université PARIS-SACLAY

FACULTÉ DE MÉDECINE

Inserm

Desimmunization
Present and perspectives

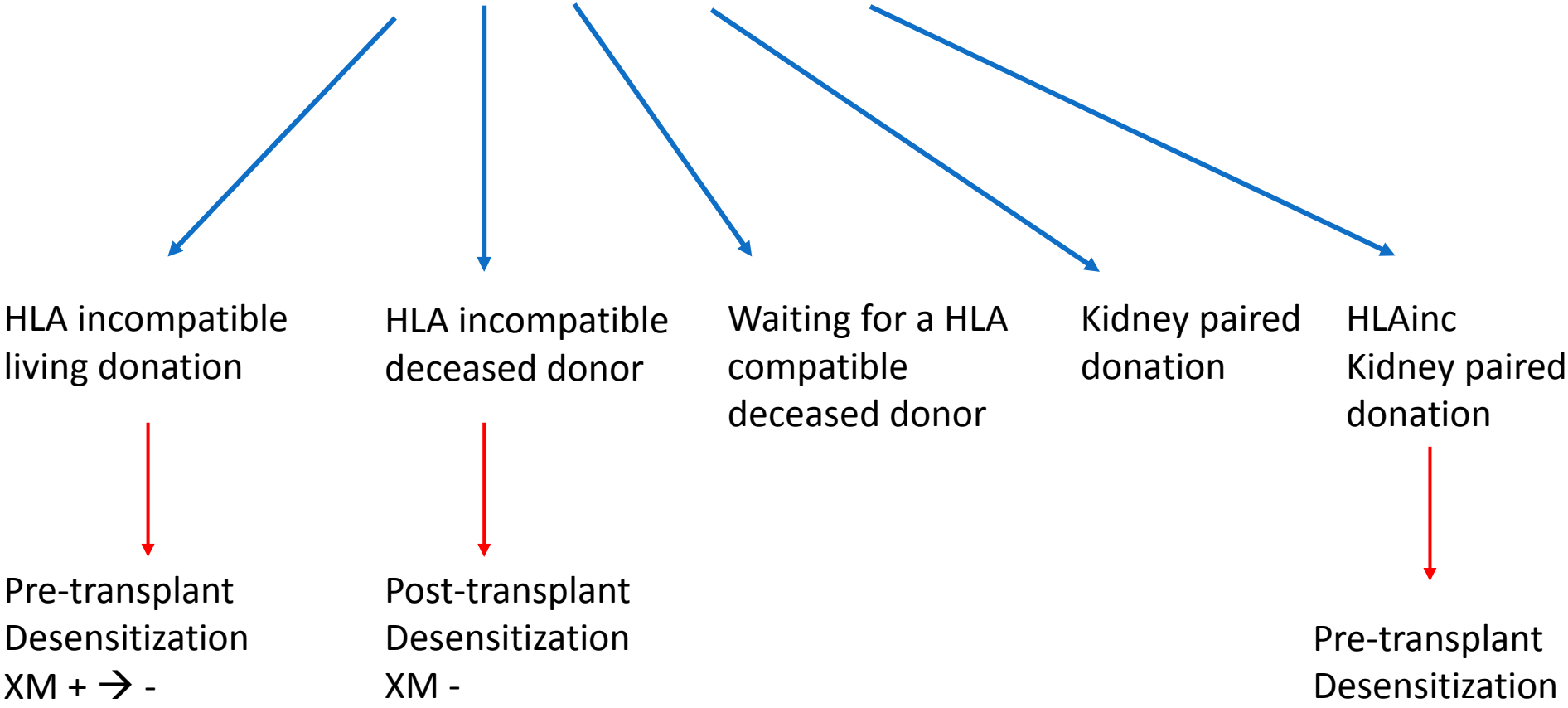
Renaud SNANOUDJ

Hôpital Bicêtre

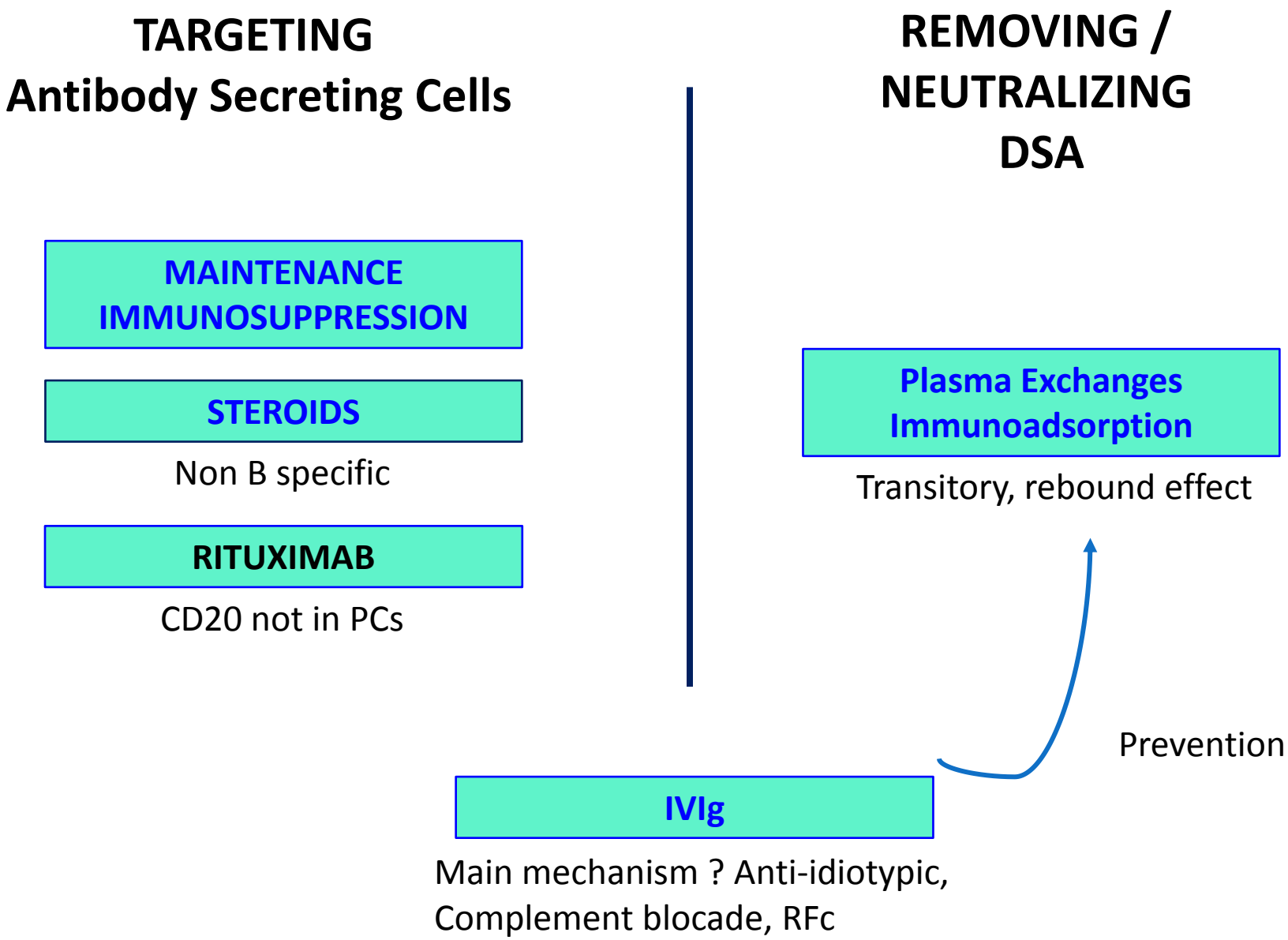
INSERM U1018- CESP

Introduction : impact of hyperimmunization

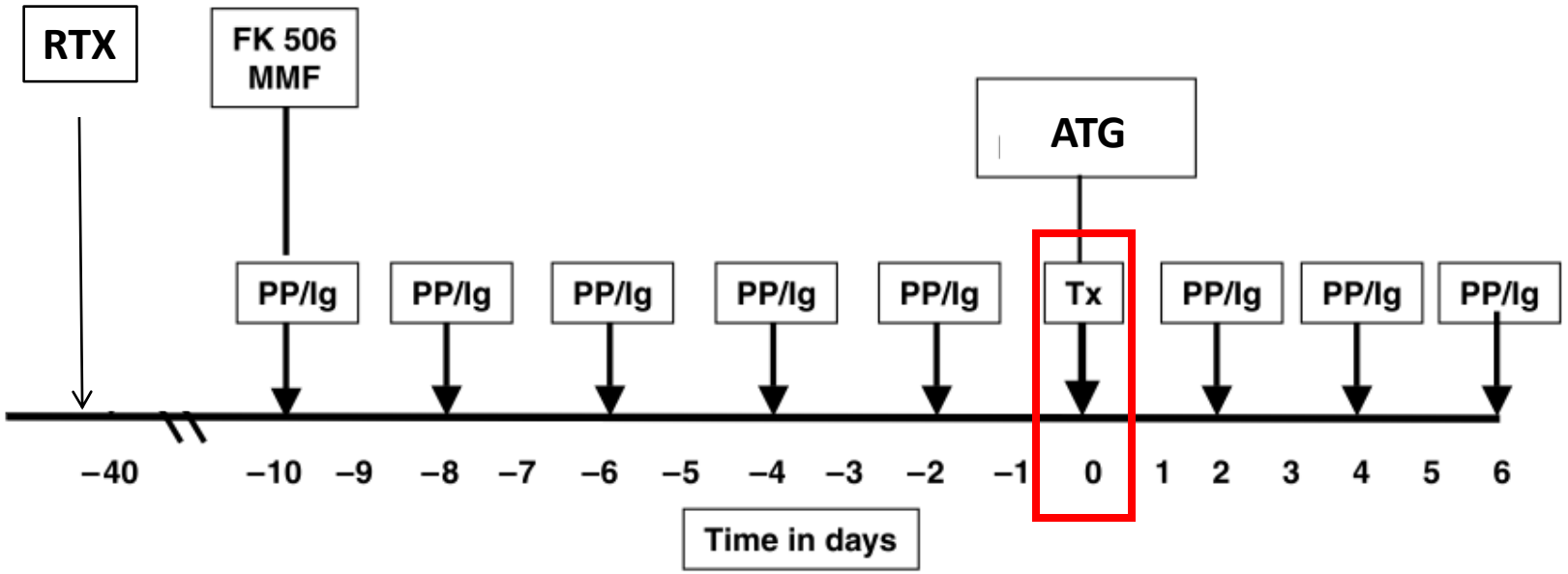
