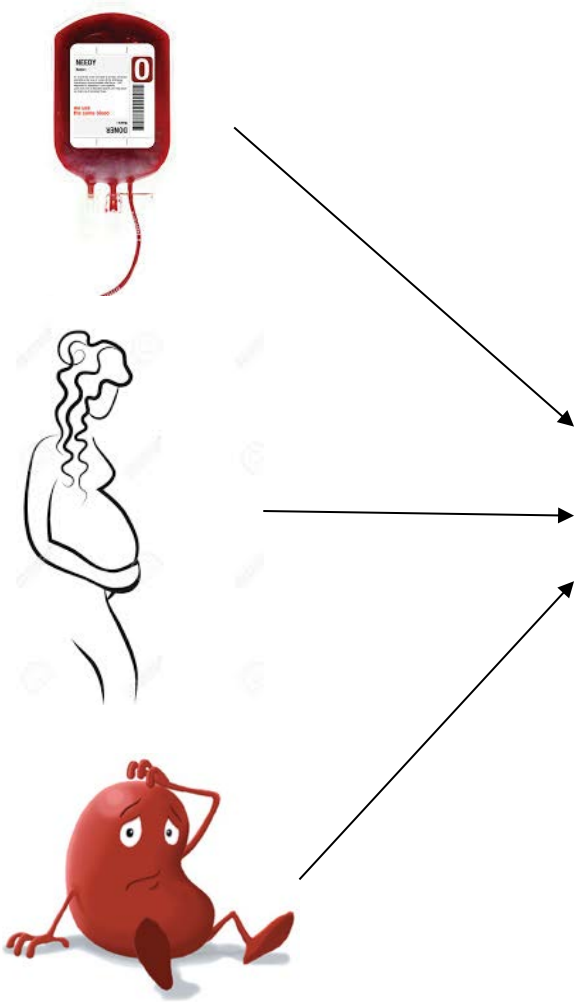


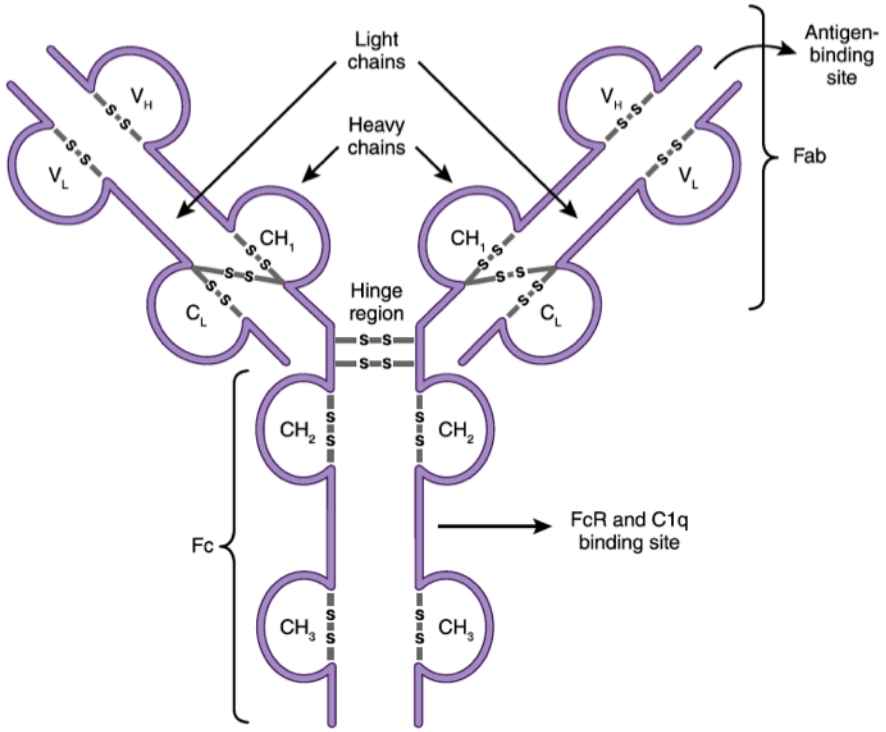
New **KAS** has **modest** impact on total rate of transplantation in highly sensitized



OPTN/SRTR 2015 ADR, Am J Transplant, 2017, Volume 17, Issue, Supplement S1, 1–564

The Problem: **IgG**





Hoffman et al, Clin J Am Soc Nephrol 11: 137–154, January, 2016

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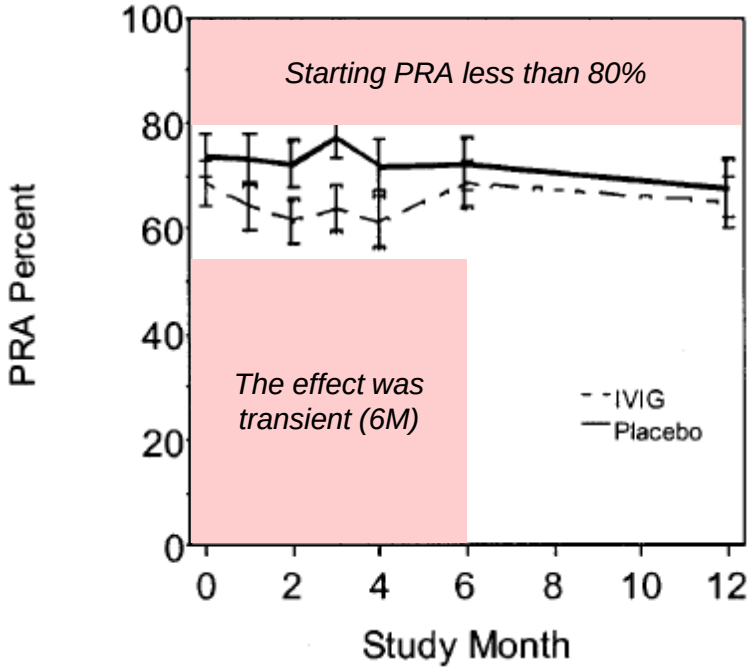
IVIG decreases sensitization

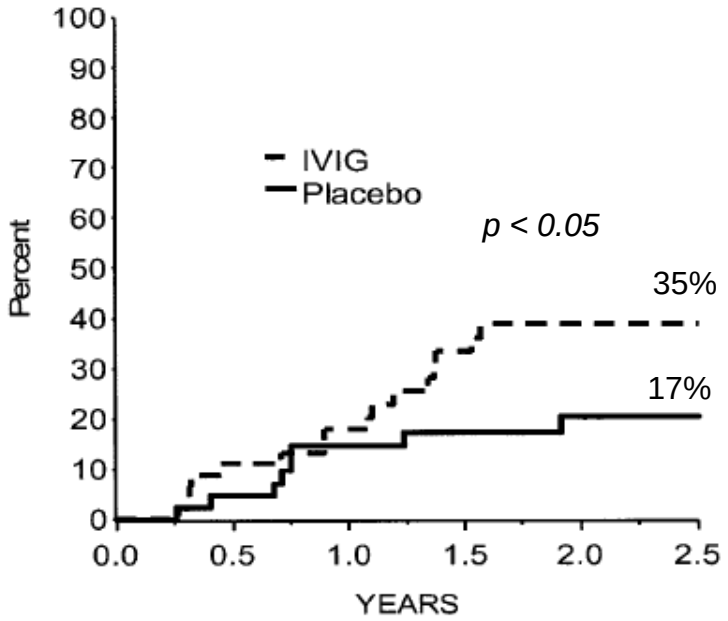
The NIH IG02 Trial

RCT of sensitized patients (n=98) to IVIG 2g/kg/m x 4 vs. placebo

Decline in **PRA** was significant but **transient** (6M)

