Approaches to desensitization

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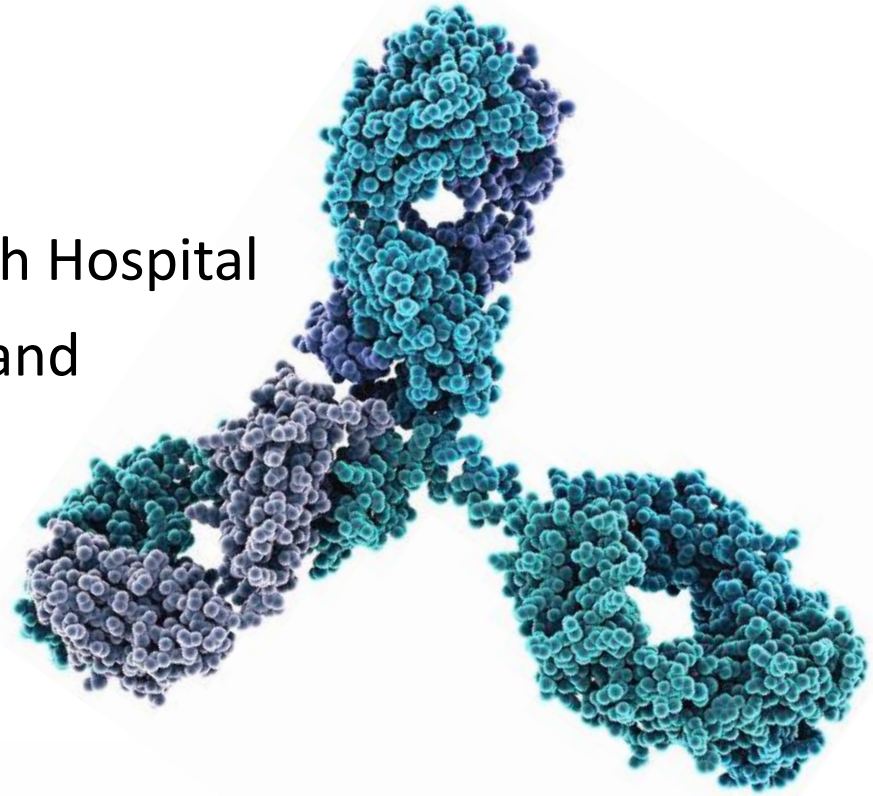
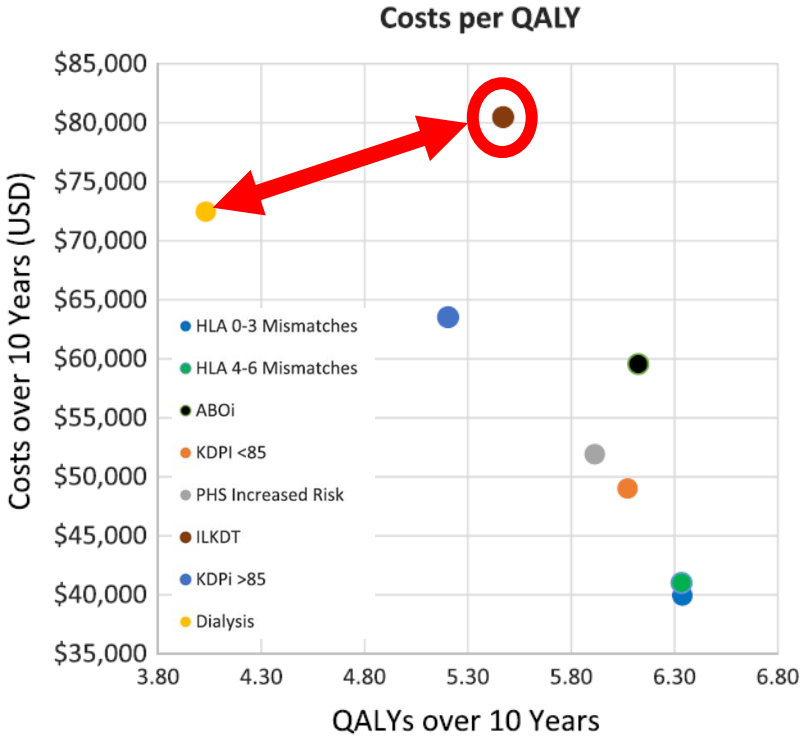


Scope of the problem

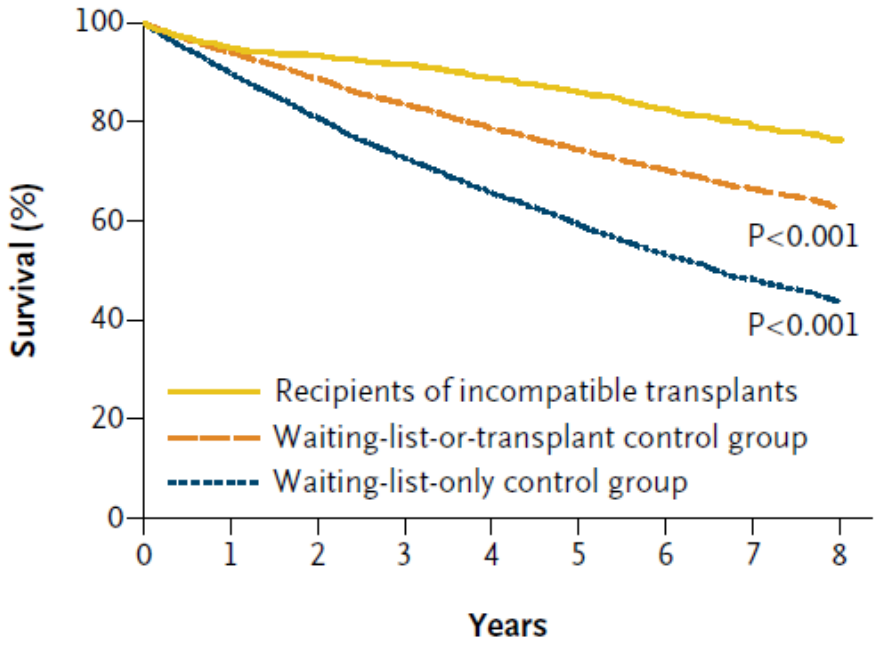
- A significant proportion of KF patients on transplant waitlists are highly sensitized (PRA > 80%):
  - Canada: approximately 20%
  - US: approximately 30%
  - UK: more than 40%
  - SA: unknown

- Presensitization reduces the probability of a donor match
  - US: only 6.5% of highly sensitized patients will receive a transplant / year

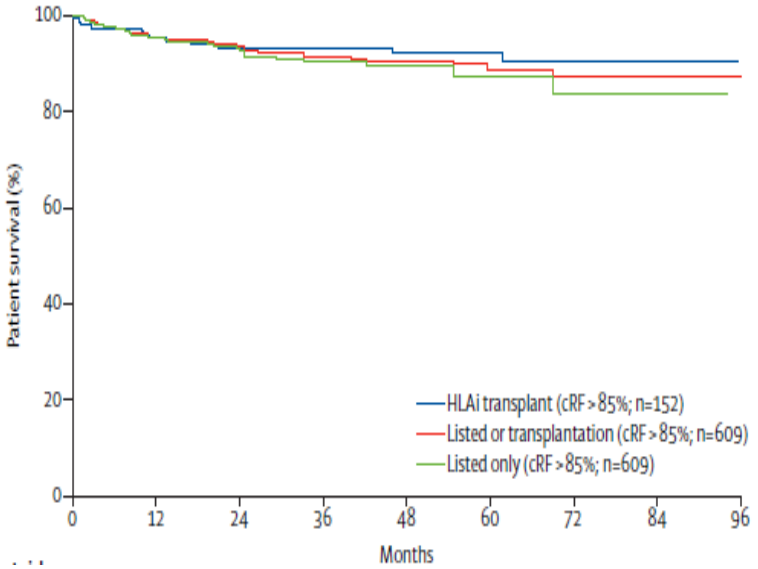
Rationale for desensitization



Axelrod DA et al. Am J Transplant 2018;18:1168



Orandi BJ et al. New Eng J Med 2016;374:940

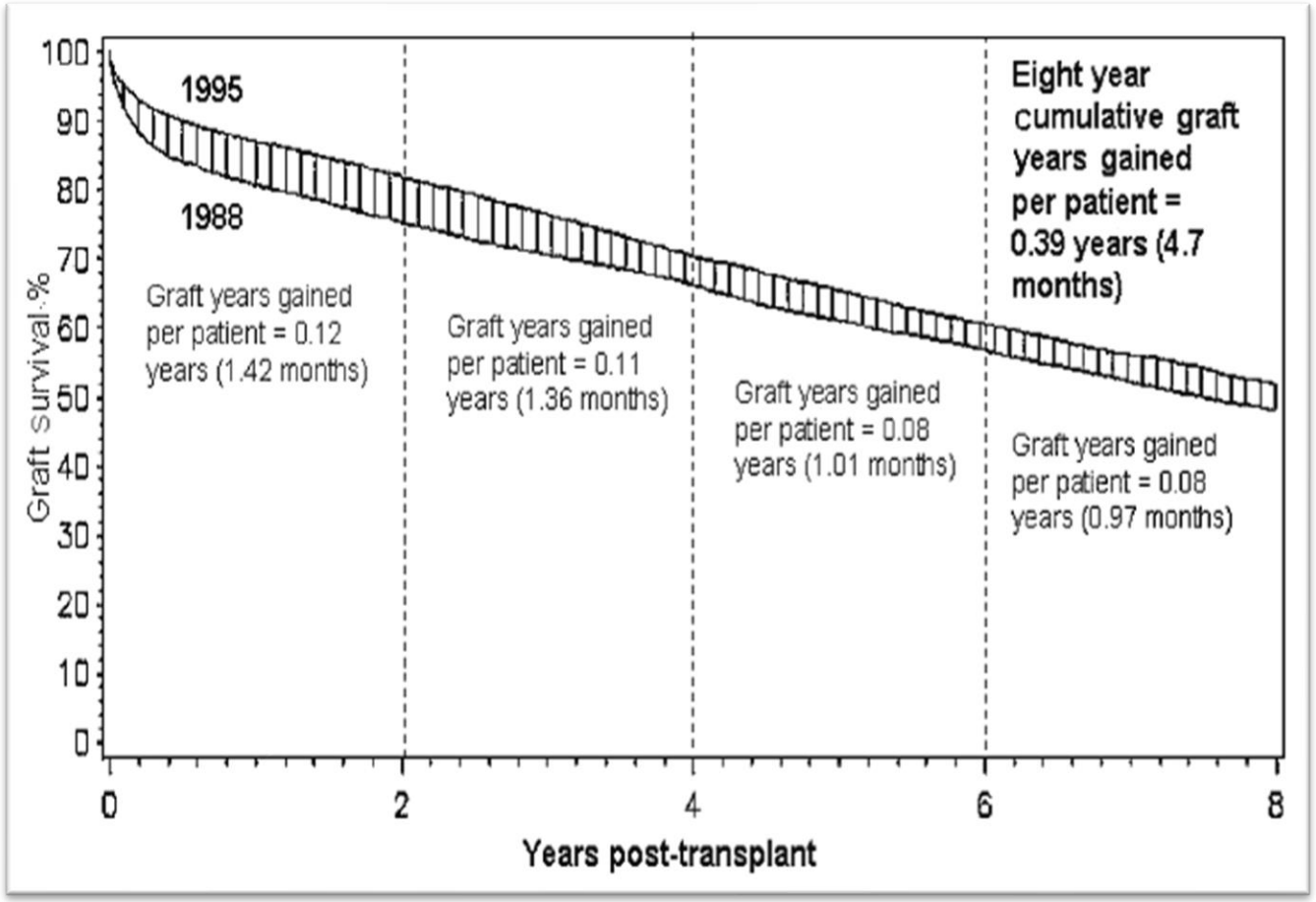


Manook M et al. Lancet 2017;389:727

- Improved QALY at a slightly higher cost than remaining on dialysis
- Possibly improved patient survival over remaining on dialysis (US vs UK data)