- High cPRA → x2 waiting times with the risk of increased « on list » mortality
- Solutions for hyperimmunized patients



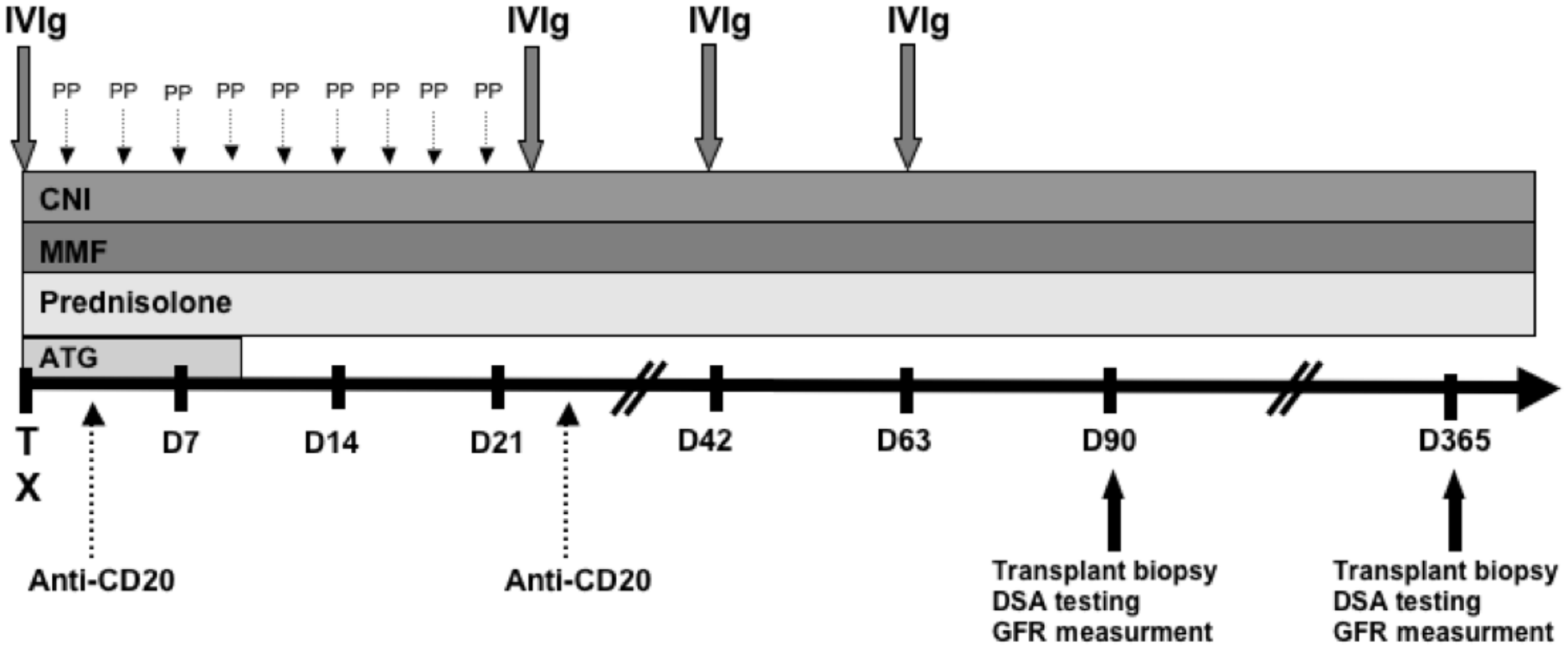
Current therapeutic tools



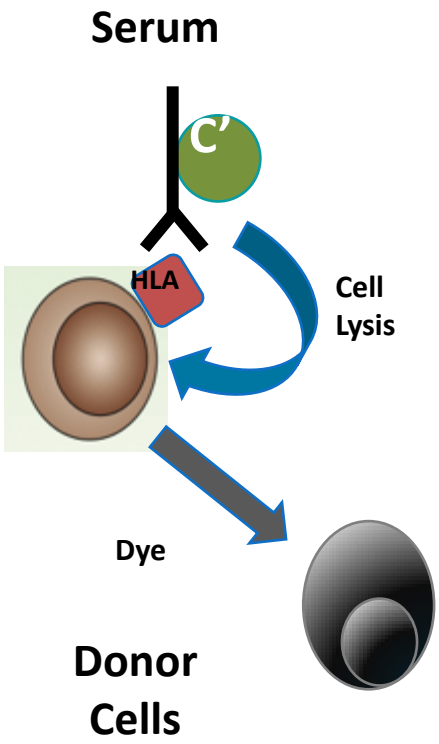
Current thérapeutic protocols
Pre-transplant desensitization
(Johns Hopkins)