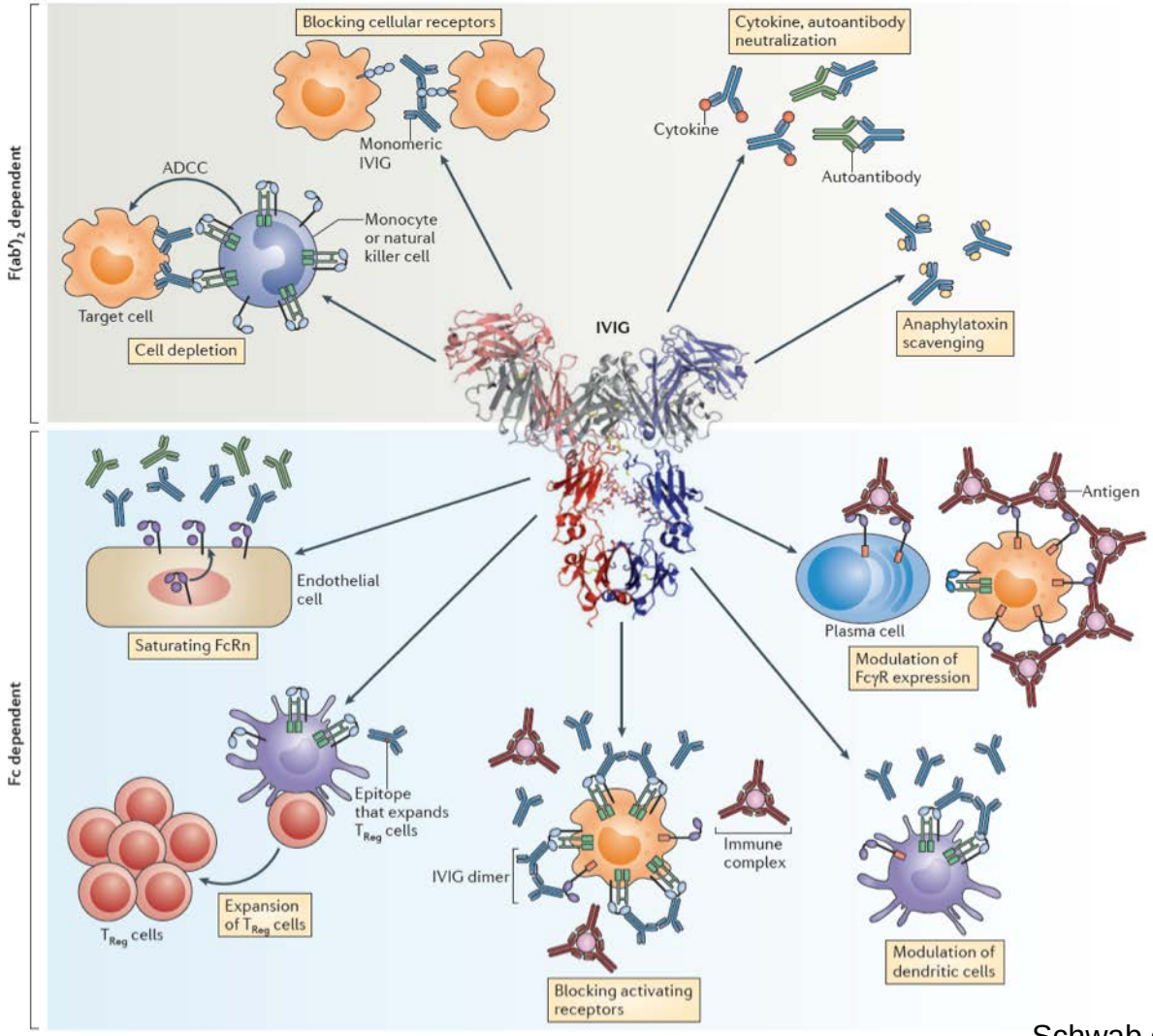


IVIG associated with **better transplantation** rate



Jordan et al, J Am Soc Nephrol 15: 3256–3262, 2004

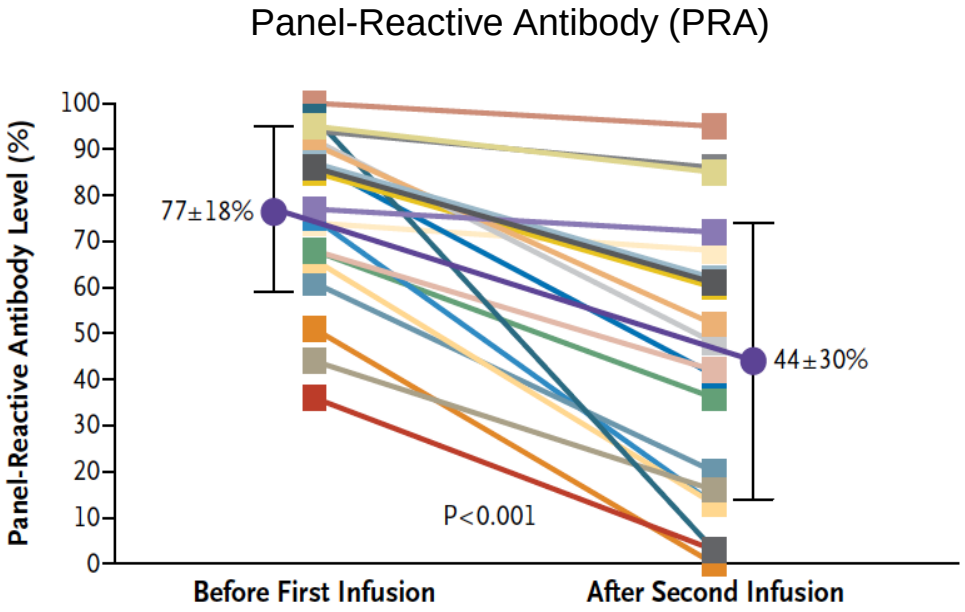
Mechanisms of action of **IVIG**

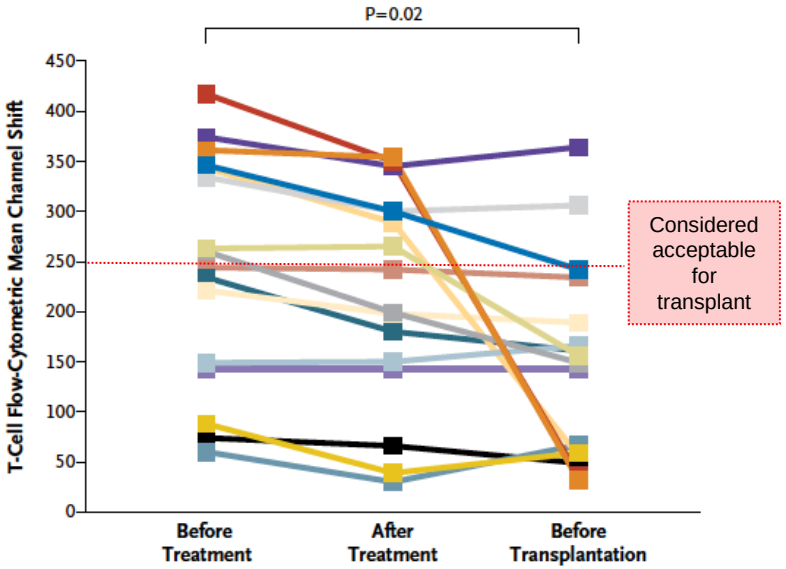


Schwab et al, Nat Rev Immunol, 2013

Rituximab and High Dose **IVIG**

Successful Desensitization





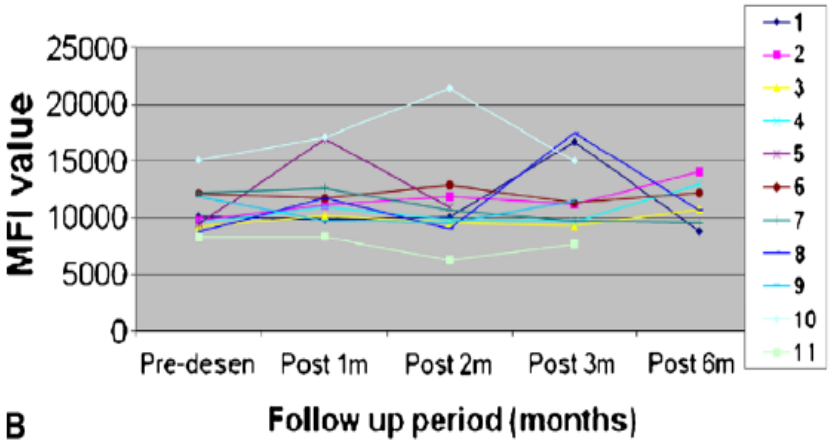
Vo AA, et al. *N Engl J Med*. 2008;359:242-251.