- In SA: shortage of donors and shortage of dialysis slots may favour HLAi

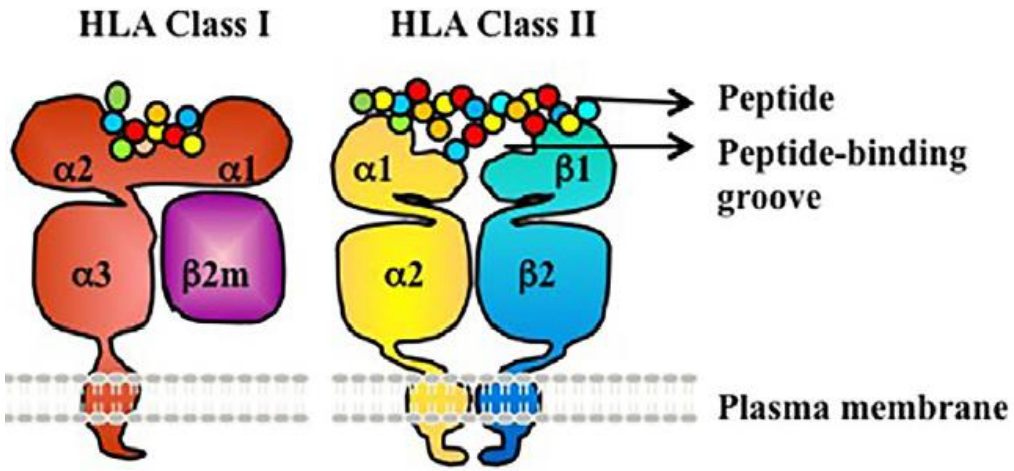
Rationale for desensitization cont./

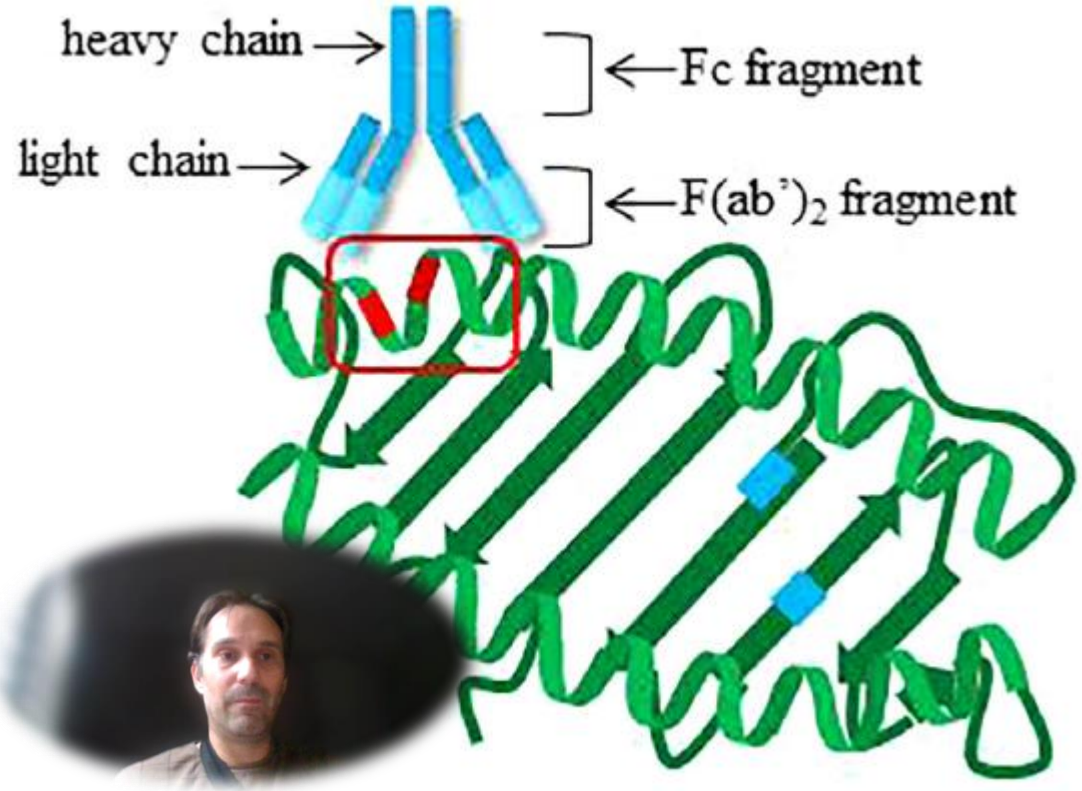


Meier-Kriesche H-U et al. Am. J. Transplantation 2004;4:1289-1295

Reference	N	% of biopsies with ABMR
Einecke G et al Am. J. Transplant 2009;9:2520-2531	27	C4d+ ABMR: 26% All ABMR: 63%
Regele H et al. J. Am. Soc. Nephrol 2002;13:2371-2380	213	C4d+ ABMR: 34%
Matas AJ et al. Am. J. Transplant 2010;10:315-323	240	C4d+ ABMR: 38% DSA+: 40%

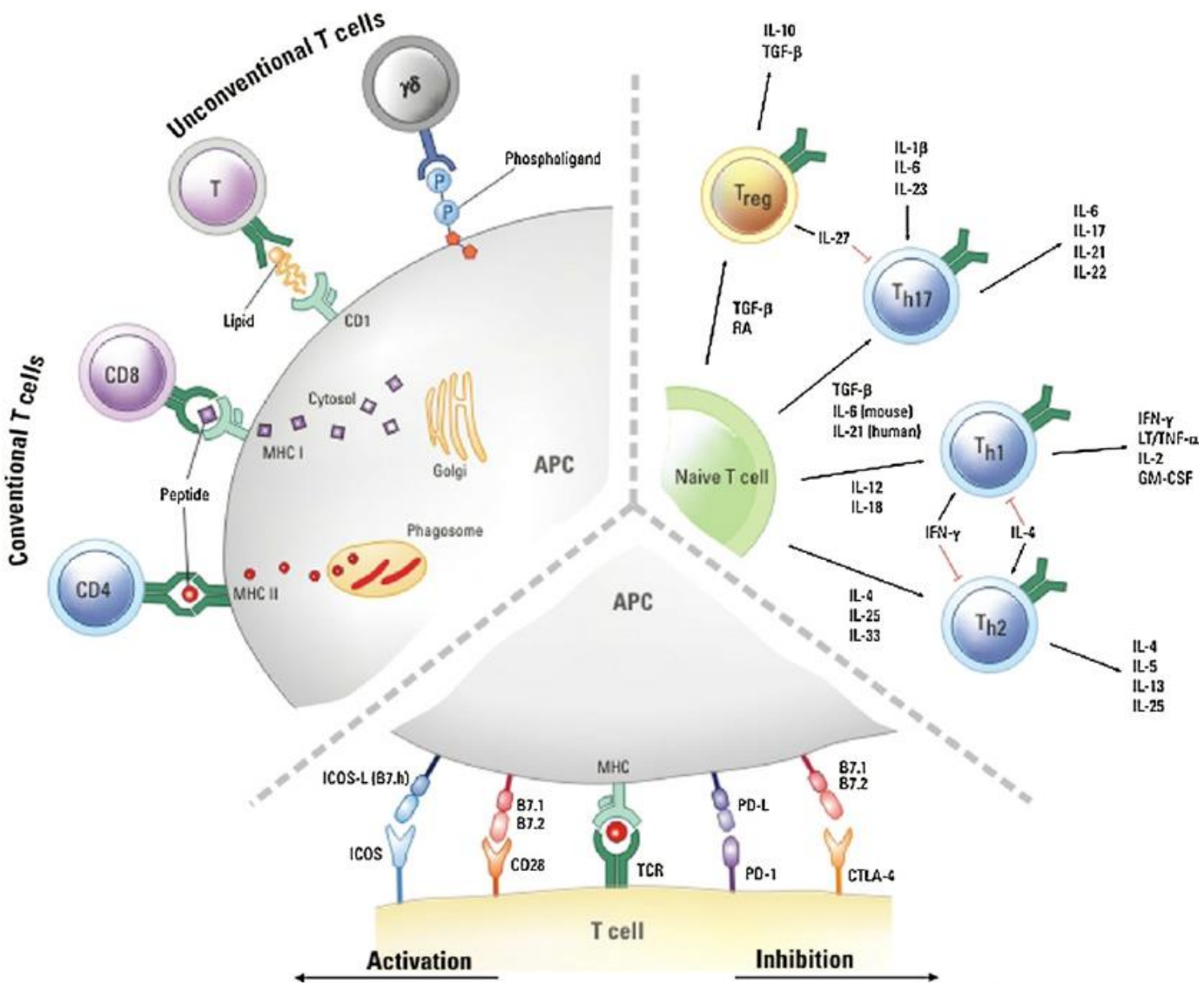
Immunogenicity of HLA

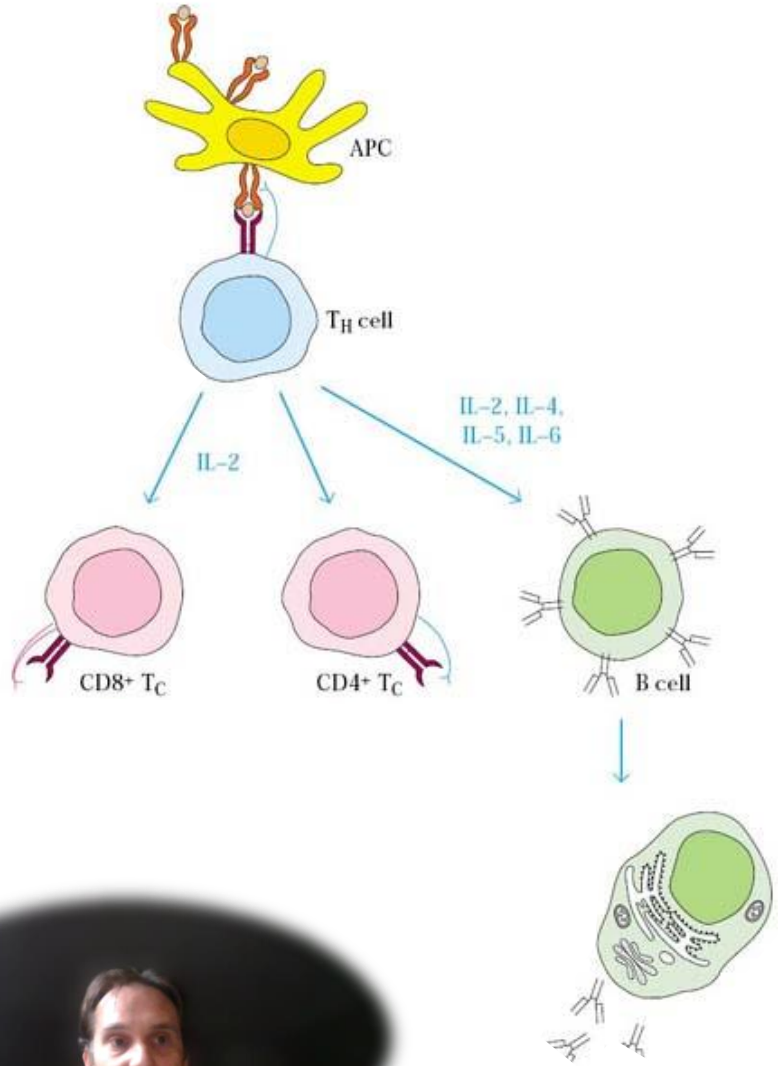




- Non-self HLA can be detected to the resolution of 1 amino acid difference in 1 epitope
- Bound α1 and β1 chains of HLA II can constitute an epitope for non-self recognition
- Gene conversion in HLA subtypes results in public epitopes and CREGs, allowing recognition of multiple non-self HLA types in a single sensitizing event

Where did it all go (conventionally) wrong?