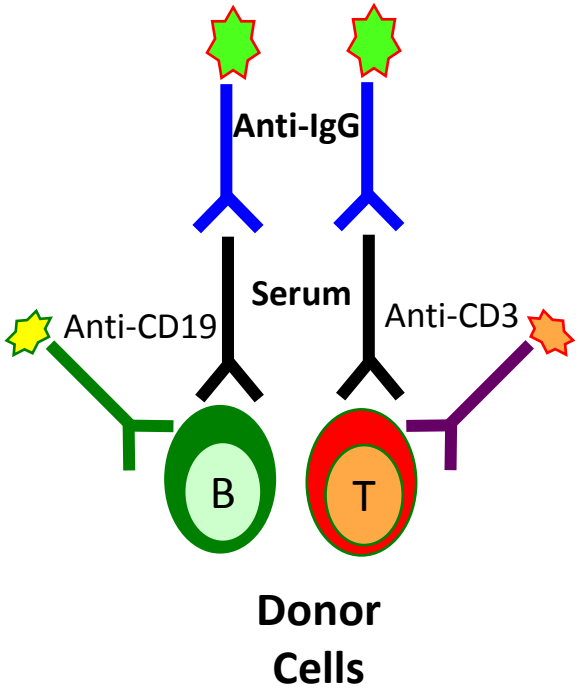


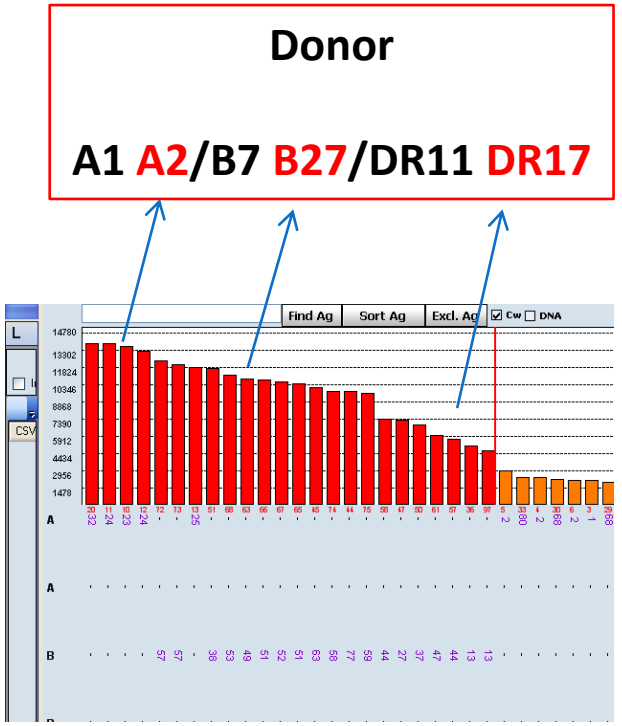
Current therapeutic protocols
Post-transplant desensitization
(Necker)