Rituximab and High Dose **IVIG**

Unsuccessful Desensitization for very high PRA

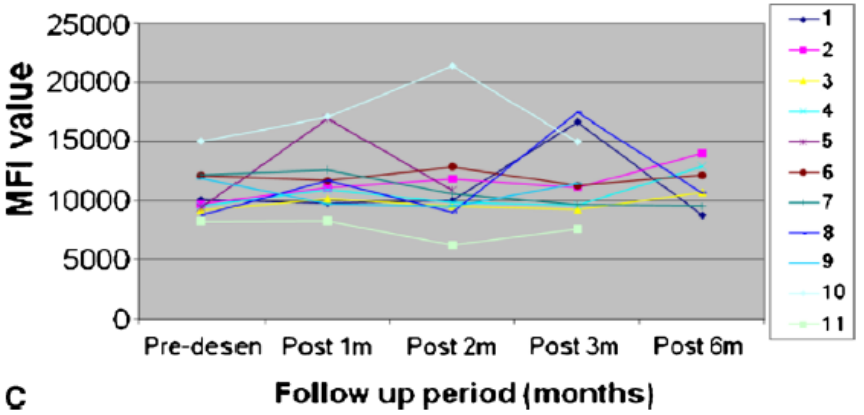
Pretransplant desensitization with IVIG and rituximab was not successful in highly sensitized kidney transplant candidates with **cPRA > 90%**

Class I DSA



B

Class II DSA



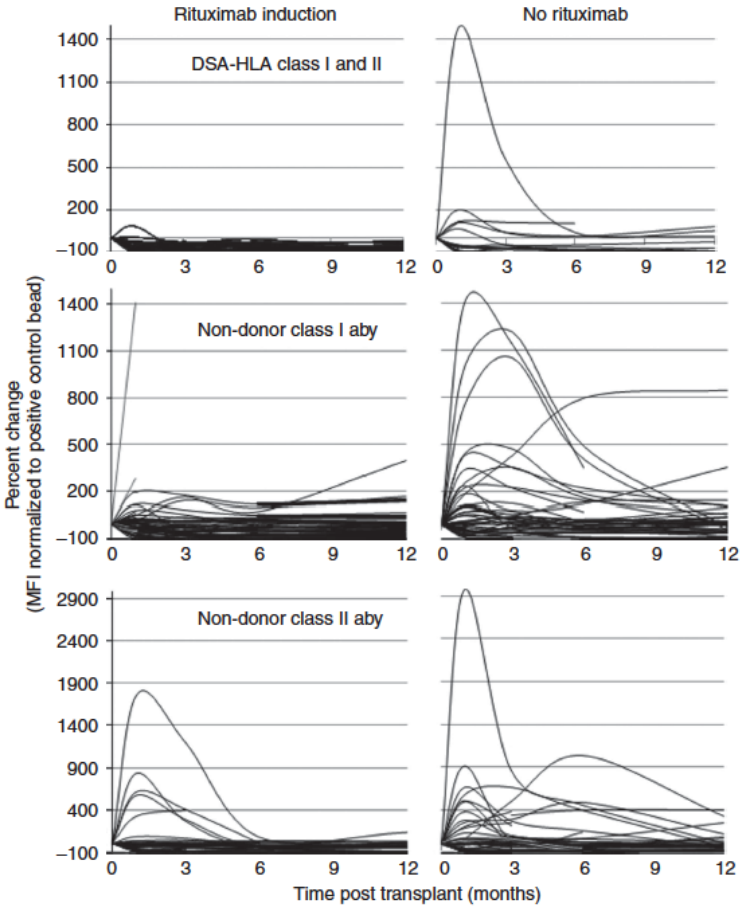
C

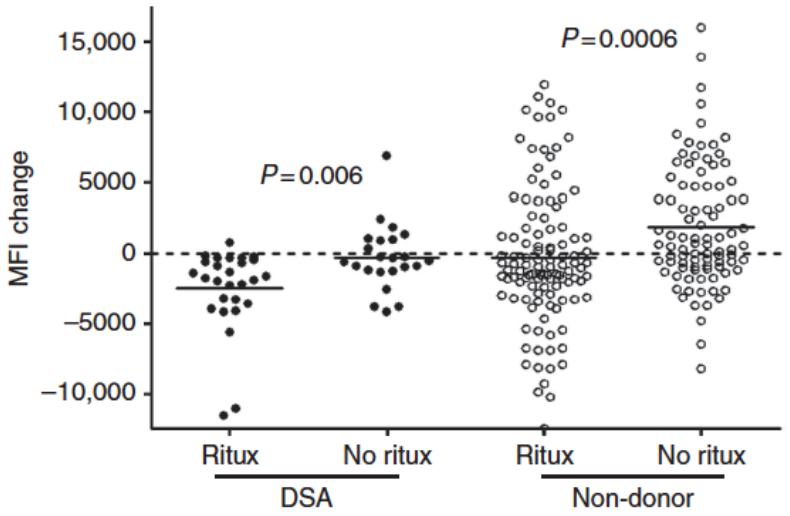
- Marfo, Akalin, et al, Transplantation 2012;94: 345-351
- Lobashevski et al, Transplantation 2013;96: 182-190
- Alachkar et al, Transplantation 2012;94: 165-171

Rituximab induction

*Reduced incidence and magnitude of HLA antibody **rebound***

Rituximab reduced antibody strength and **rebound**



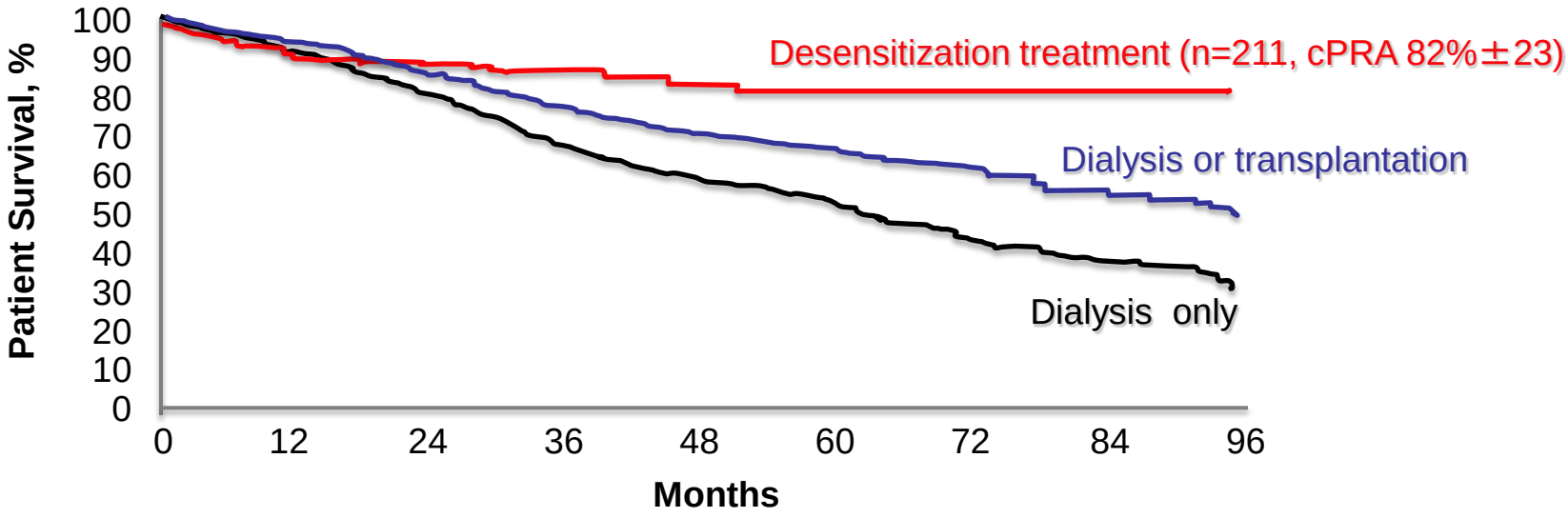


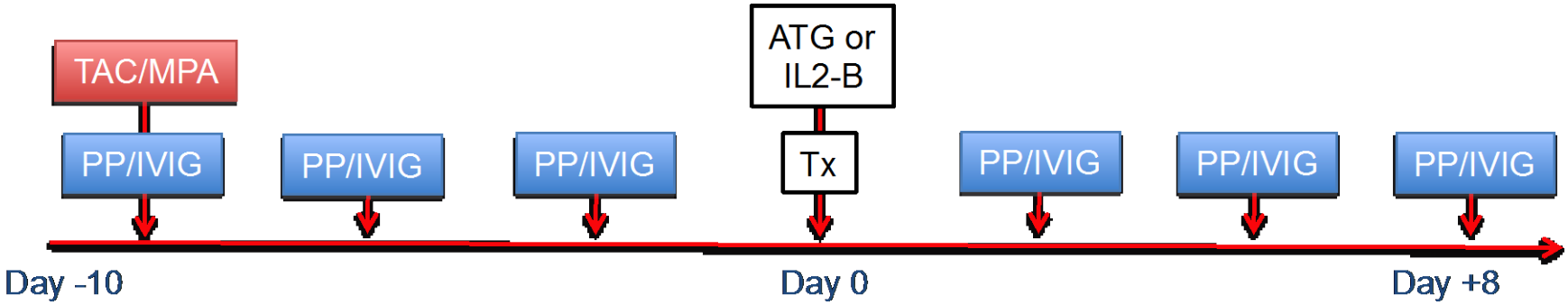
No difference in DSA elimination, AMR, and 5 year graft survival