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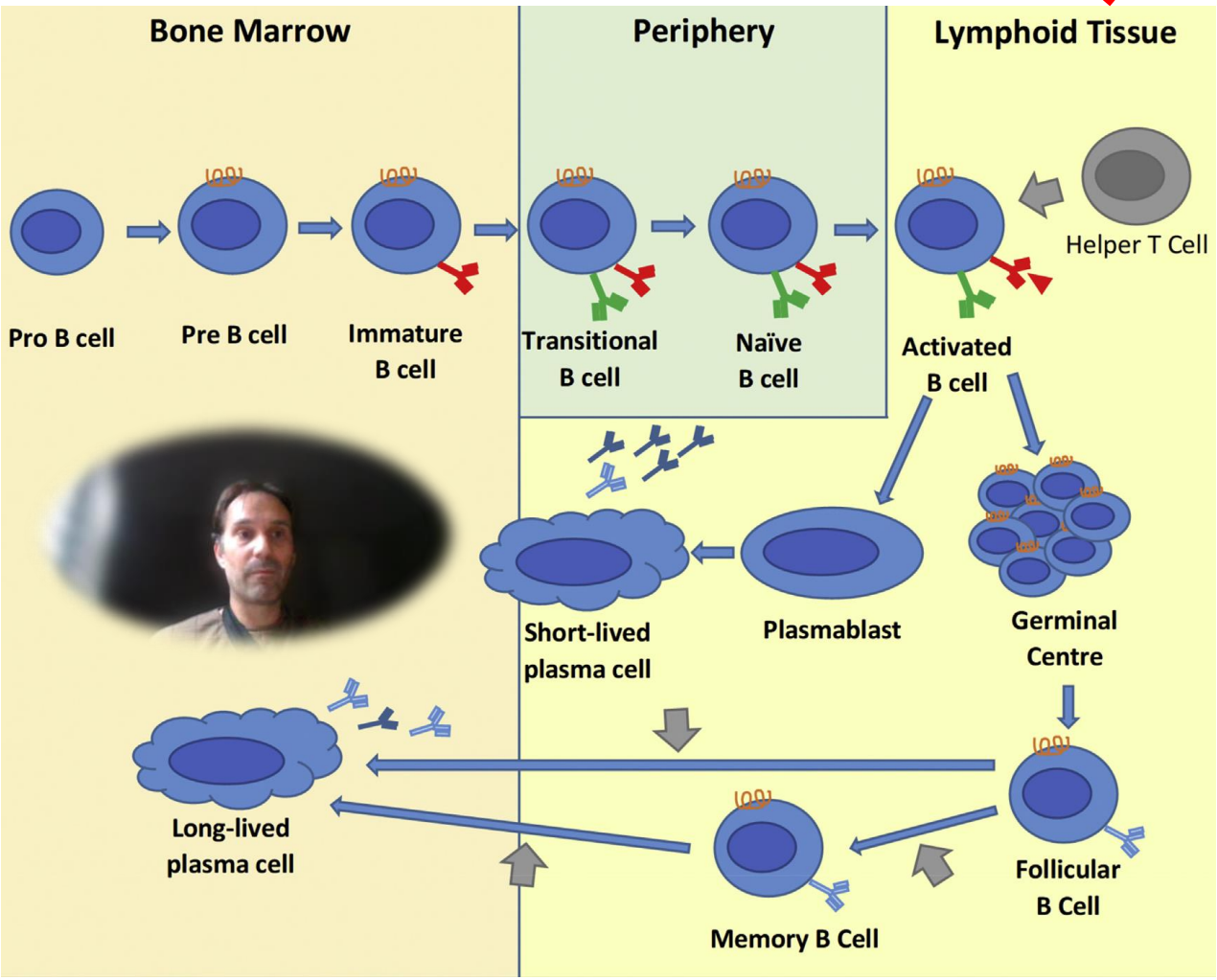
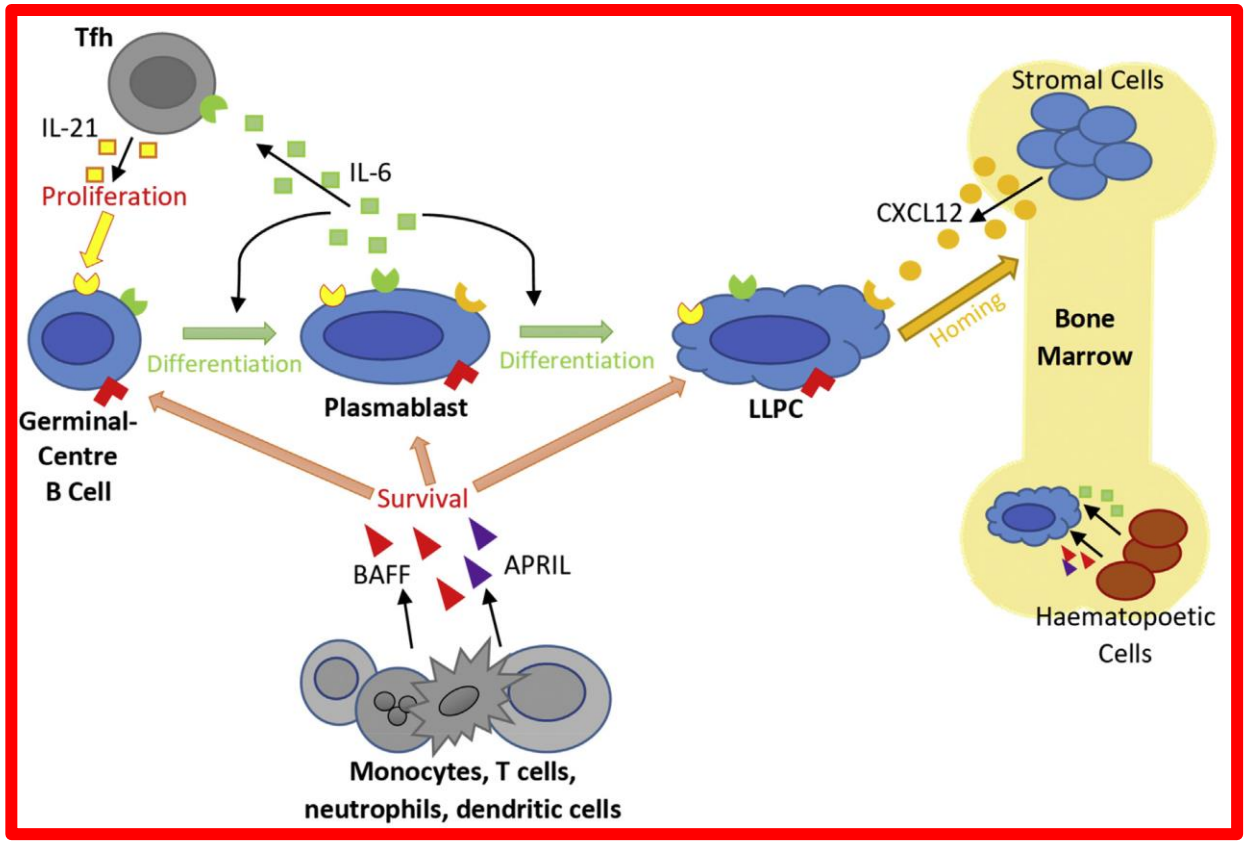




- LLPC are more likely to be generated through chronic, relatively low-dose antigen exposure (i.e., post-engraftment with immunosuppression onboard) (less likely in transfusion, pregnancy)
- Once sensitization has occurred, LLPC can be re-generated from Bmem through antigen-dependent and antigen-independent pathways

May FNJ et al. Transplant Rev 2021;35:100596

Consequences of humoral immortalization

- Differences in LLPC generation may account for differential success rates of pre-engraftment / early ABMR and LPABMR intervention
- LLPC produce large amounts of high-affinity antibody on an ongoing basis (do not require re-exposure)
  → contributes to the “slow burn” of LPABMR
- Peripheral blood antibody and LLPC counts are poor correlates of LLPC presence and activity in the BM compartment
- Immortalization / independence from replacement via antigen-dependent pathways from immature B-cell pool reduce the efficacy of standard T- and B-directed interventions
- Survival signals from stromal supporters further abrogate the efficacy of interventions targeting the LLPC

It ain’t all about the antibody

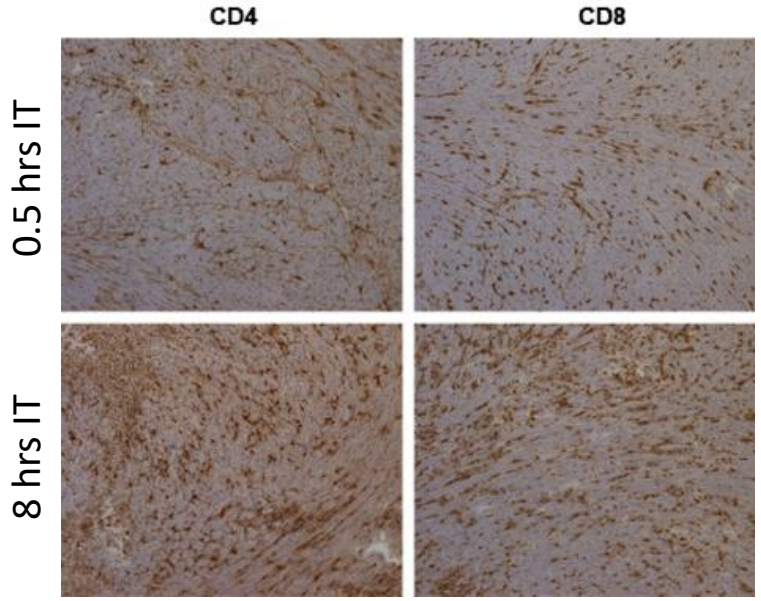
- Most rejection in the context of (dn)DSA is **MIXED**
- Mixed rejection carries a poorer prognosis than “pure” ABMR
  - This may partly account for poorer outcomes in LPABMR (dnDSA more frequent)
- Presence of mixed rejection contributes to refractoriness towards desensitisation interventions
- Development of DSA is associated with non-compliance with CNI (T cell suppression)
- Development of dnDSA in particular is probably best viewed as an overall measurement of inadequate immunosuppression

Memory T cells

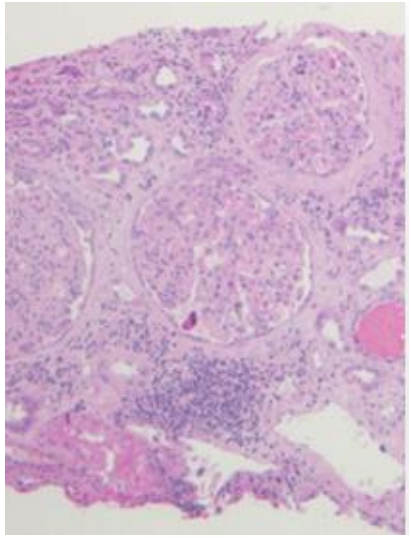
- Memory T cells contribute effector function after engraftment
  - CD4 memT provide efficient helper function to B lineage to generate DSA

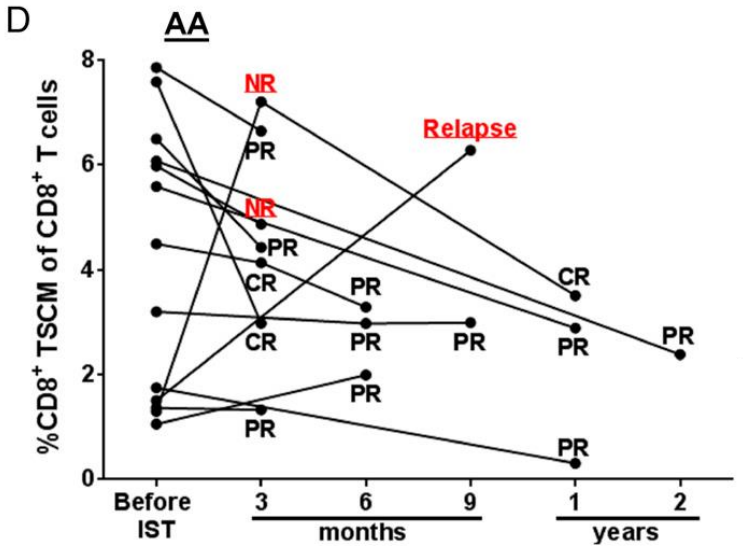
Multiple subsets:

- Tissue resident (T_{RM}) provide intragraft effector function
- Terminally differentiated effector (T_{EMRA}) CD8 require less IL-2 for survival
- Follicular helper ($memT_{FH}$) are better B-cell helpers than "conventional" T_{FH}
- Peripheral helper ($memT_{PH}$) share T_{FH} characteristics but are able to activate B outside of secondary lymphoid tissue (intragraft TLT)
- Memory stem (T_{SCM}) rapid increase after T depletion with ATG to reconstitute immune response



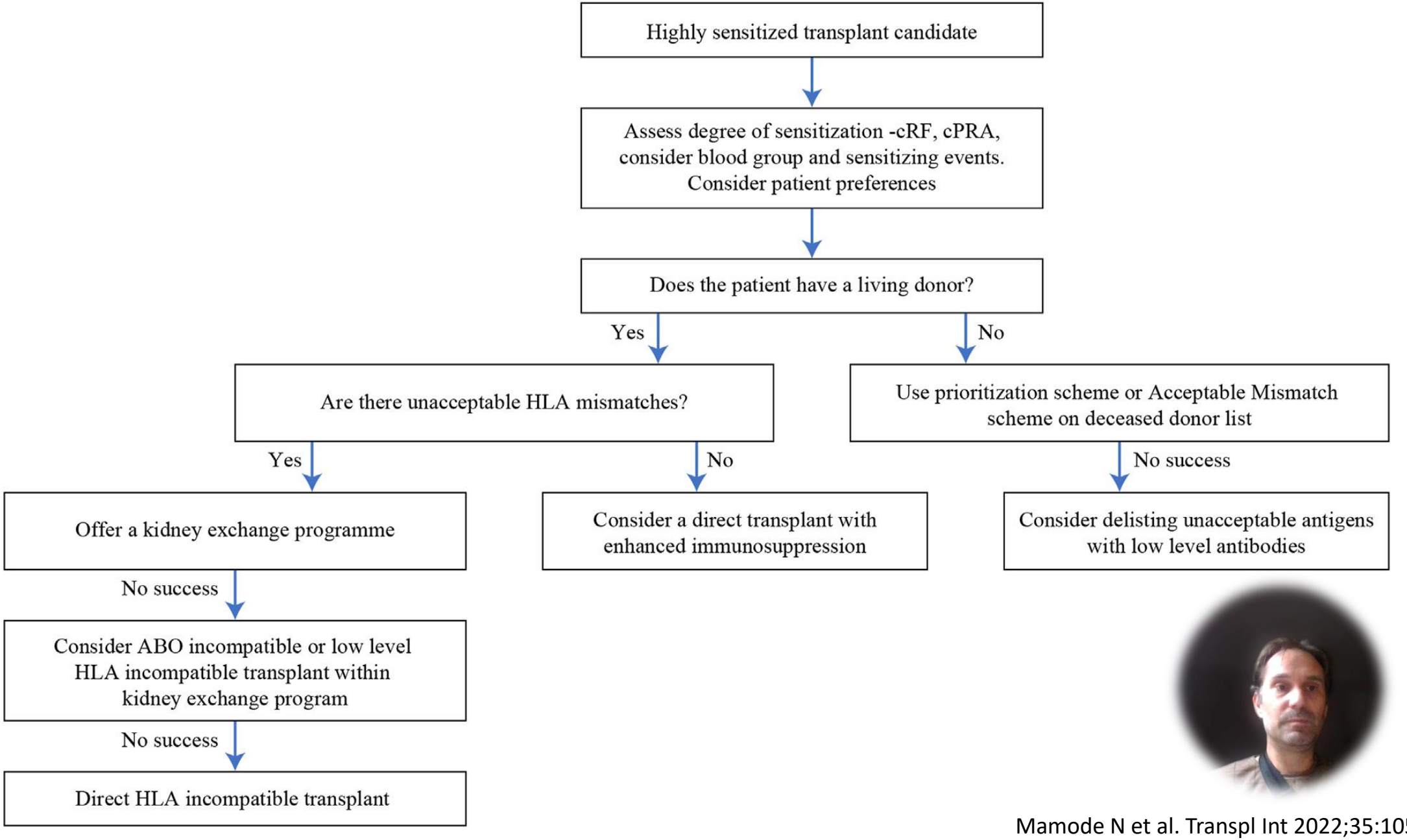
Su CA et al. Am J Transplant 2014;14:568





Hosokawa K et al J Immunol 2016;196:1568

ESOT guidelines: pretransplant desensitization



Mamode N et al. Transpl Int 2022;35:10511

Assessment of immunological risk

HUMORAL RISK	RISK CATEGORIES & MANAGEMENT	HUMORAL MEMORY
	1. Day-zero DSA with positive CDC → **Tx impossible. Require desensitization before Tx**	**SEROLOGICAL MEMORY**
	2. Day-zero DSA with positive flow and negative CDC → **Tx possible** but very high risk for acute AMR and accelerated chronic AMR. Require adaptation of follow-up and maintenance IS	
	3. Day-zero DSA with negative flow → **Tx possible** with risk for acute AMR, and acceptable medium-term graft survival. Require adaptation of follow-up and maintenance IS	
	4. Absence of day-zero DSA but potential cellular memory against donor HLA → **Tx possible** with risk for AMR increased. **4.a. Probably cellular memory if:** – historical DSA – pregnancy and/or previous transplant with repeat Ag **4.b. Possible cellular memory if:** – transfusion(s) with no information on blood donors	**CELLULAR MEMORY**
	5. No DSA and no cellular memory → **Tx possible** lower risk for AMR but de novo DSA still possible *NB: patient with day-zero non DSA HLA antibodies are "good humoral responders" with possible increased risk for subsequent de novo DSA generation*	**NAIVE**

Mamode N et al. Transpl Int 2022;35:10511

Pre-engraftment desensitization protocols

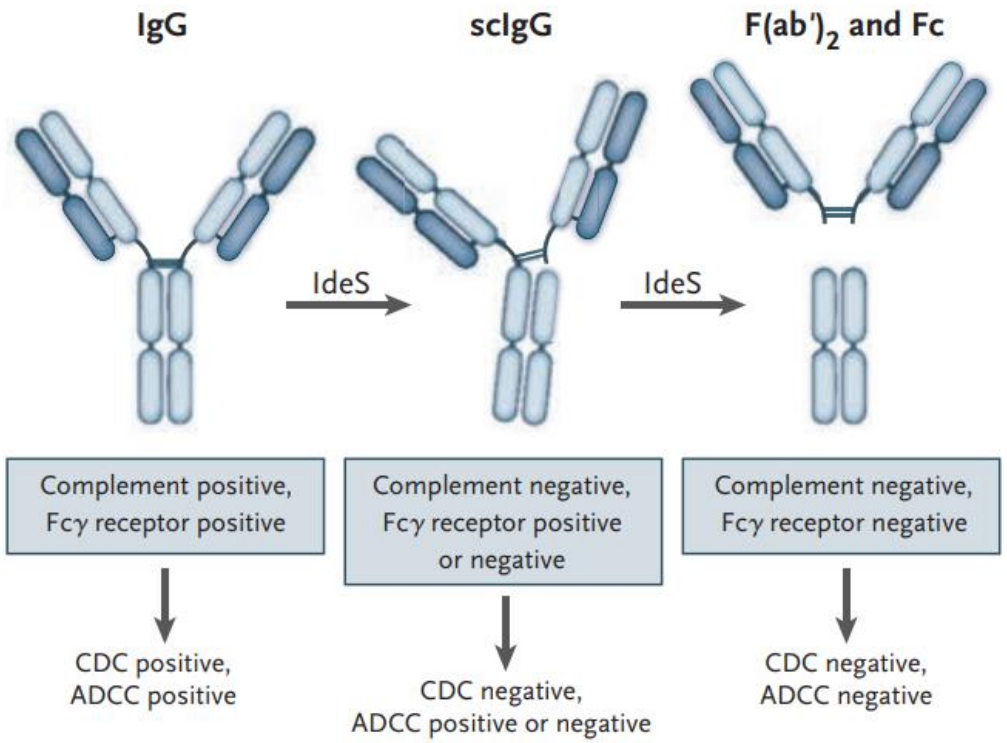
	Antibody removal	Antibody synthesis blockade	Induction	Maintenance
Johns Hopkins	PEX, LD IVIg	RTX	ATG	CNI, MMF, steroid
Mayo	PEX, LD IVIg	-	ATG	CNI, MMF, steroid
Cedars-Sinai	HD IVIg	RTX	Alemtuzumab, ATG, or antiCD25	CNI, MMF, steroid
University Hospital Conventry	PEX	-	AntiCD25	CNI, MMF, steroid
University of Illinois	PEX, LD IVIg	-	ATG	CNI, MMF, steroid
University of Maryland	PEX, LD IVIg	-	ATG	CNI, MMF, steroid