Three levels of immunological risk



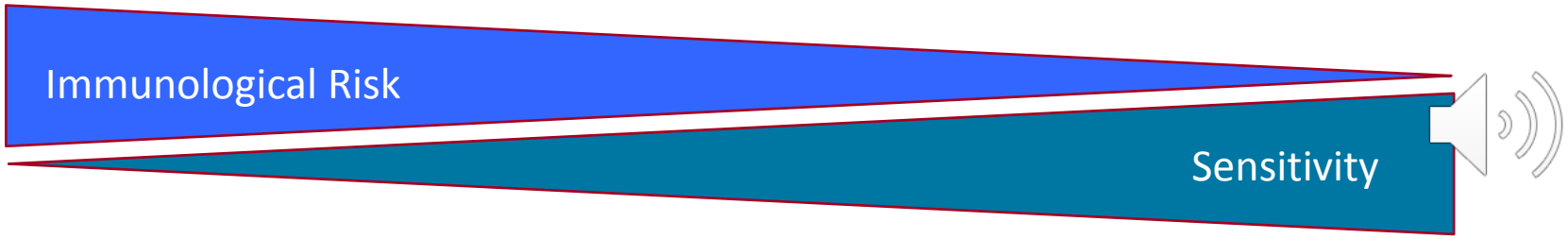




XM LCT

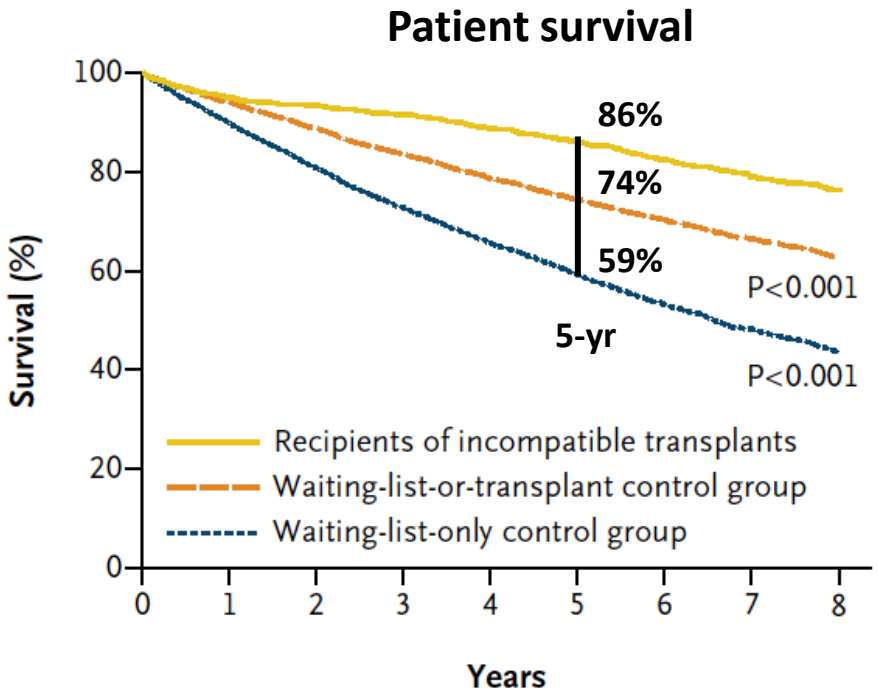
XM CYTOMETRY

XM VIRTUAL



Current results : Waiting or not waiting ? US

US multicentric (n=22)
Study
Verified with
- Luminex XM
- Flow XM
- CDC XM

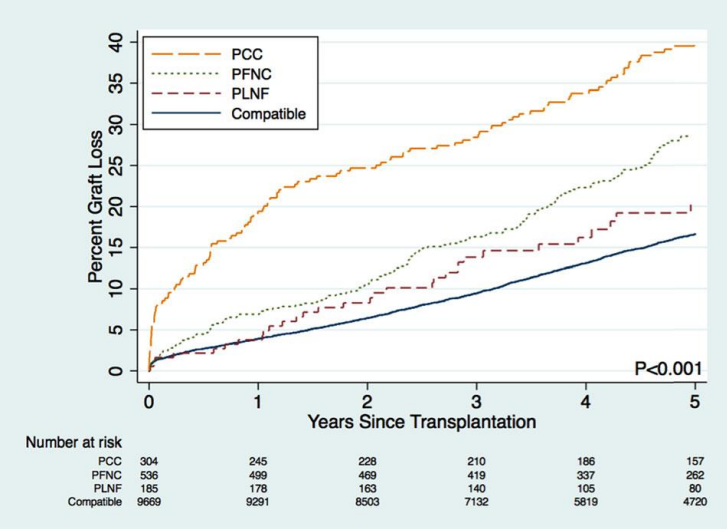


No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

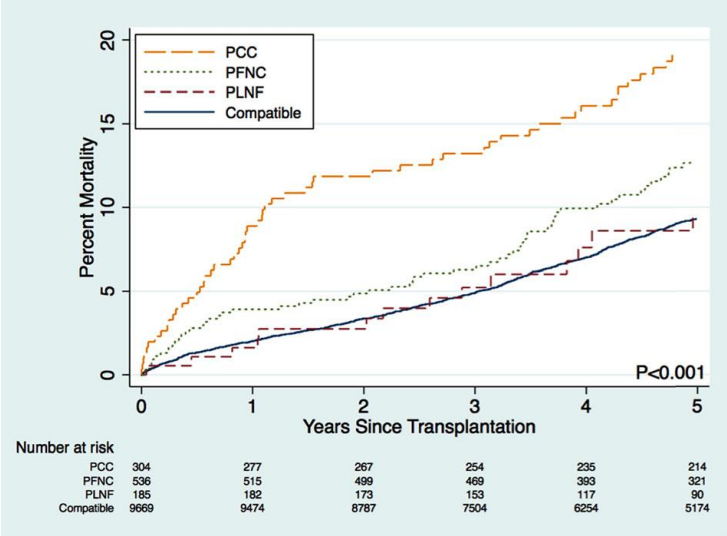
Orandi et al, N Engl J Med 2016

Outcome related to immunological risk

Graft loss



Mortality



+ CDC XM

+ Flow XM

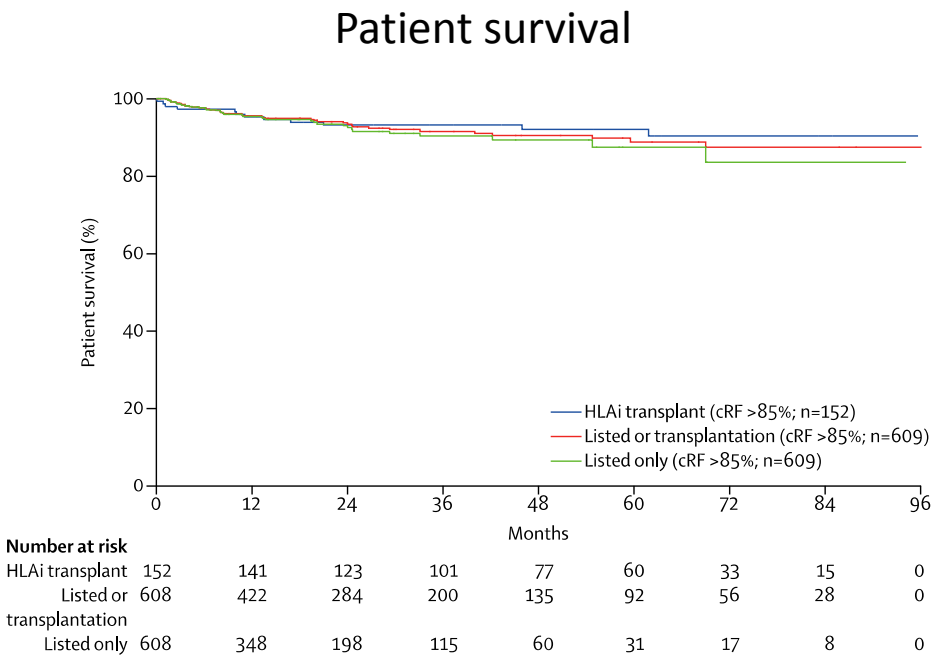
+ Luminex

Negative

Orandi et al, Am J Transplant 2014

Current results : Waiting or not waiting ? UK

213 HLA inc Living Donor Tx
852 controls
At 5 years:
39% transplanted comp. DD
20% transplanted comp. LD
41% not transplanted



Number at risk

HLAi transplant	152	141	123	101	77	60	33	15	0
Listed or transplantation	608	422	284	200	135	92	56	28	0
Listed only	608	348	198	115	60	31	17	8	0

No benefit in patient survival

Manook et al, Lancet 2017

Current results : Waiting or not waiting ? UK

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At 5 years:
39% transplanted DD
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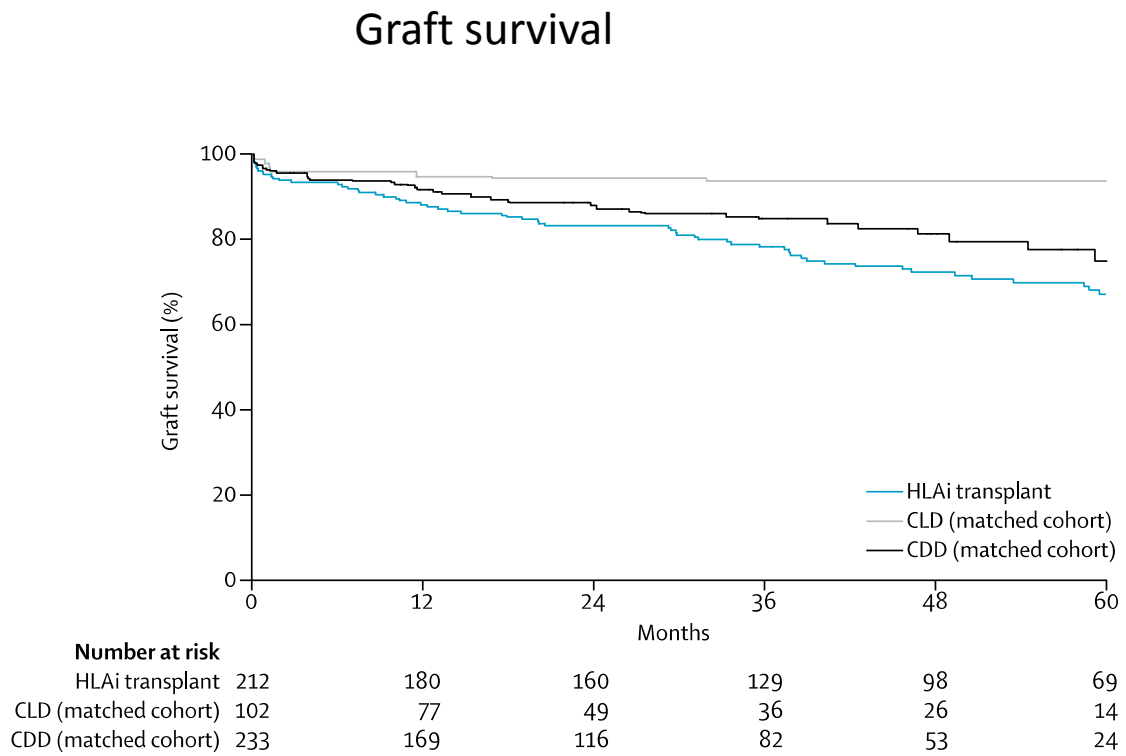
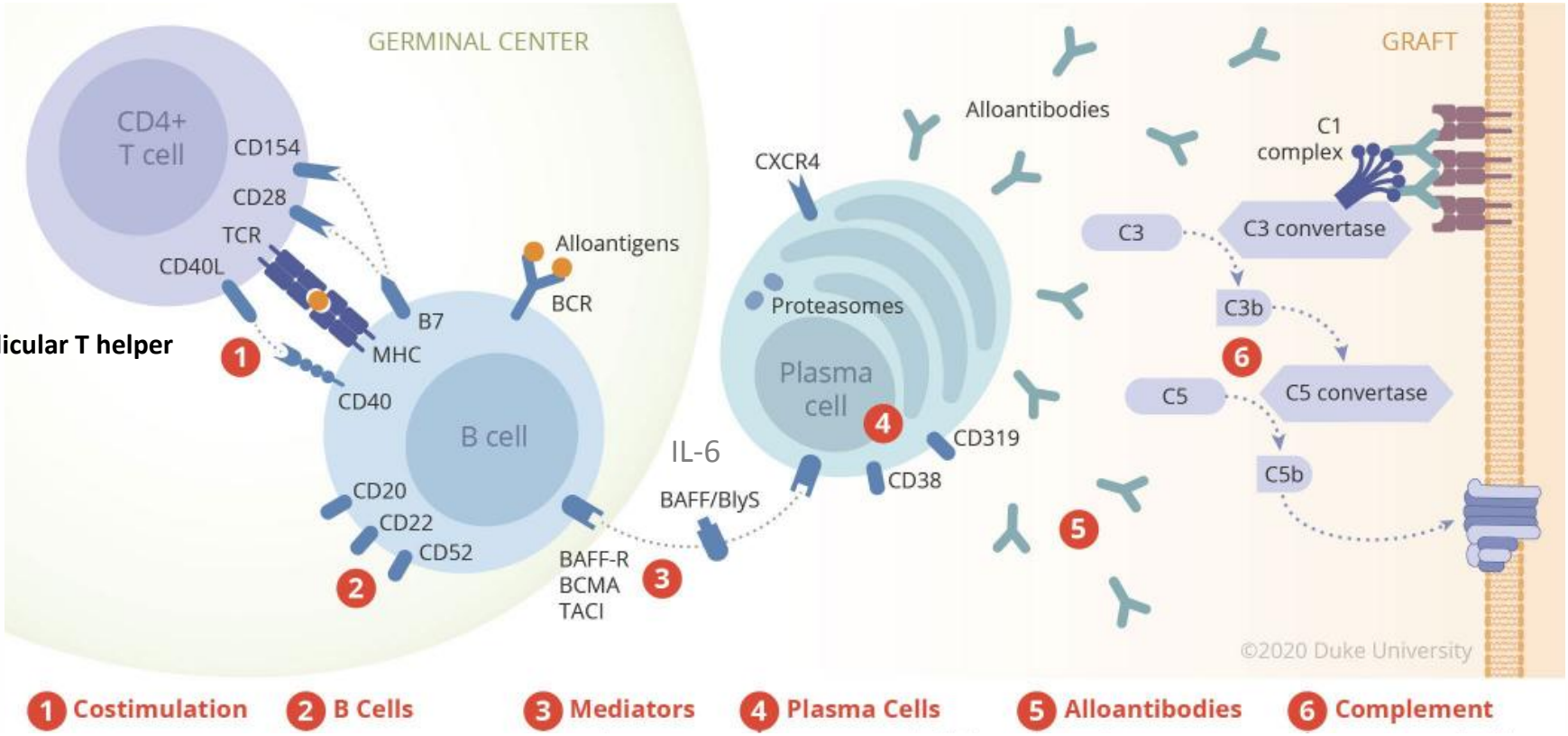