Jackson et al, Kidney International (2015) 87, 409–416

PLEX and **low-dose IVIG**

in live donor Kidney Recipients





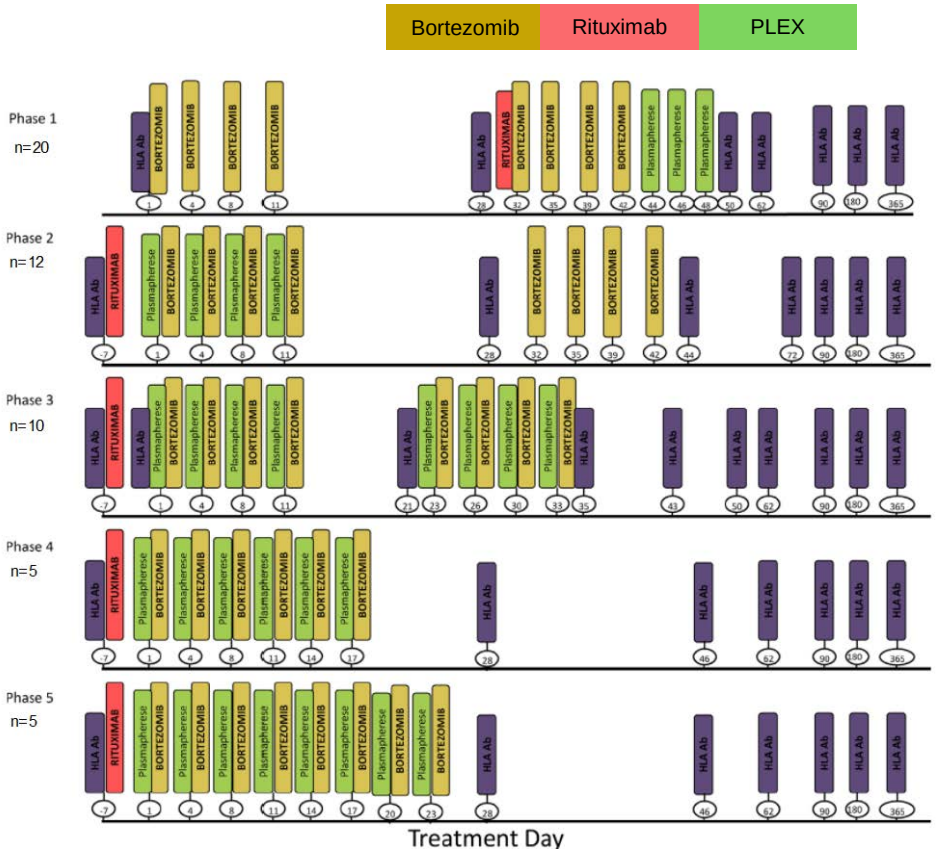
Montgomery et al, N Engl J Med 2011
Orandi et al, N Engl J Med 2016

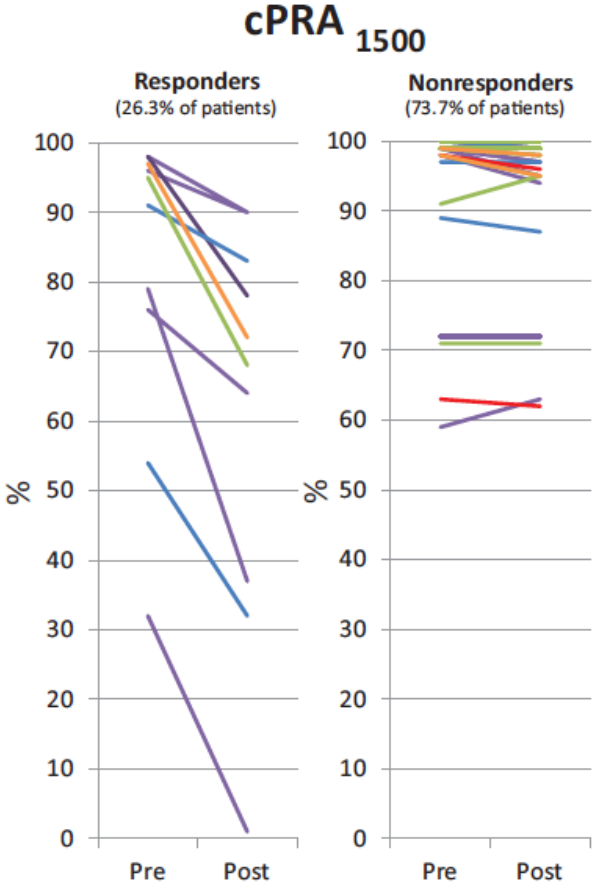
Proteasome Inhibitor-Based Desensitization

Was relatively successful in live and deceased donor Tx

Intent to treat 52 patients → Completed 38 (73%) → 19 transplanted (37%)

$cPRA_{1500}$ 91%





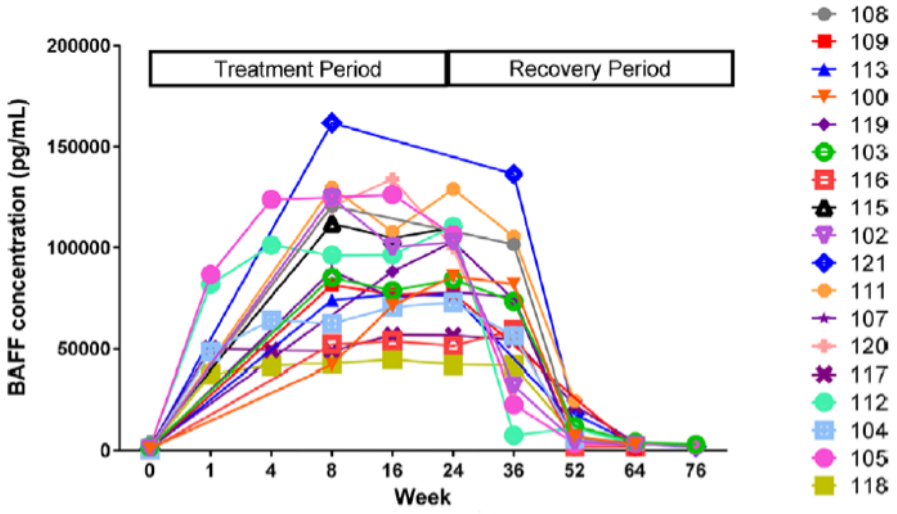
Woodle et al, American Journal of Transplantation 2015; 15: 101–118

Tabalumab (**BAFF inhibitor**)

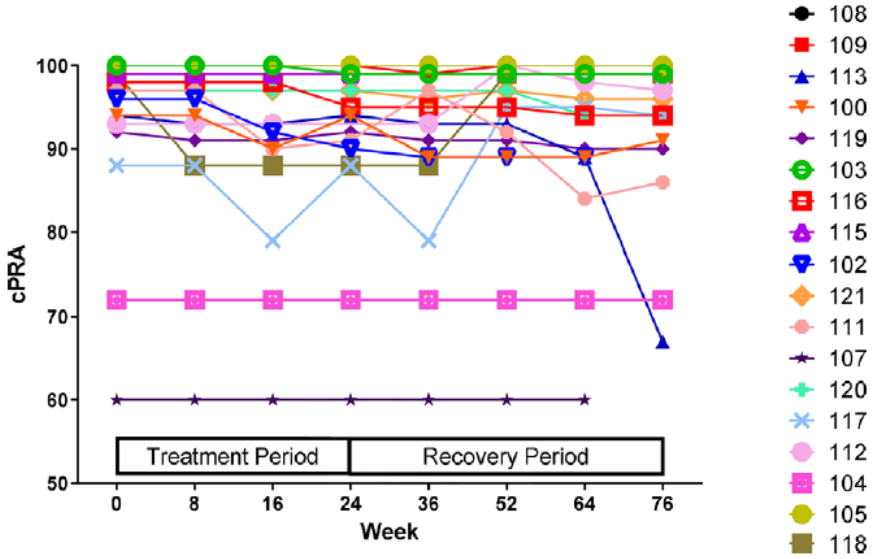
had Minimal Effect in Highly Sensitized

Tabalumab (anti-BAFF), at doses of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC monthly for 5 additional months (Baseline cPRA 94.4±9.1%, n=18 -> 3 transplanted)