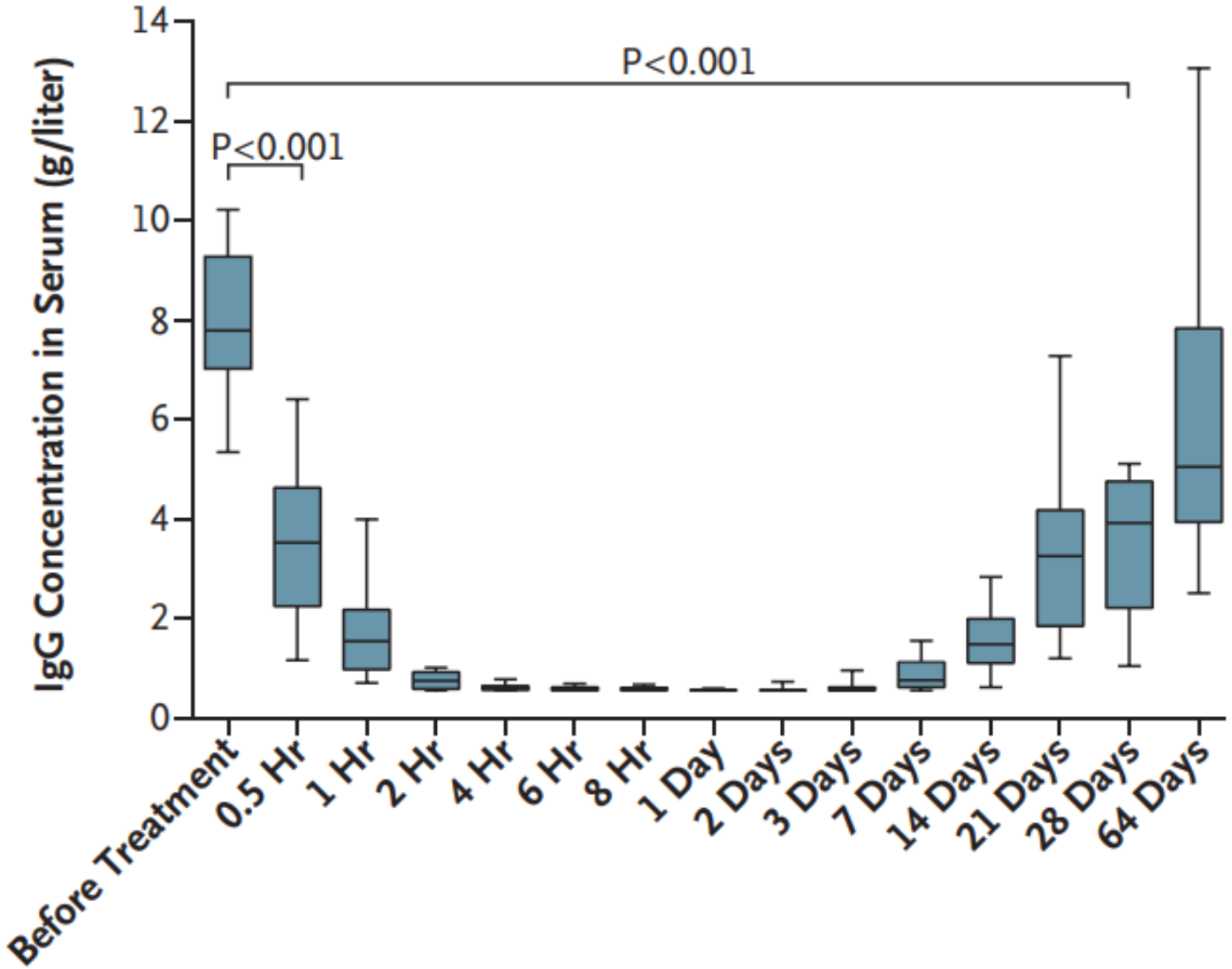
TTS guidelines: desensitization of ABMR

	Antibody type	Banff	First-line Rx	Evidence	Second-line Rx	Evidence
Early (< 30 days)	Preformed DSA	Active AMR	PEX daily or alt day x 6 cycles IVIG 100mg/kg daily AFTER PEX or 2g/kg stat AFTER PEX course	1C 1C	Complement inhibitors RTX 375mg/m^2 stat Splenectomy	2B 2B 3C
Late (> 30 days)	Preformed DSA	Active AMR	PEX daily or alt day x 4 – 6 cycles IVIG 100mg/kg daily after PEX or 2g/kg stat after PEX course Corticosteroids	2C 2C EO	RTX 375mg/m^2 stat	2B
	Preformed DSA	Chronic AMR	Optimize baseline IS	1C	IVIG	3C
	De novo DSA	Active AMR	Optimize baseline IS Evaluate non-adherence	1C	PEX with IVIG RTX 375mg/m^2 stat	3C 3C
	De novo DSA	Chronic AMR			IVIG	3C

Schinstock CA et al. Transplantation 2020;104:911

IgG endopeptidase (IdeS)



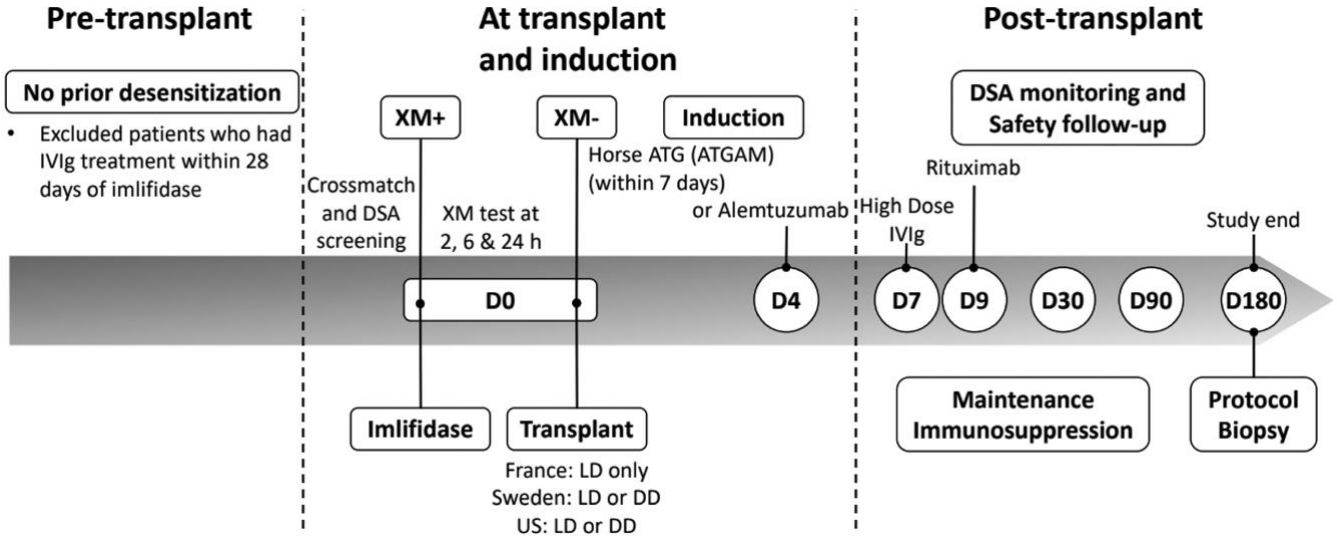


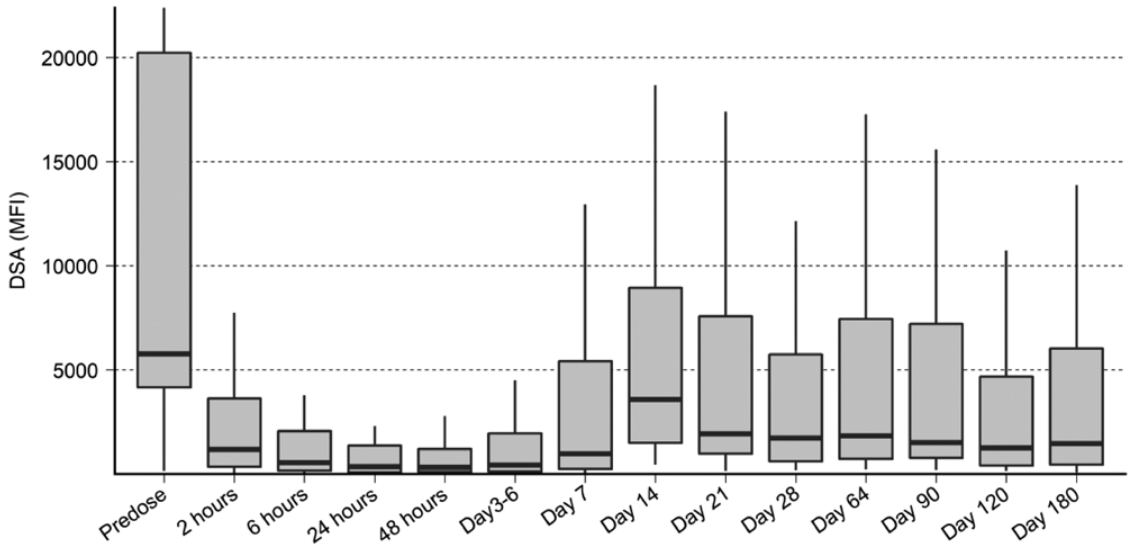
Jordan SC et al. New Eng J Med 2017;377:442

Imlifidase

- Cysteine protease that cleaves IgG

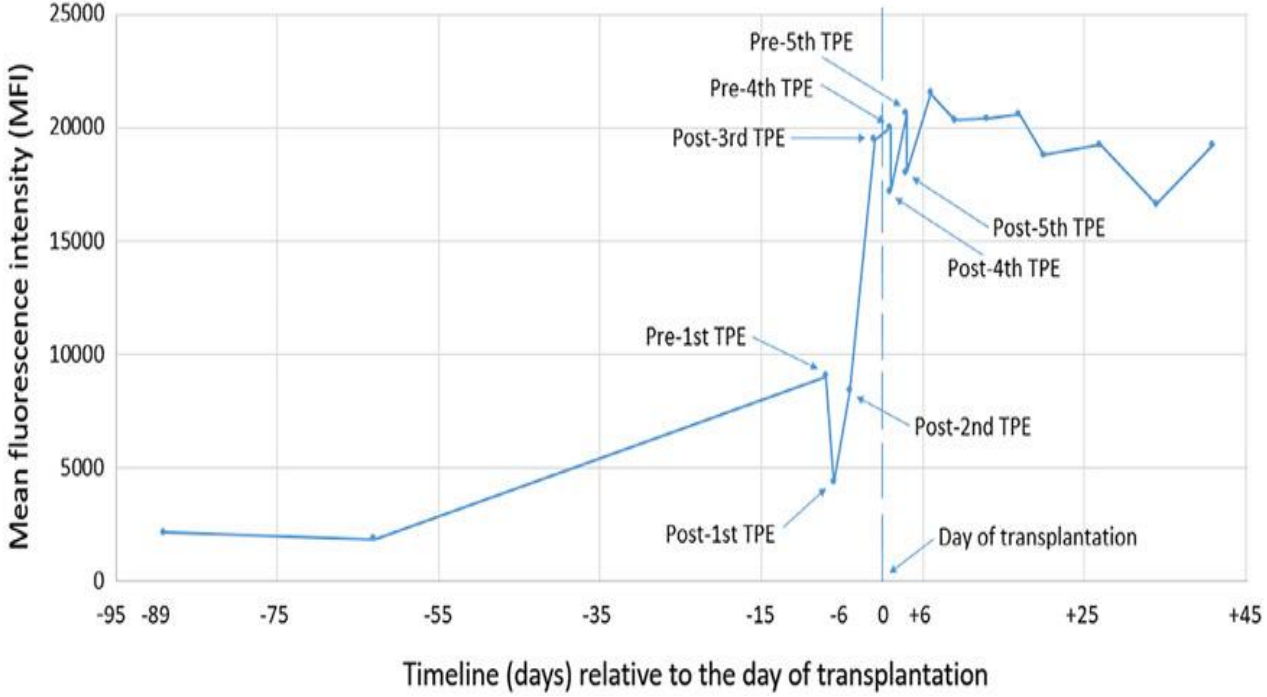
- Highdes study
  - Single arm, prospective study, n = 18
  - Highly presensitized patients undergoing HLAi transplant
  - 6 months follow-up



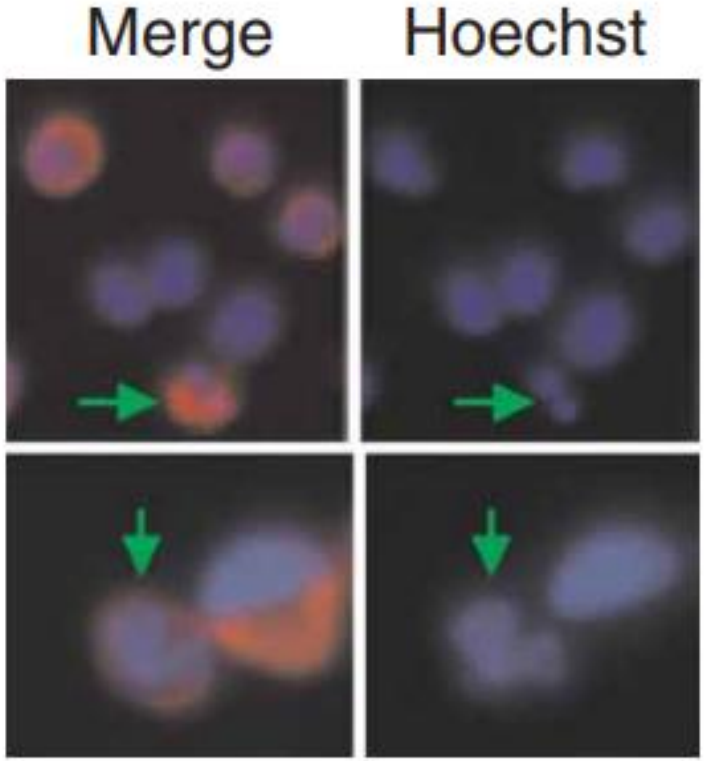


Jordan SC et al. Transplantation 2021;105:1808

Antibody depletion is insufficient



Hassan S et al. Transfusion 2021;61:1980



Xiang Z et al. Nat Immunol 2007;8:419

- Removal of antibody is temporary with rebound expected from uncontrolled LLPC / memB cell source on discontinuation