	Comp. LD	Comp. DD	HLA inc
1-yr, %	**96**	**92**	**88**
5-yr, %	**89**	**77**	**68**

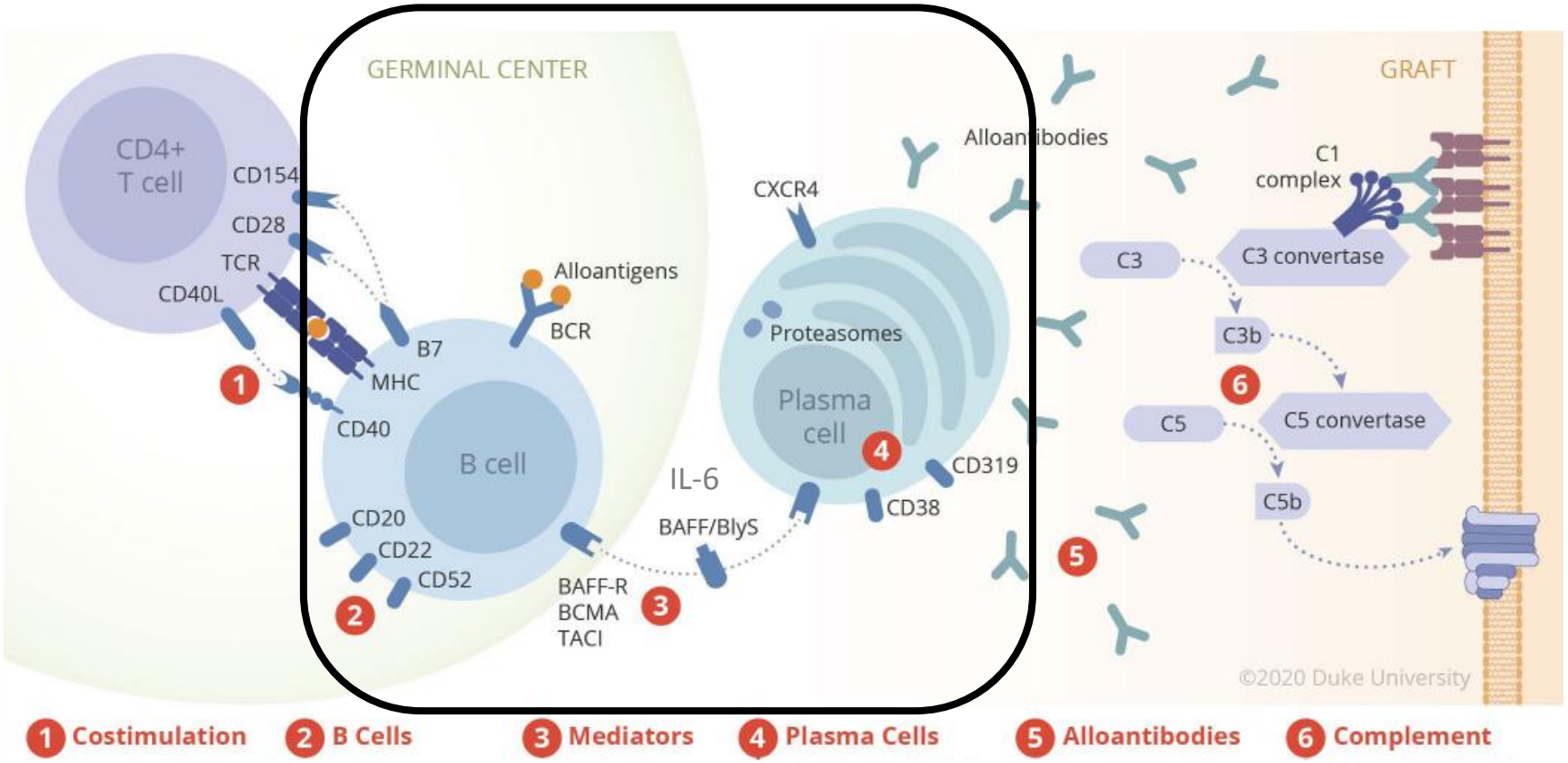
Manook et al, Lancet 2017

New options

Follicular T helper

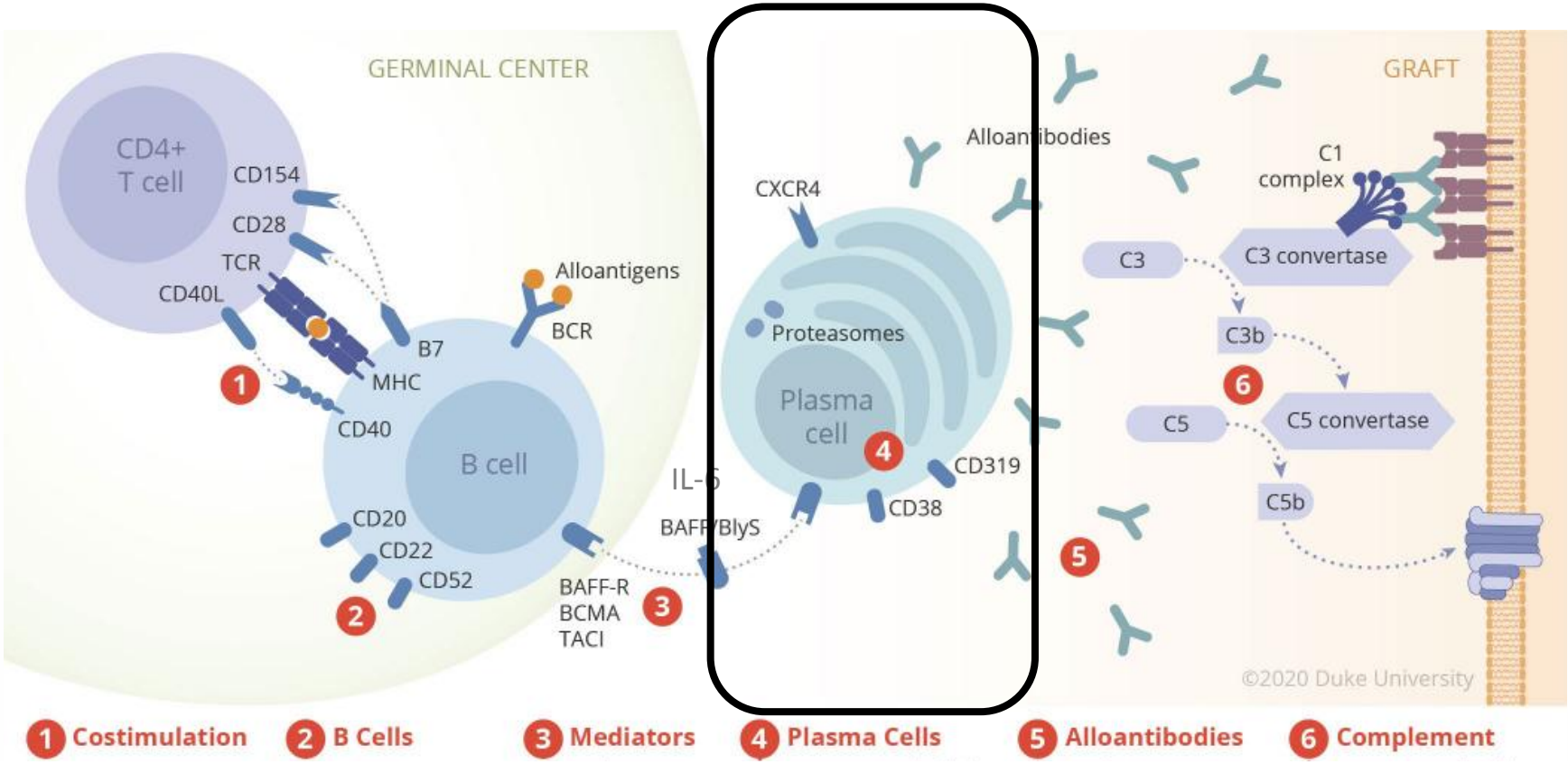


B cells and Plasma Cells

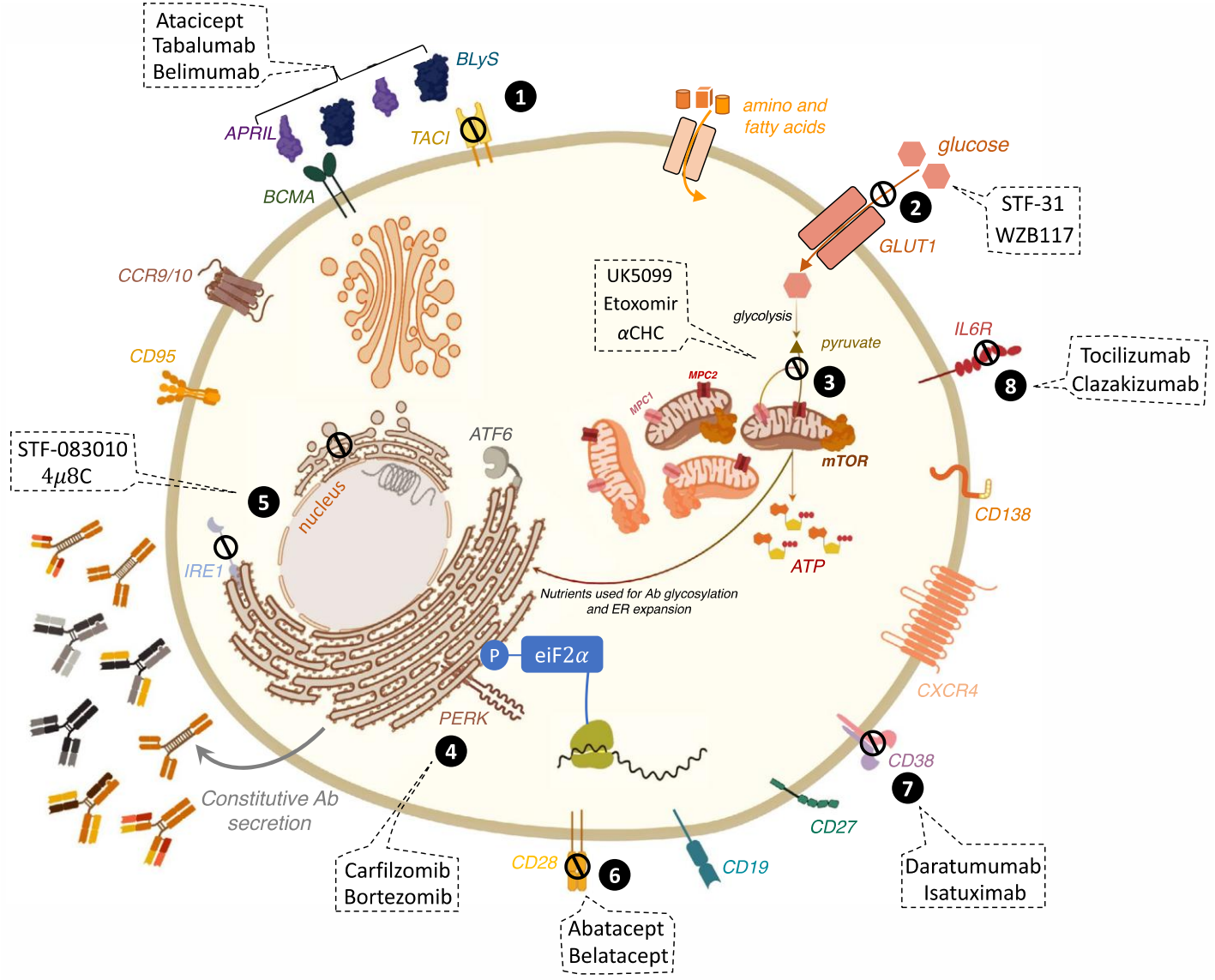


Inebilizumab anti CD19 mAb

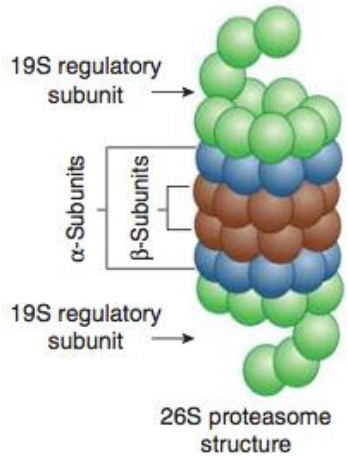