BAFF levels



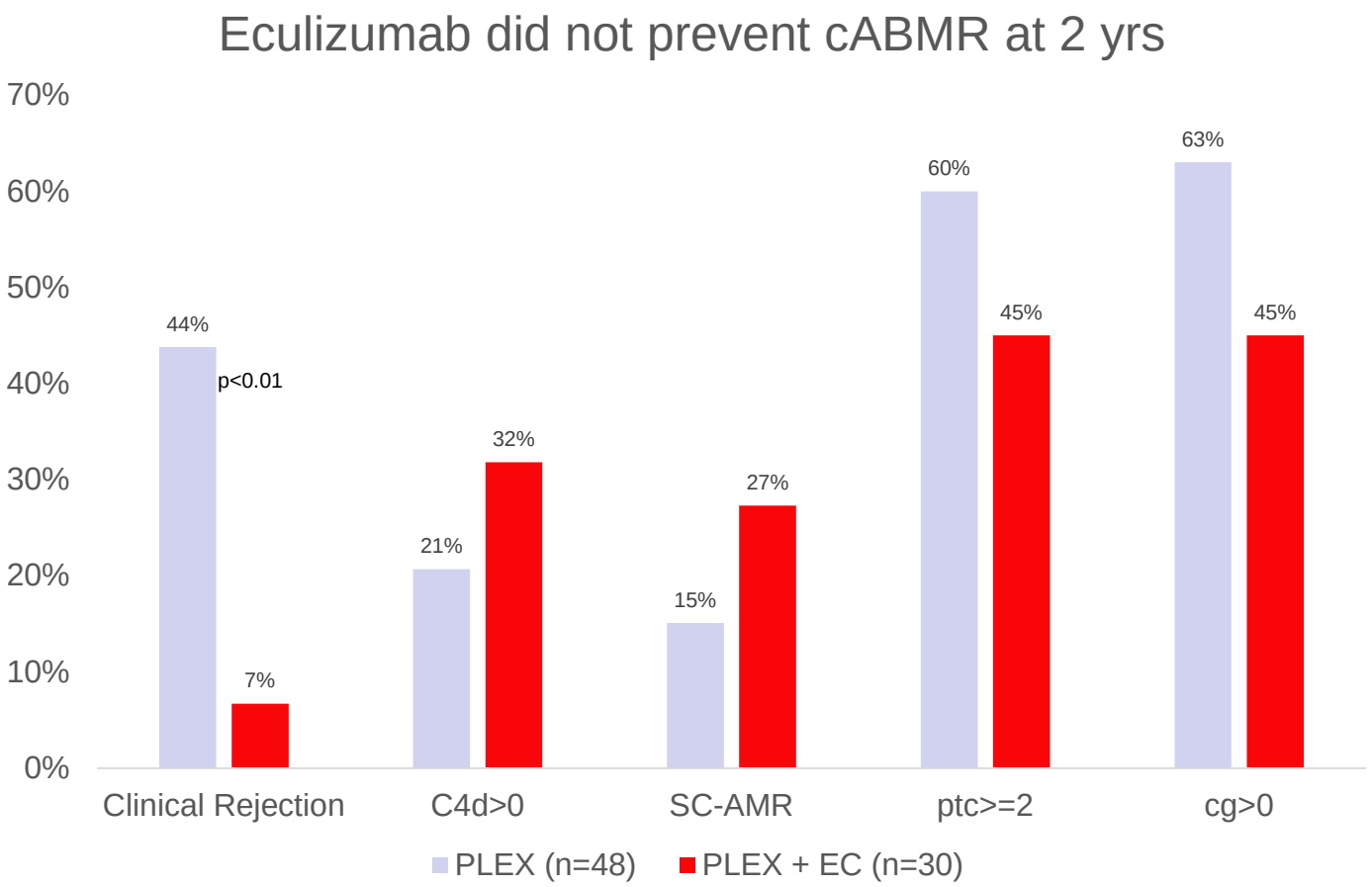
cPRA levels



Mujtaba et al Am J Transplant, 2016

Desensitization with **Eculizumab**

Short term success but limited outcome beyond 1 year



Cornell et al, American Journal of Transplantation 2015; 15: 1293–1302

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Summary of clinical studies

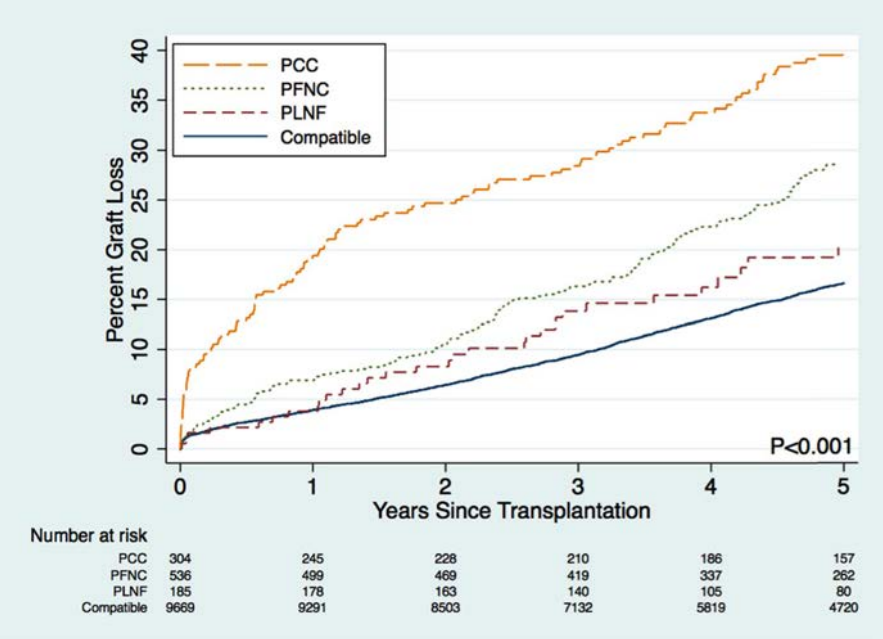
Limited impact on PRA and transplant rates

	PI	N	c/PRA	Regimen	Effect PRA	Transplant	Reference
1	*Jordan*	98	~70%	IVIG	~5%	35% *v.* 17%	*J Am Soc Nephrol 2004*
2	*Vo*	20	77%	IVIG-Ritux	(-) 33%	16 (80%)	*N Engl J Med 2008*
3	*Lobashevski*	31	65-100%		-	2 (6%)	*Transplantation 2013*
4	*Marfo*	13	>90%		-	2 (15%)	*Transplantation 2012*
5	*Alachkar*	27	100%		-	11 (41%)	*Transplantation 2012*
6	*Stegall*	26	N/A	Eculizumab	N/A	26 (100%)	*Am J Transplant 2011*
7	*Woodle*	52	91%	Bortez-Ritux-PLEX	25% responders	19 (37%)	*Am J Transplant 2015*
8	*Mujtaba*	18	94%	Tabalumab (BAFF)	±	3 (17%)	*Am J Transplant 2016*
9	*Vo*	10	74% (I) 93% (II)	IVIG-Tocilizumab (IL6-R)	(-) 15% (I) (-) 4% (II)	5 (50%)	*Transplantation 2015*
10	*Naji*	8	N/A	Belimumab (BAFF)	-	1 (13%)	*NCT01025193*
11	*Redfield*	24	N/A	IVIG-Obinutuzumab (CD20)	N/A	N/A	*NCT02586051*
12	*Woodle*	8	N/A	Carfilzomib (PI)	N/A	N/A	*NCT02442648*
13	*Jordan*	15	N/A	Ides (IgG endopeptidase)	N/A	N/A	*NCT02790437*

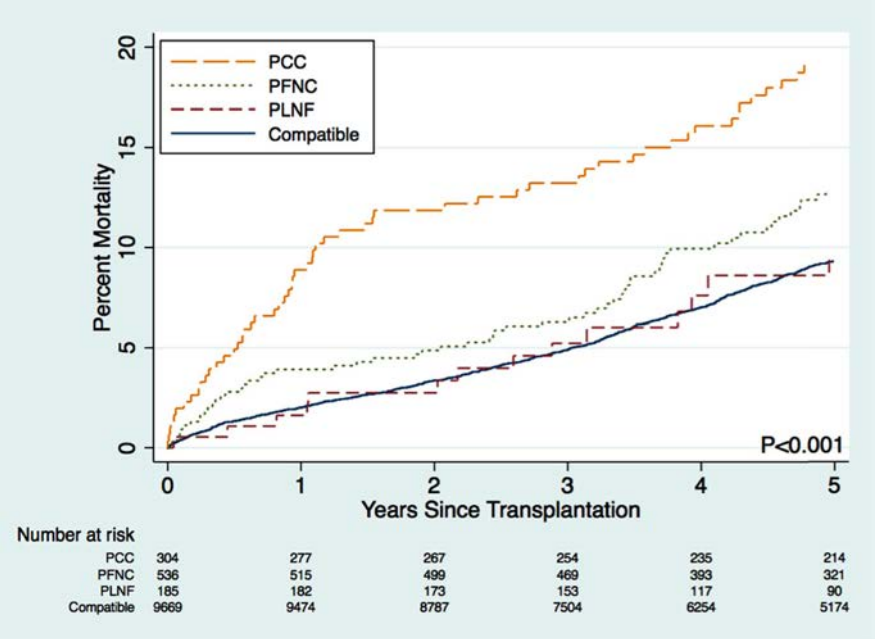
Quantifying the risk of incompatible kidney transplantation: a multicenter study