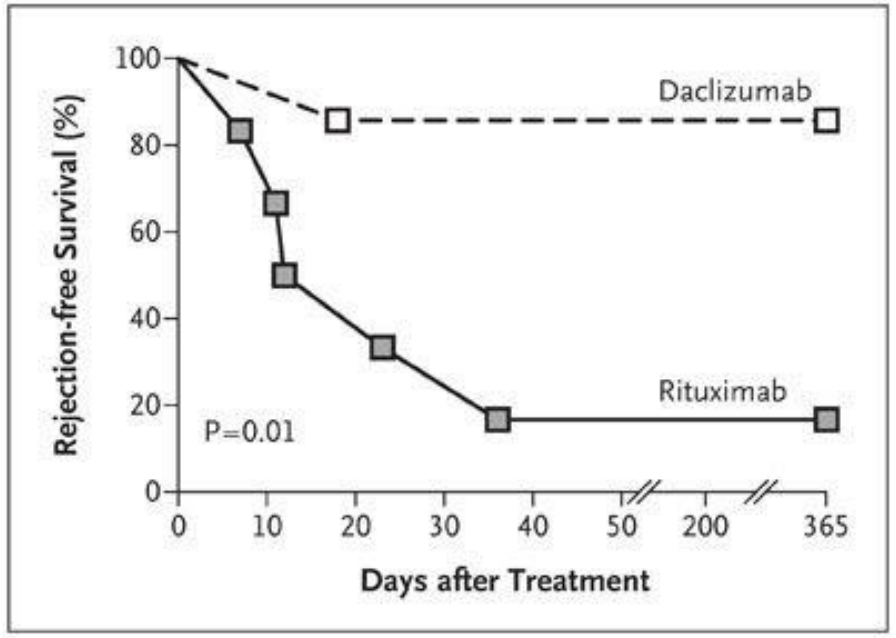
- Antibody exerts suppressive effect on LLPC populations: removal of antibody by PEX reduces apoptosis

Control of cellular source: B lineage depletion

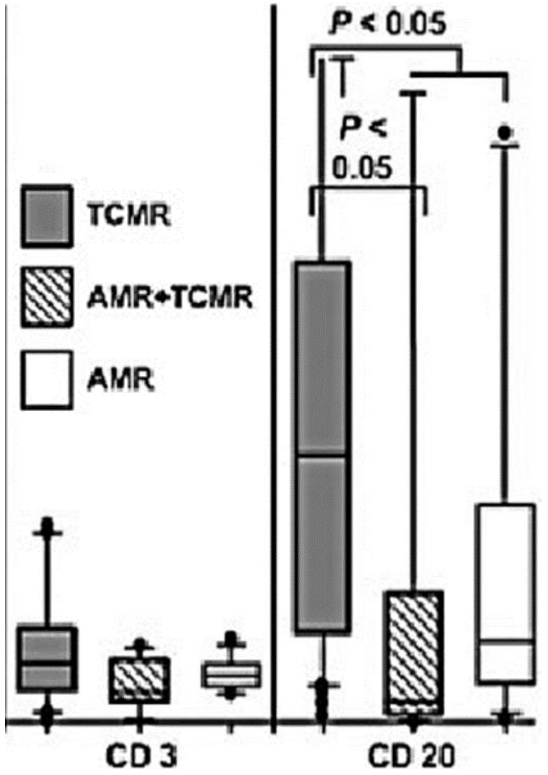
		n	Patient survival	Graft survival	Incident rejection	Graft function
High PRA *(PRA > 80%)*	Vo 2013	11	No difference	No difference	**Favours RTX**	Not reported
	Vo 2010	152	No difference	**Favours RTX**	**Favours RTX**	No difference
	Laftavi 2011	37	No difference	**Favours RTX**	**Favours RTX**	Not reported
Positive DSA	Hirai 2012	113	No difference	**Favours RTX**	**Favours RTX**	No difference
	Loupy 2010	96	No difference	No difference	**Favours RTX**	**Favours RTX**
Positive CDC	Stegall 2006	61	Not reported	Not reported	**Favours RTX**	No difference
	Umanath 2012	27	Not reported	Not reported	**Favours RTX**	No difference
High risk *(PRA > 20% or peak PRA > 50%,or current/historic CDC, or current/historic DSA, or previous graft loss due to rejection)*	Ejaz 2013	20	No difference	No difference	Not reported	No difference

Macklin PS et al. Transplantation 2014;98:704

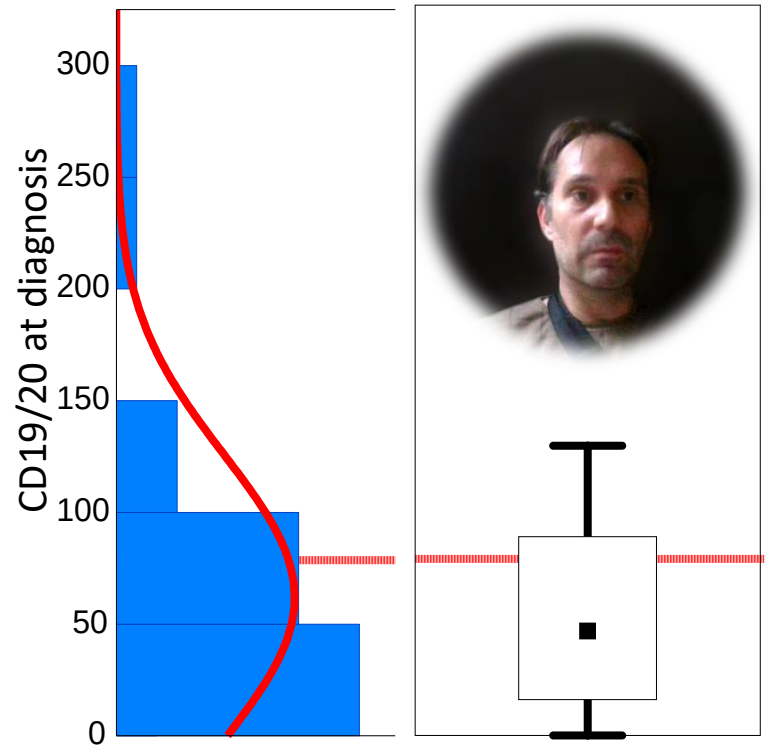
Rethinking RTX

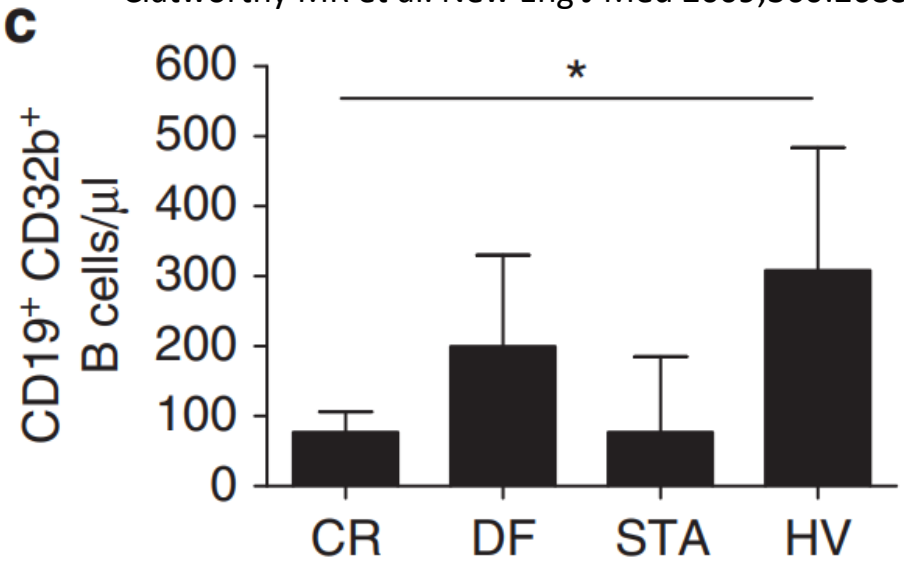


Clatworthy MR et al. New Eng J Med 2009;360:2683



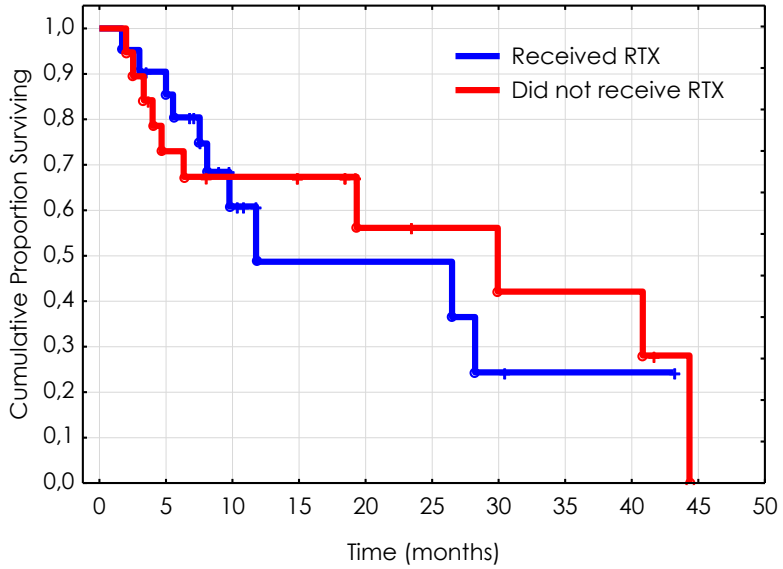
Viklicky O et al. J Am Soc Nephro 2010;21:1730





Pallier A et al. Kidney Int 2010;78:503

- Pan Bcell depletion may accelerate graft loss through loss of Breg



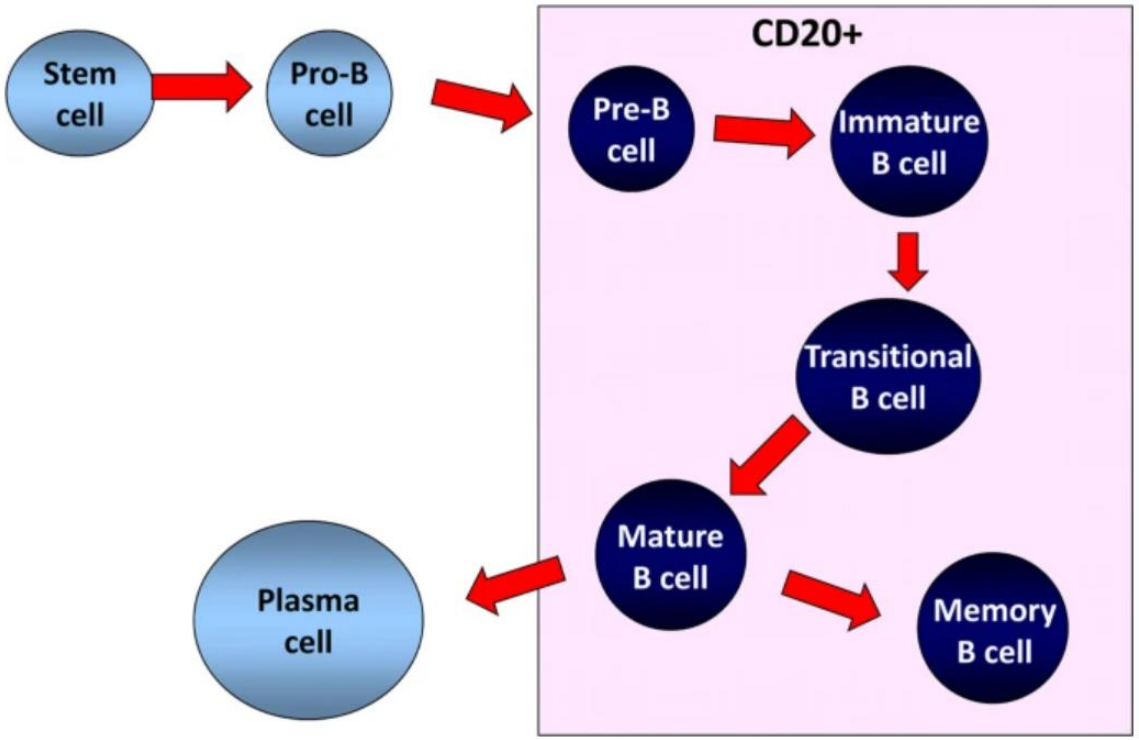
Differential susceptibility of B cell populations to depletion