Plasma Cells



Targeting Plasma cells



Targeting plasma cells : Proteasome Inhibitors



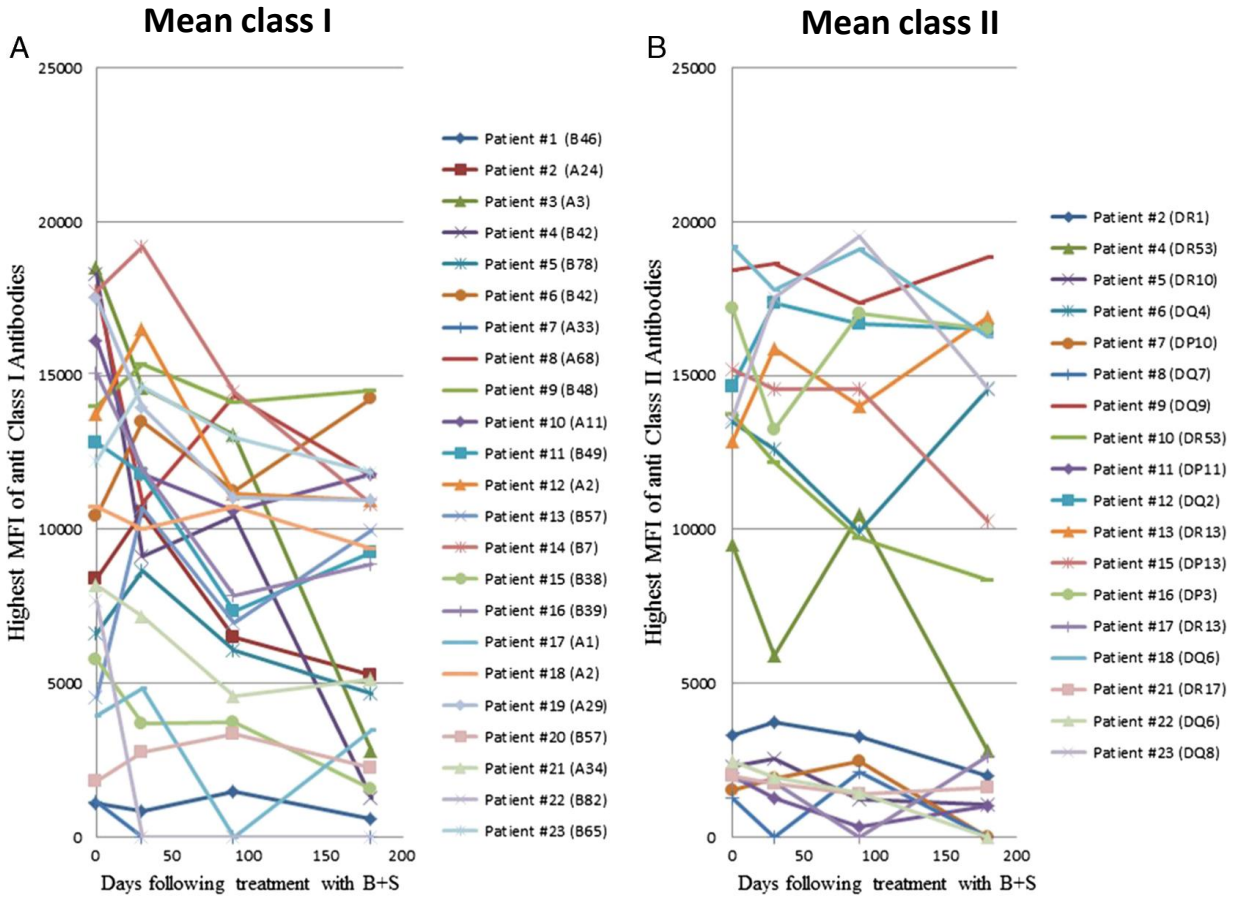
- ***Proteasome*** : Degradation of unfolded/misfolded proteins
- ***Inhibition of proteasome : BORTEZOMIB***
  - Inhibition of NF-kB
  - Induction of apoptosis (stress of reticulum)
  - Inhibition of antigenic presentation