DSA Strength Associated with Poor Outcomes

Graft Loss



Patient Death



PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch

Orandi et al, American Journal of Transplantation 2014; 14: 1573–1580

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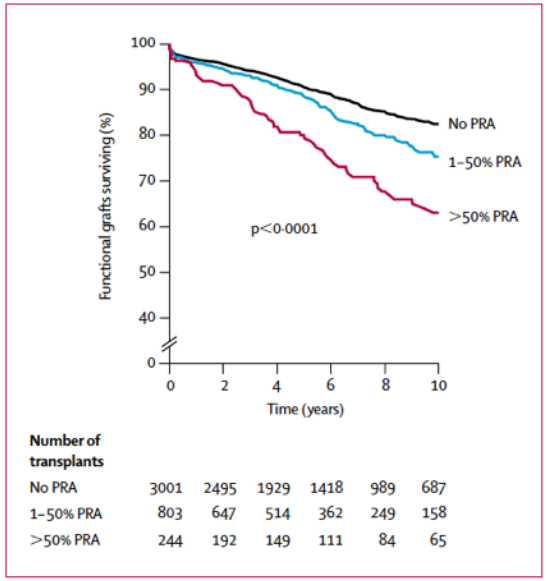
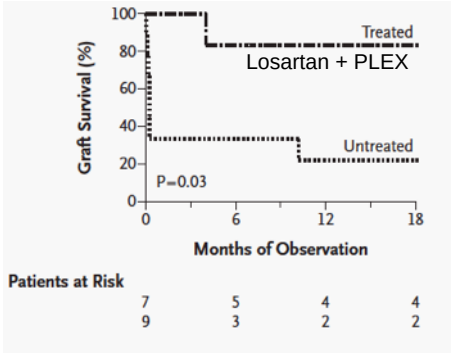
Considering **Non-HLA** antigens

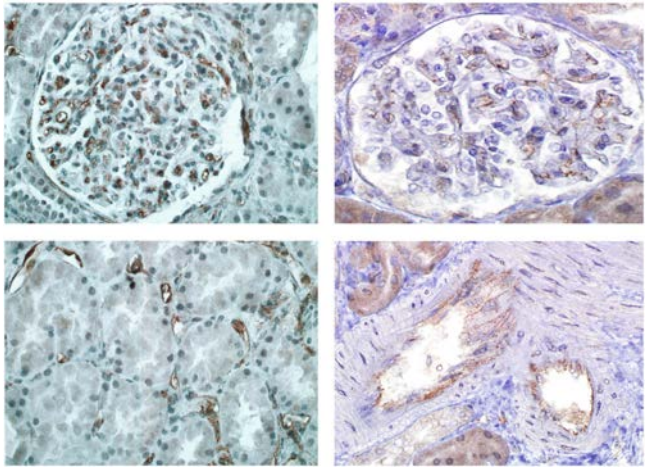
(1) High PRA associated with poor graft survival in HLA-identical sibling transplants



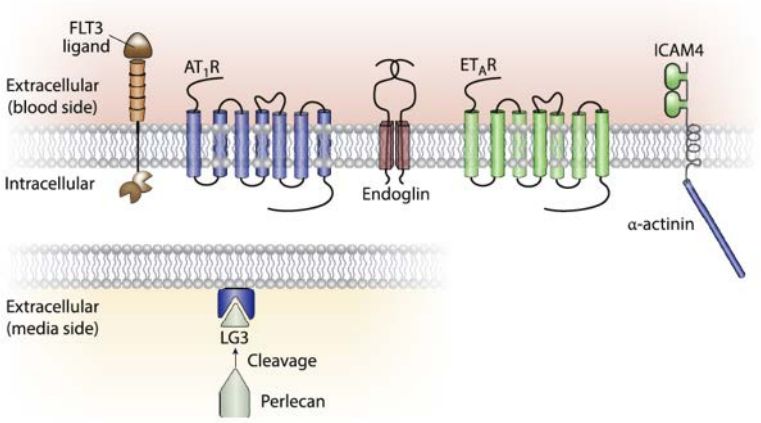
(2) AT1R mediated Rejection



(3) Endoglin Fms-like tyrosine kinase-3 (FLT3) ligand

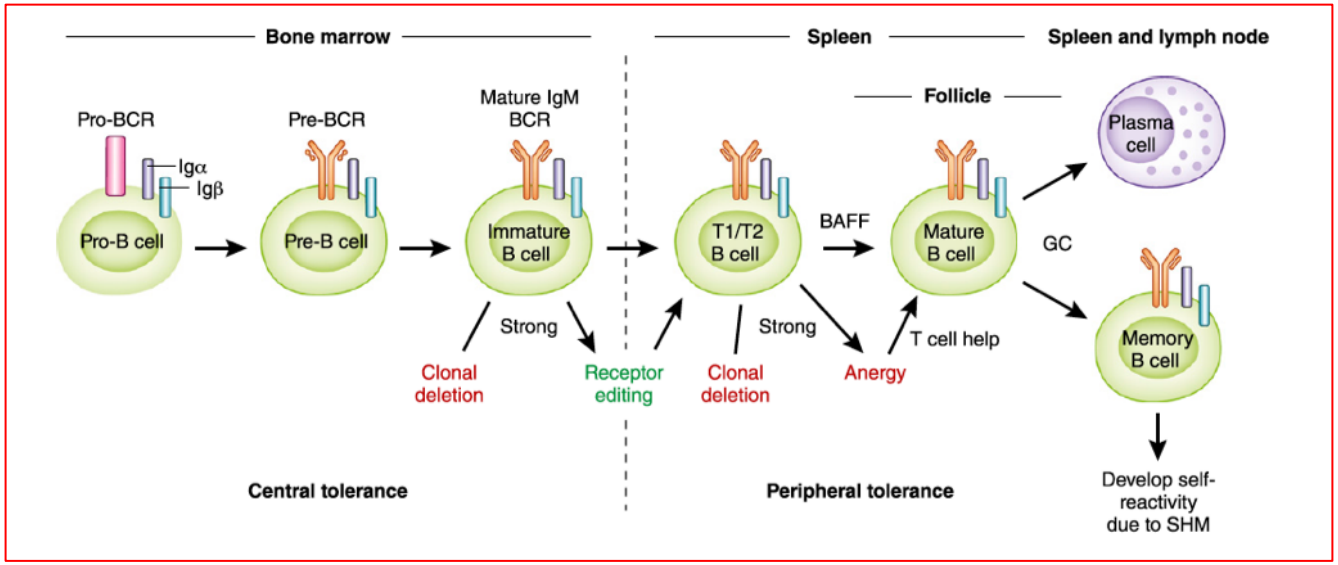


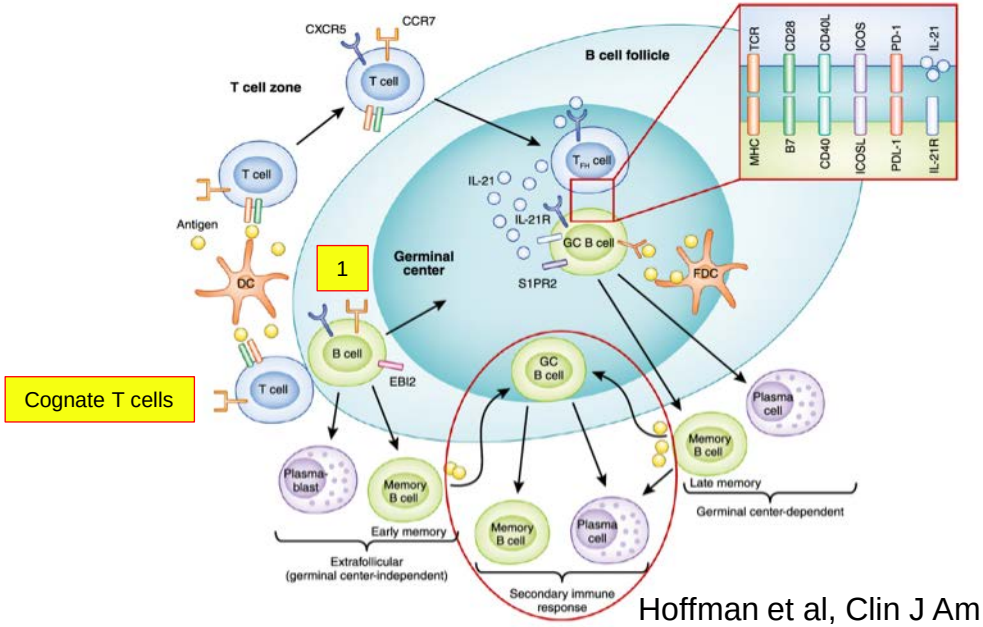
(4) Overview of non-HLA antibodies directed against endothelial targets



1. Opelz et al, Lancet 2005
2. Dragun et al, N Engl J Med 2005
3. Jackson et al, J Am Soc Nephrol 2015
4. Dragun et al, Kidney International 2016