- Germinal centre and marginal zone B (memB) are less sensitive (LAD > spleen) to RTX than peripheral blood B cells

Vugmeyster Y et al. Int Immunopharm 2003;3:1477

- Peripheral blood memB appear resistant to RTX
- RTX may shift naïve B cell phenotype on repopulation to enhance T stimulation

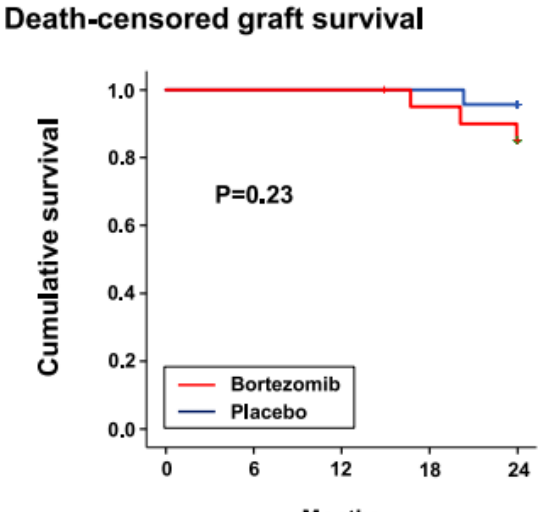
Gong Q et al. J Immunol 2005;174:817

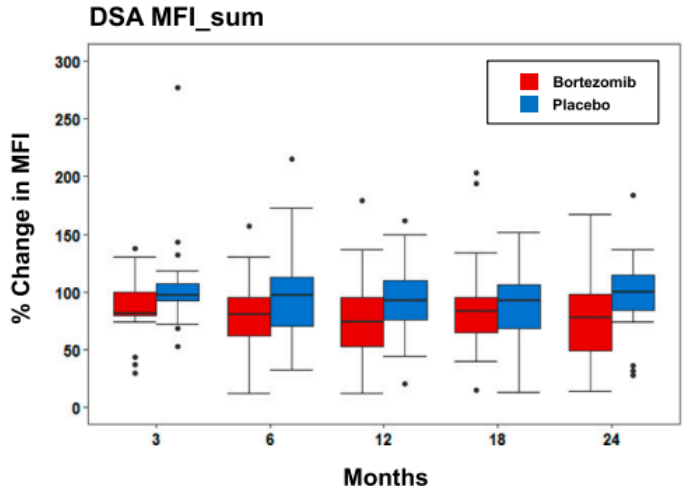


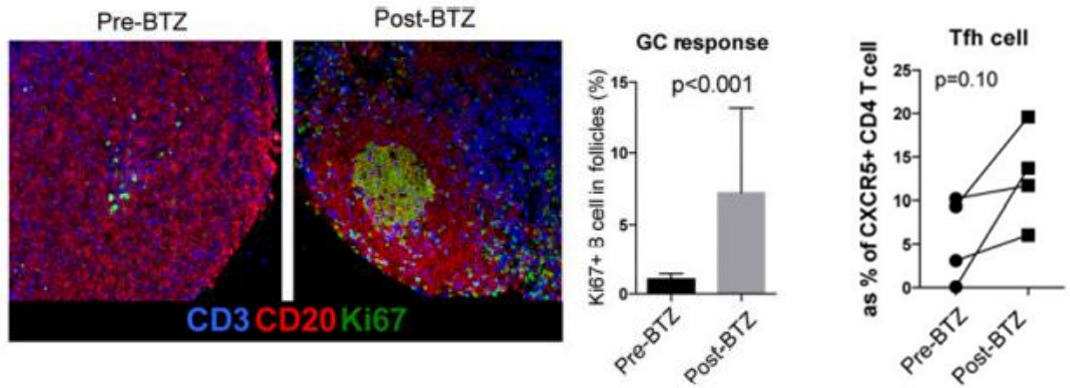
Bcell intrinsic factors	Lack of CD20 expression
	CD20 modulation / endocytosis
	Lipid raft composition
Patient factors	FcγRIIIA polymorphism
	FcγRIIB expression
	C1q polymorphisms
	Exhaustion of cytotoxic mechanisms (complement depletion)

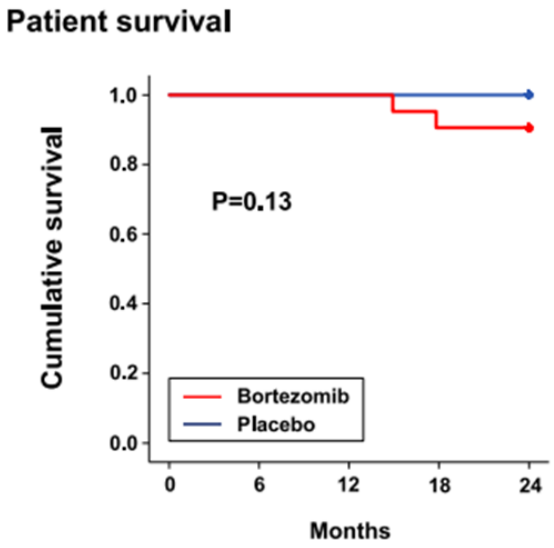
Directed plasma cell depletion

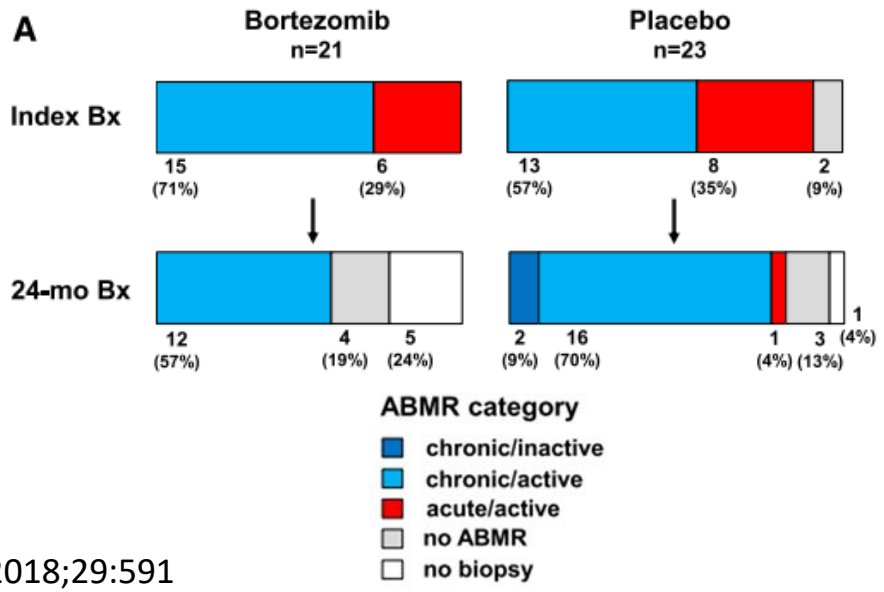
- Antibody removal decreases FcγIIbR suppression on PC proliferation and DSA production
- Blockade of 26S proteosome protein degradation results in accumulation of proteins in PC and PC apoptosis

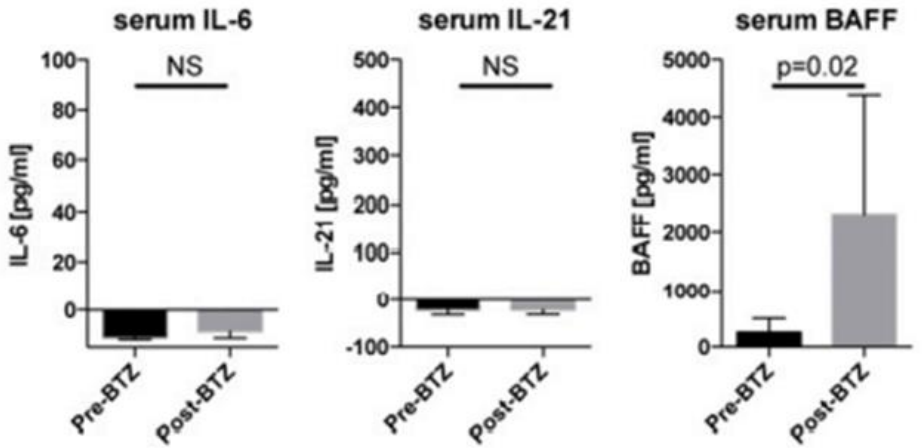












Kwun J et al. J Am Soc Nephrol 2017;28:1991

Eskandary F et al. J Am Soc Nephrol 2018;29:591

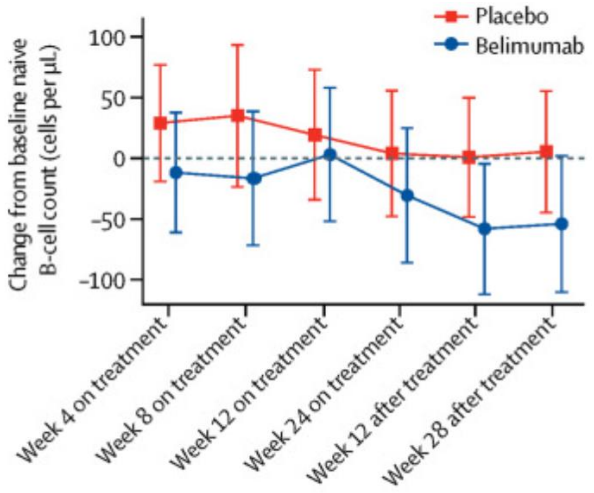
Tocilizumab

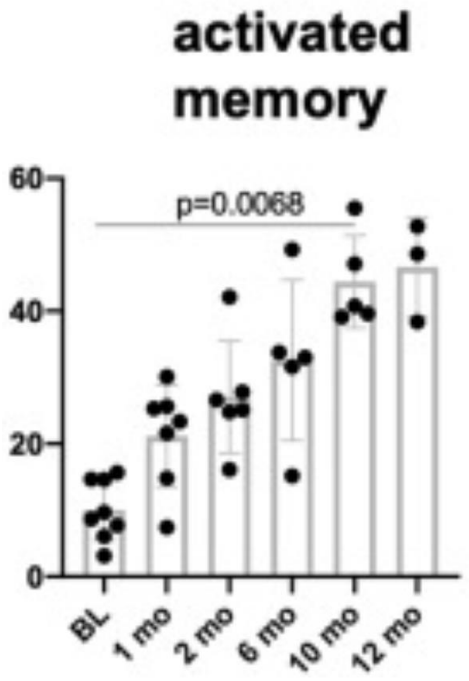
- IL-6 inhibition theoretically could reduce survival signal to LLPC
- No good evidence yet exists to support Tocilizumab use in desensitization:

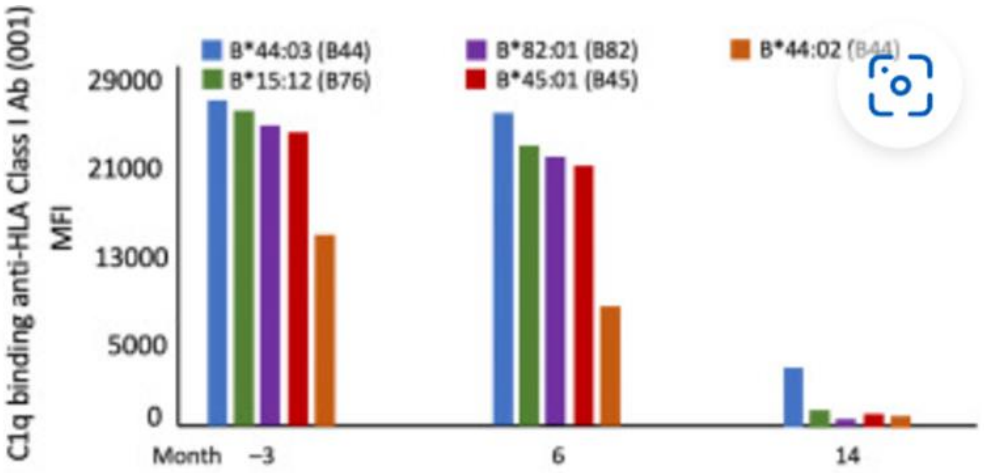
Reference	n	Details	Outcome
Pottebaum AA et al Transplantation 2020;6:e543	7	Observational study: acute active ABMR	50% DSA reduction in 2/3rds of patients Stable graft function at 12 months 3 patients had subsequent rejection episode within 2 years
Shin B-H et al Transplantation 2020;104:856	12	Observational: chronic ABMR	8 patients showed non-significant reduction in DSA
Kumar D et al Kidney360 2020;1:663	10	Observational: chronic ABMR	No improvement in graft function decline at 1 year Progression of chronic histology lesion
Massat M et al Am J Transplant 2020;21:1641	9 (Toc) vs 37 (SOC)	Retrospective cohort: chronic ABMR	No difference in 1 year graft survival Similar progression of chronic histology lesion
Noble J et al Front Med 2021;24	40	Observational chronic ABMR	15% graft loss at 1 year No improvement in graft function in surviving grafts at 1 year Progression of chronic histology lesion

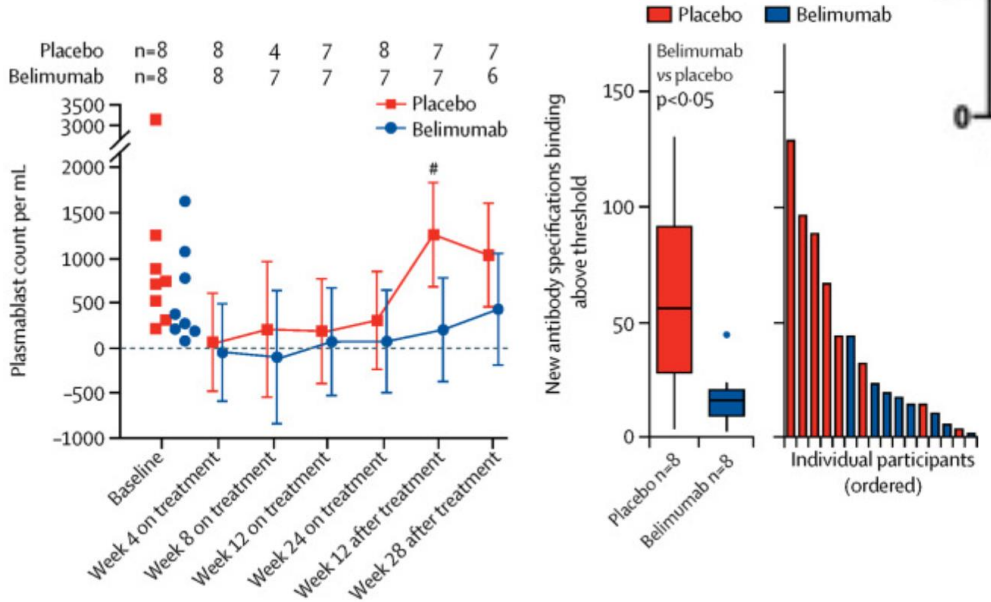
Belimumab

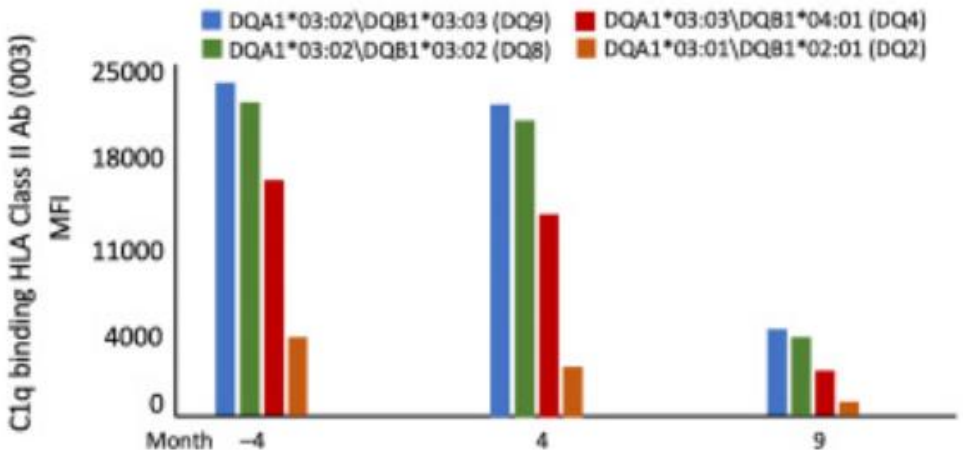
- BAFF (=BLyS) is an important mediator of B maturation and provides a survival signal to LLPC







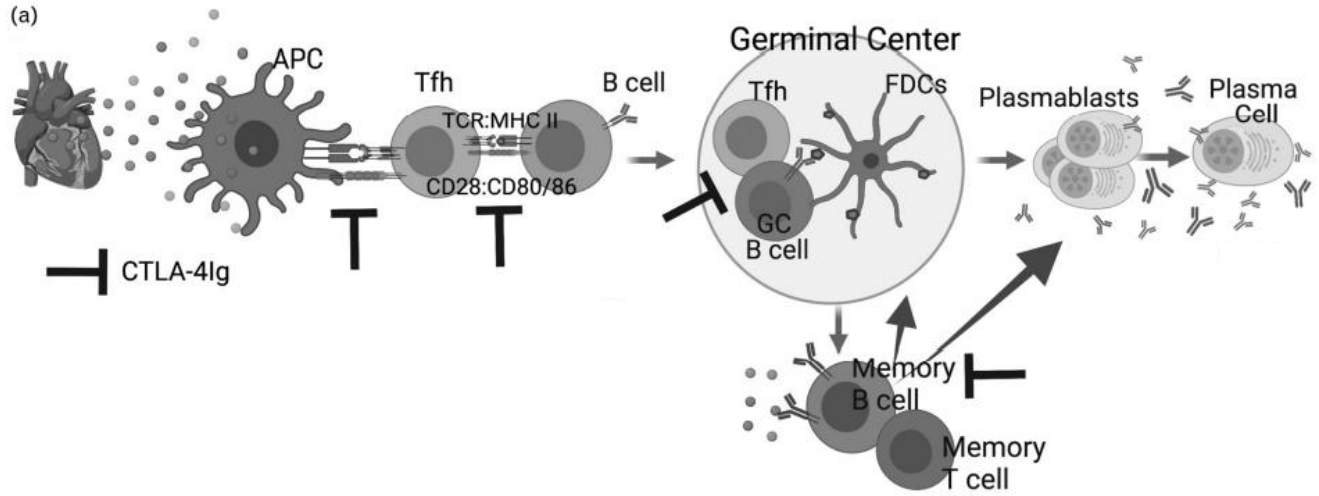




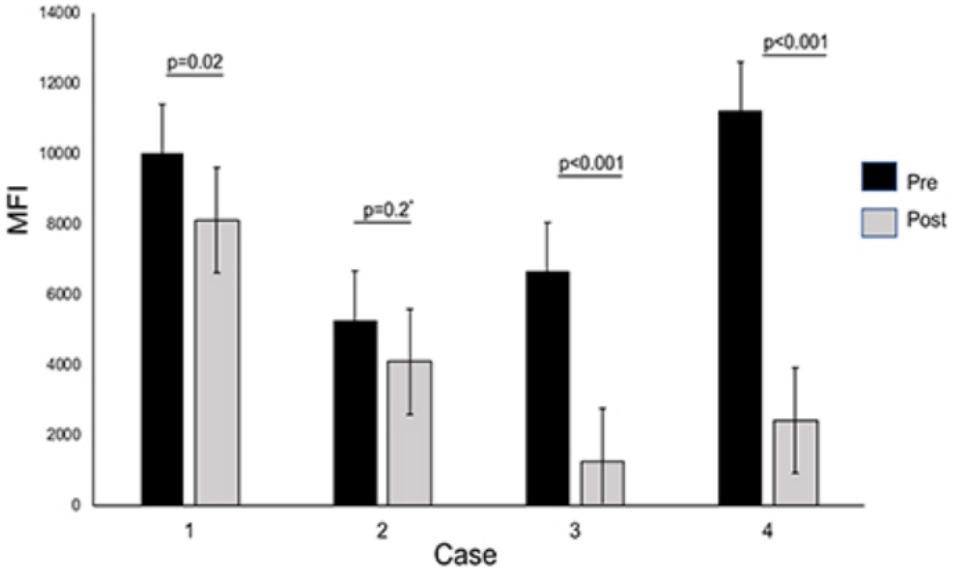
Agarwal D et al. Transpl Immunol 2021;69:101465

Banham GD et al. Lancet 2018;391:2619

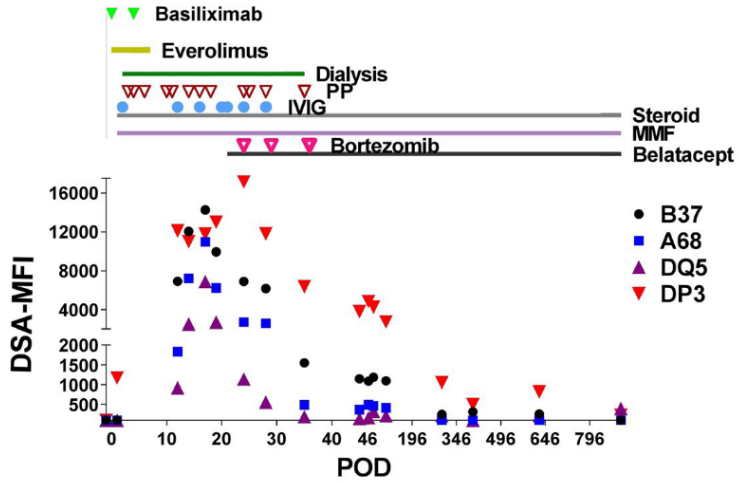
Belatacept

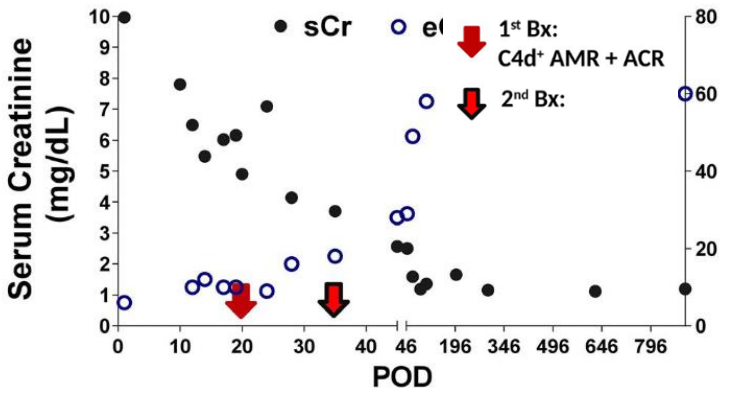


- Belatacept (CTLA-4Ig) interferes with T : B interactions mediated by CD28 biding to CD80/86
- Inhibits Bcell including memB activation and differentiation towards PC



Alishetti S et al. Am J Transplant 2020;20:3620





Jain D et al. Am J Transplant 2020;20:2675

Conclusions

- Pre- and post-engraftment sensitization remain significant barriers in kidney transplantation

- Despite a well-established understanding of the pathways to sensitization we still lack a nuanced knowledge of the regulation of these pathways

- Current desensitization protocols are “heavy-handed” and efficacy may be limited by our inability to address the effect of these interventions on innate counter-regulatory pathways
- This is compounded by an inability to characterize the “balance” of the immune system in the individual patient

- Multiple levels of intervention are required to desensitize
- Use of multiple immunosuppressants is likely to increase the probability of adverse events and cost of intervention

- Prevention is better than cure