- 1-2 cycles of bortezomib + RTX + plasmapheresis (n=44) in 5 groups
- Reduction in DSA in 38/44 (86%) patients and in FlowXM
- 19/44 patients transplanted : 43%
- AMR 12.5% at 6 Mo
- 1-yr Graft survival 95%

Woodle et al, Am J Transplant 2015

Targeting PCs : Proteasome Inhibitors

23 patients with stable immunization – 1 cycle of bortezomib + DXMT
Median MFI of highest Ab 10734/11189
At m6 54% of Ab sustained decrease >25% and 36% decrease >50%



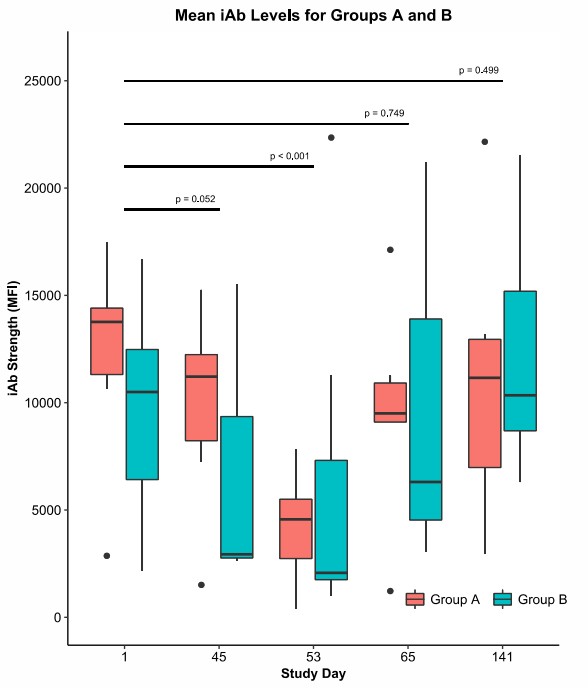
Aubert et al, Transplantation 2014

New Proteasome Inhibitors

- ***Carfilzomib*** : non-reversible 2nd generation IP + PEx

  → n=13, 2 regimen escalating doses, 73-80% reduction of immunodominant HLA Ab

  →After depletion rapid rebound and return to baseline

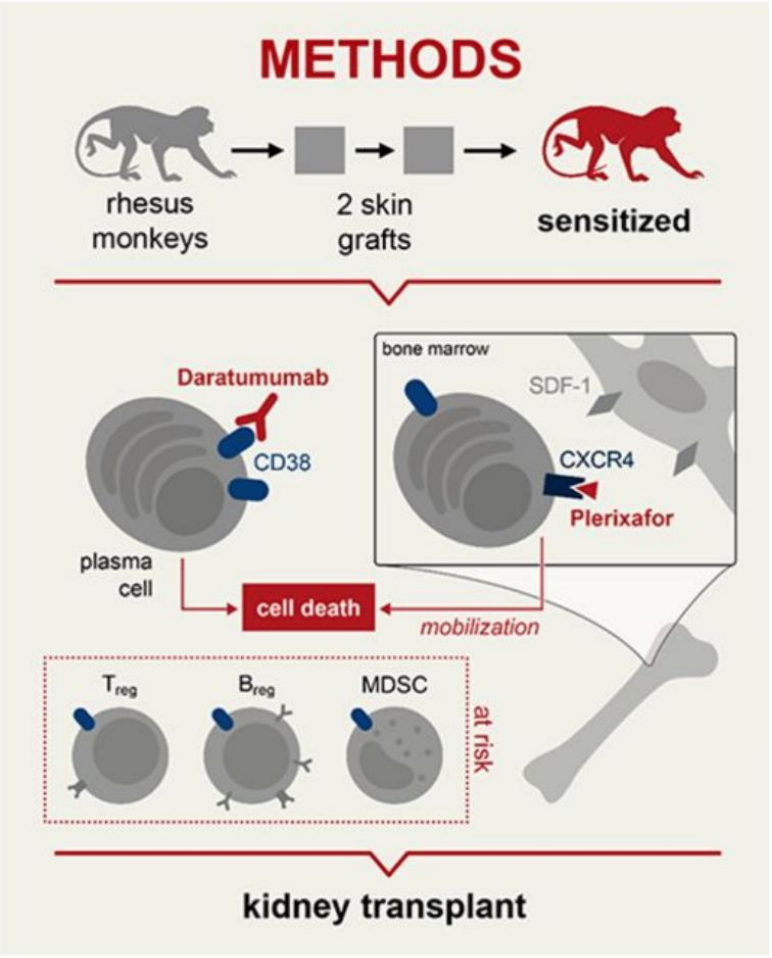


- ***Immunoproteasome inhibitors***
  - Target specific proteasome in T, B and PC
  - Expression in tissues exposed to γIFN or TNFα
  - Better safety
  - Superior to PI in animal models in preventing TCMR and CAMR