Targeting **B cell Development**

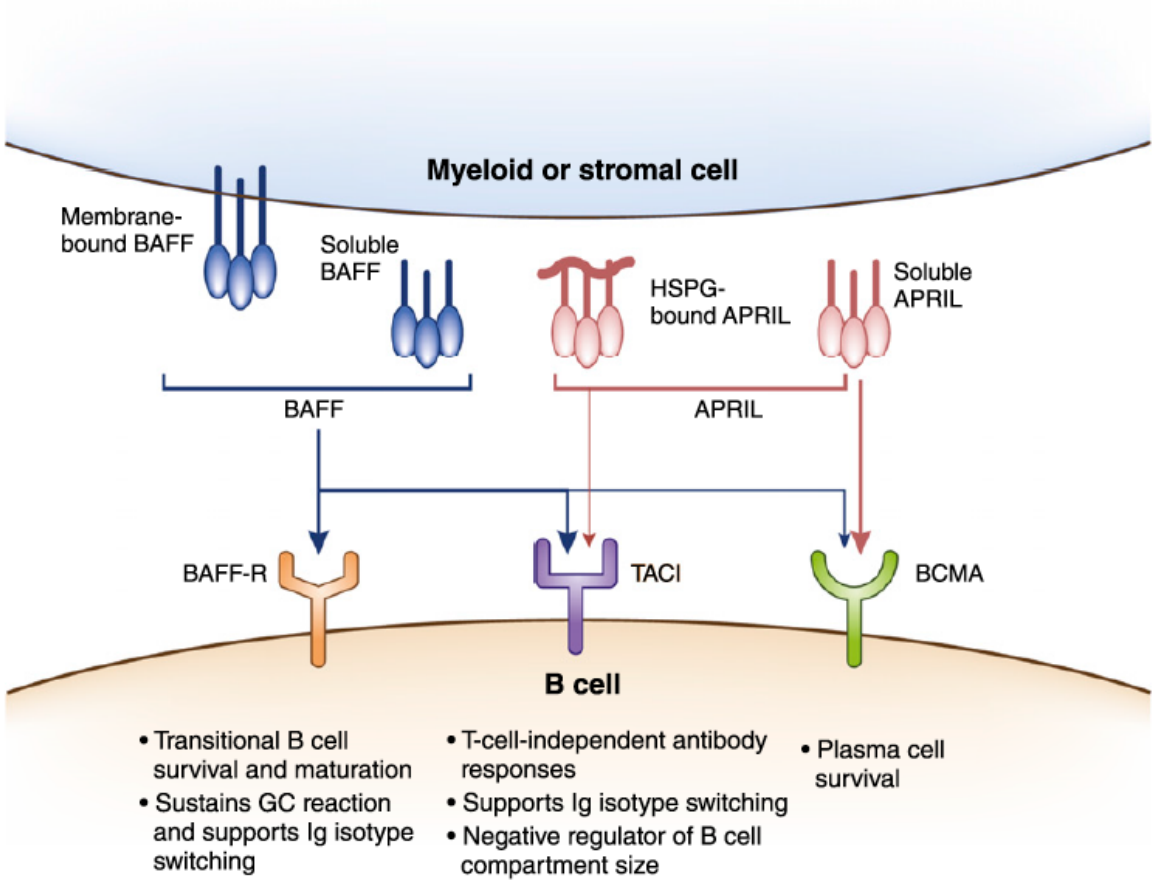




Hoffman et al, Clin J Am Soc Nephrol 11: 137–154, January, 2016

Targeting B cell **Activation**

BAFF, APRIL and their Receptors

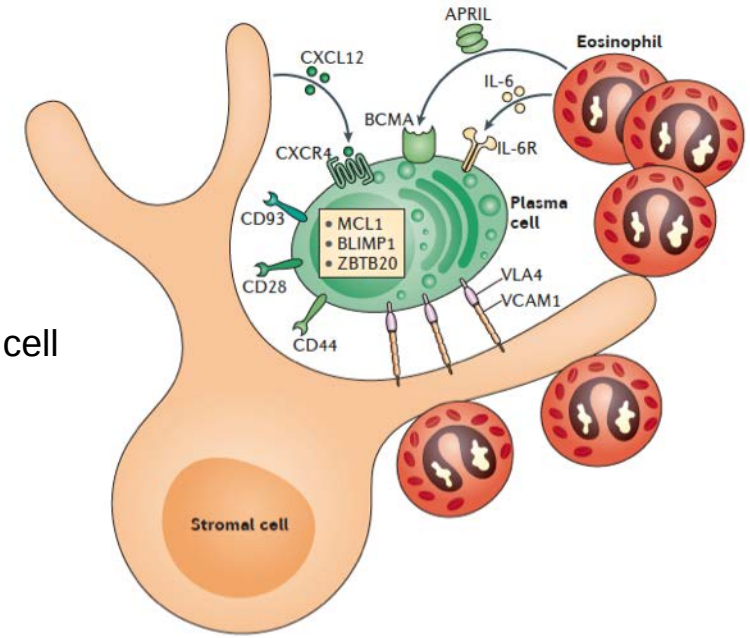


Hoffman et al, Clin J Am Soc Nephrol 11: 137–154, January, 2016

Targeting Bone Marrow

Plasma Cells and their Survival Niche

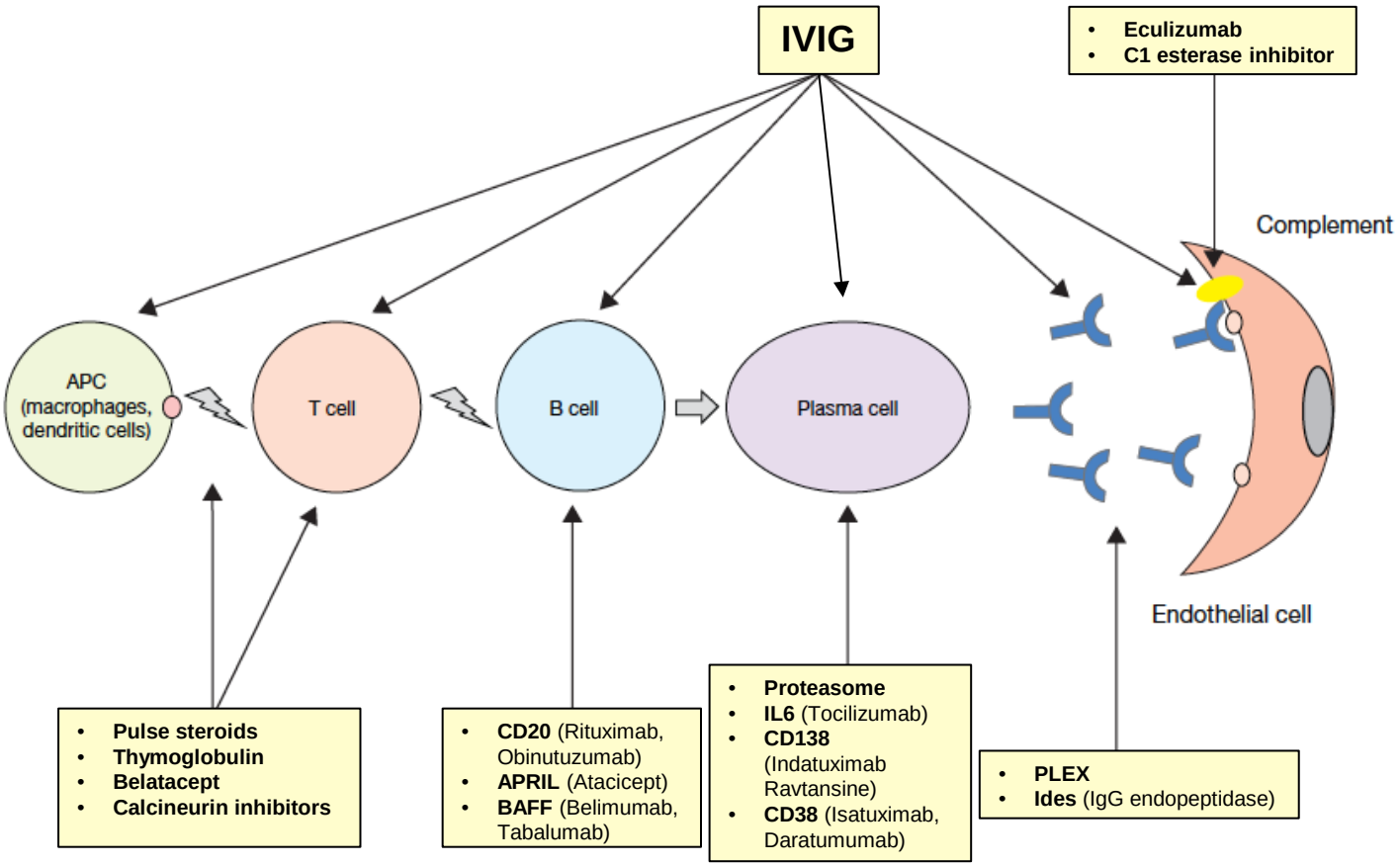
The important role of the Stromal cell



	Naïve B cell	Plasmablast	Mature Plasma Cell
Lifespan	++	+	++++
Proliferation	-	++	-
CD (27, 38, 138), CXCR4	-	+	+++
CD (19, 20, 45), MHCII	+++	++	±
Location	L.O.	Blood, L.O.	Bone marrow
Isotype	IgM, IgD	All	IgG>>IgA>IgM
BLIMP1	-	+	++

Nutt et al, Nat Rev Immunol 2015

Finding the right **combination** therapy



Modified from Djamali et al, American Journal of Transplantation 2014; 14: 255–271

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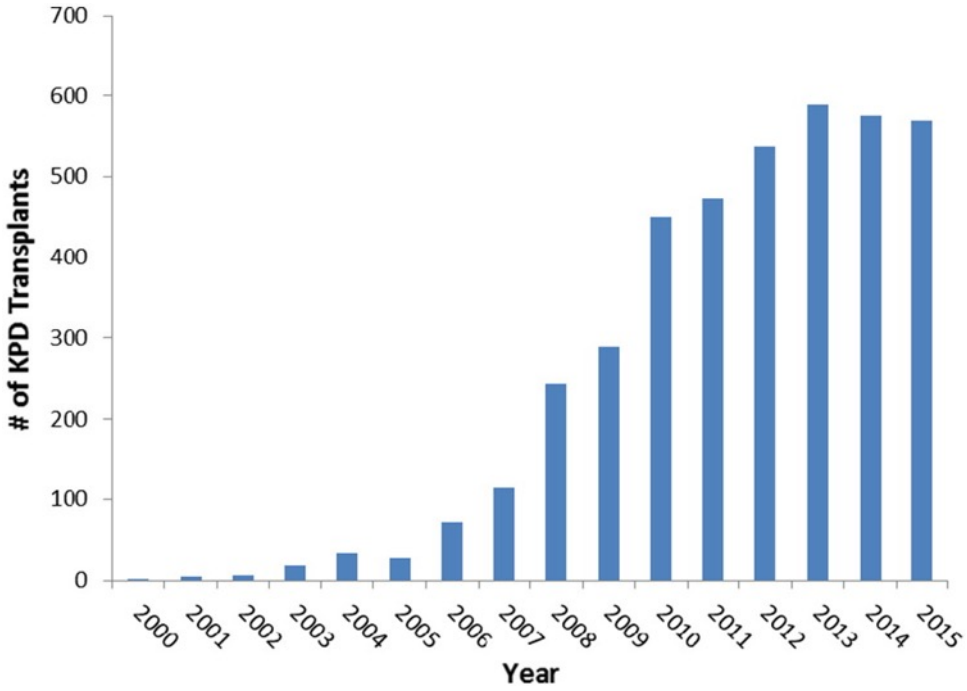
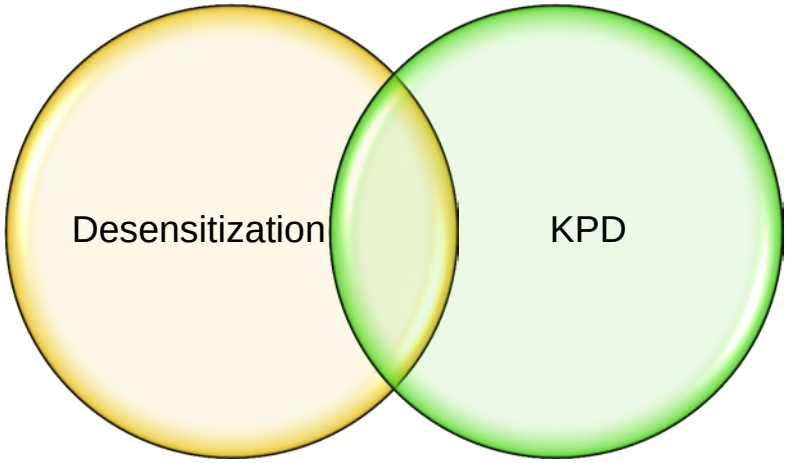
Kidney Paired Donation (KPD)



Combining DSZ + KPD

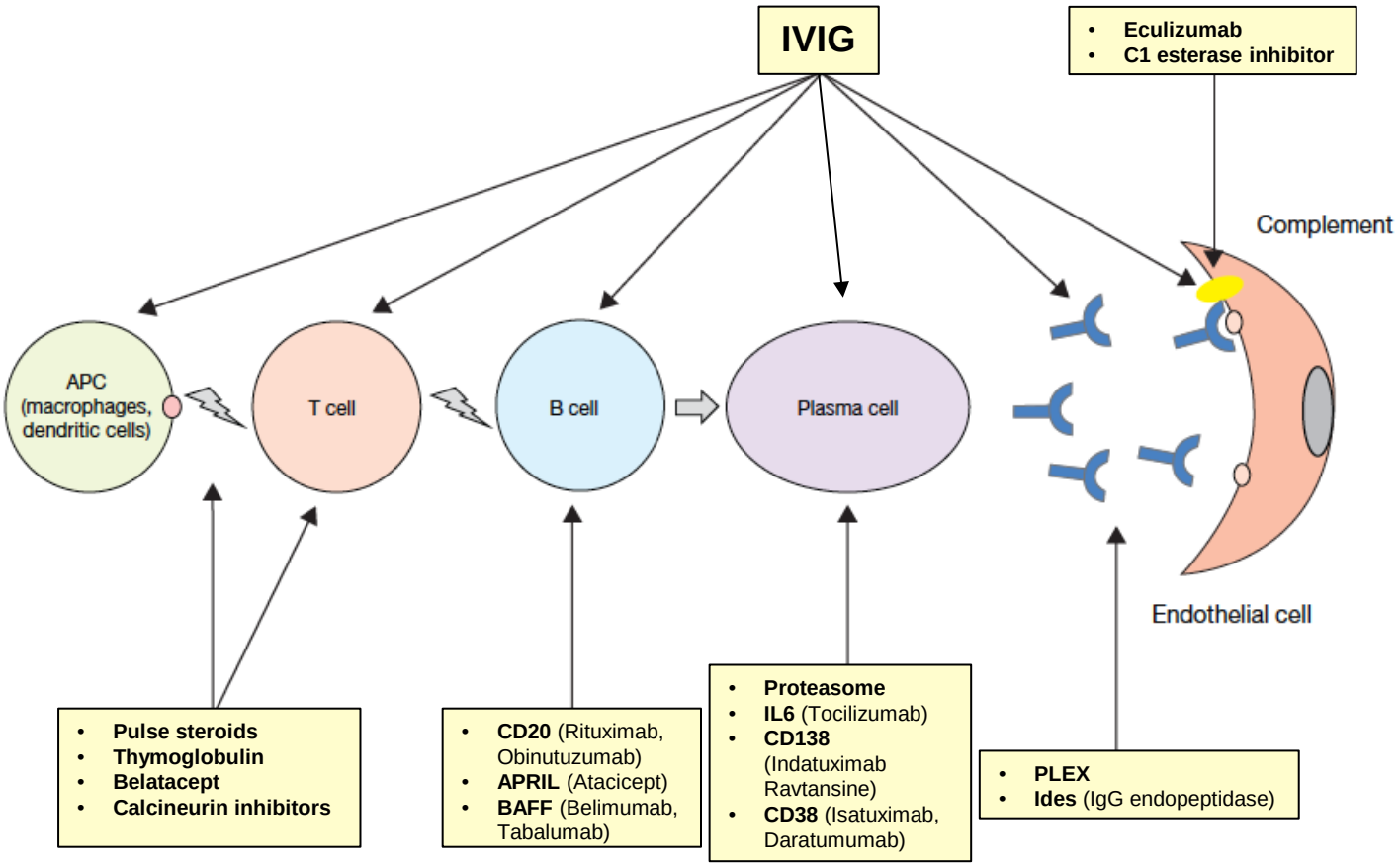


Pham et al, Transplantation Reviews 2017

Summary and Future Directions

- Desensitization of highly sensitized possible but with limited and transient impact on antibody (PRA) levels
- Need to better understand the pathogenesis of sensitization
- Define combination therapies
  - KPD ± desensitization
  - Targeting up- and downstream pathways of B cell activation
- Determine efficacy endpoints for clinical trials
  - cPRA and def. of antibody strength for unacceptable Ag?
  - Transplantation?
  - Immunodominant antibody?
  - Non-HLA antibodies?

Thank you!


IVIG
Eculizumab
C1 esterase inhibitor
Complement
APC (macrophages, dendritic cells)
T cell
B cell
Plasma cell
Endothelial cell
Pulse steroids
Thymoglobulin
Belatacept
Calcineurin inhibitors
CD20 (Rituximab, Obinutuzumab)
APRIL (Atacicept)
BAFF (Belimumab, Tabalumab)
Proteasome
IL6 (Tocilizumab)
CD138 (Indatuximab Ravtansine)
CD38 (Isatuximab, Daratumumab)
PLEX
Ides (IgG endopeptidase)