Tremblay et al, Am J Transplant 2020
Li J, Koerner J et al, Kidney Int 2019

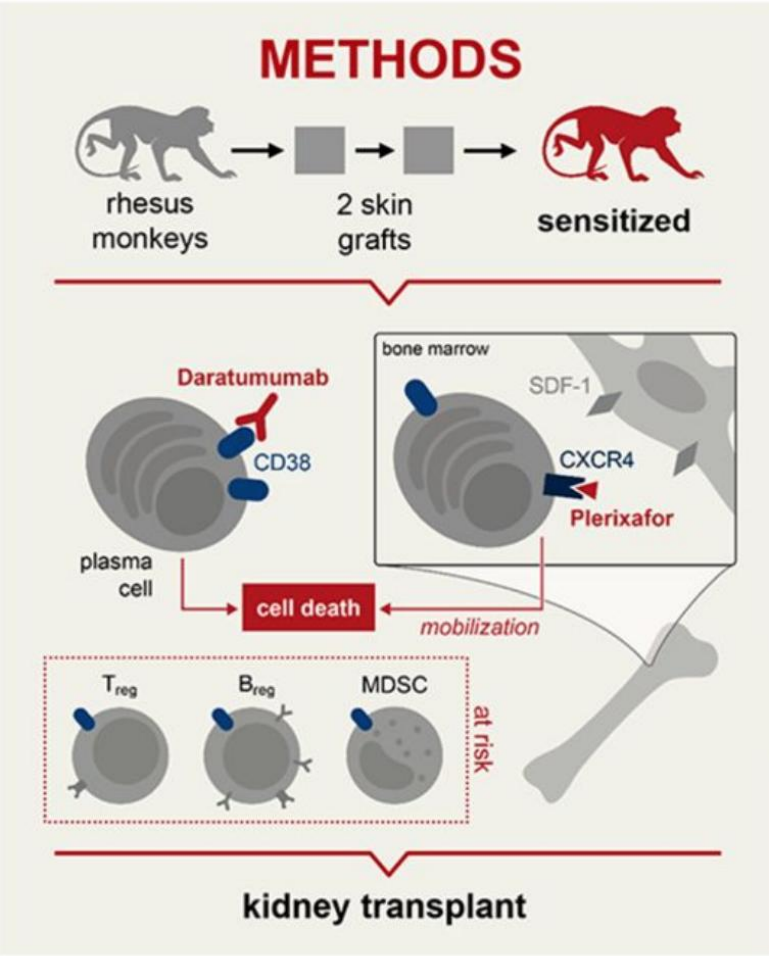
Targeting PCs : Daratumumab anti-CD38

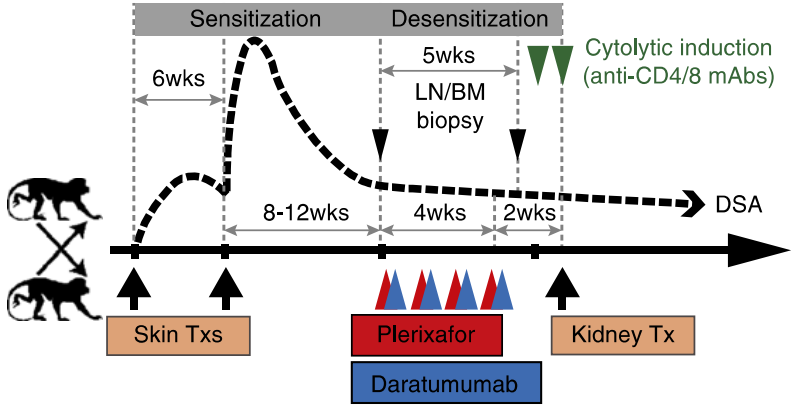
CD38 expressed by memory B cells and Plasma Cells
Daratumumab : monoclonal anti-CD38 human IgGk → apoptosis of PC

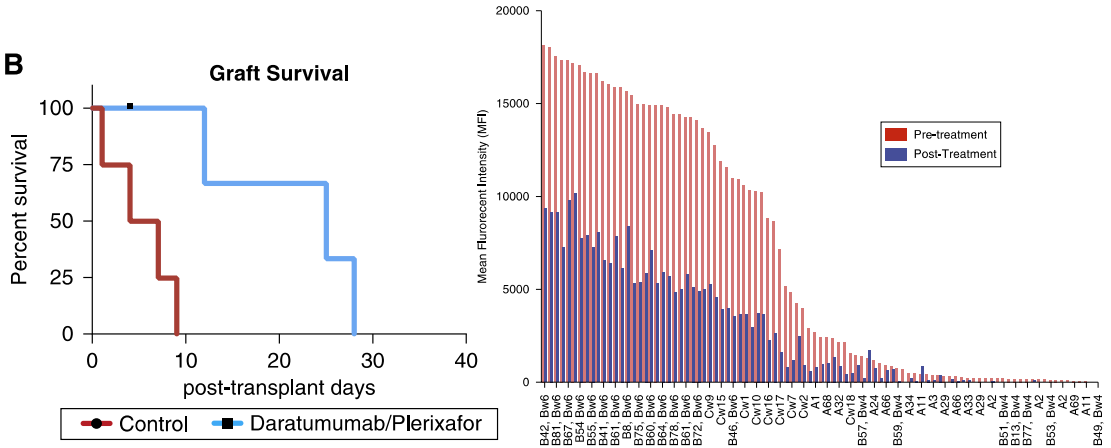


Kwun et al, JASN 2019

Targeting PCs : Daratumumab anti-CD38

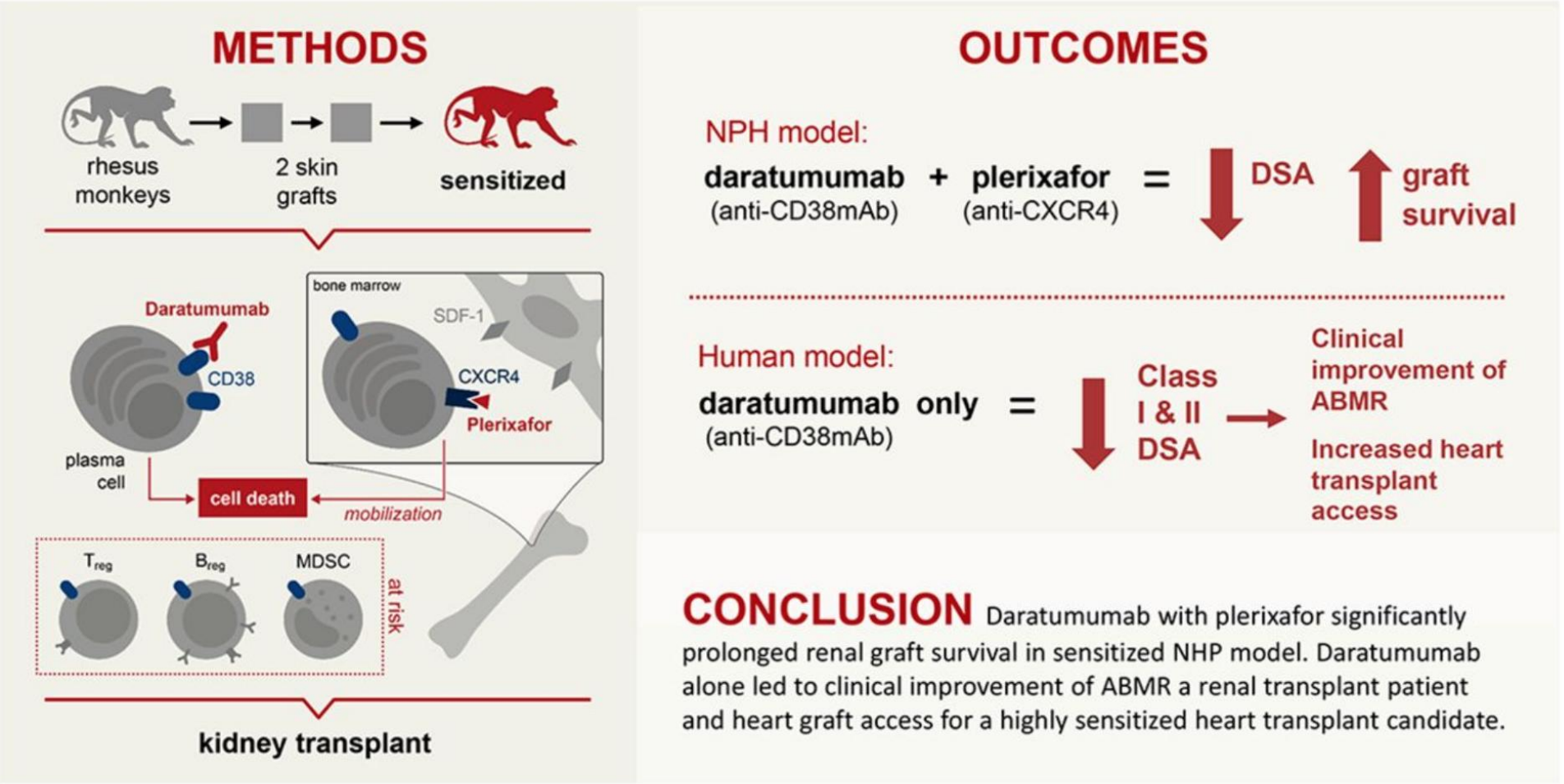






Kwun et al, JASN 2019

Targeting PCs : Daratumumab anti-CD38

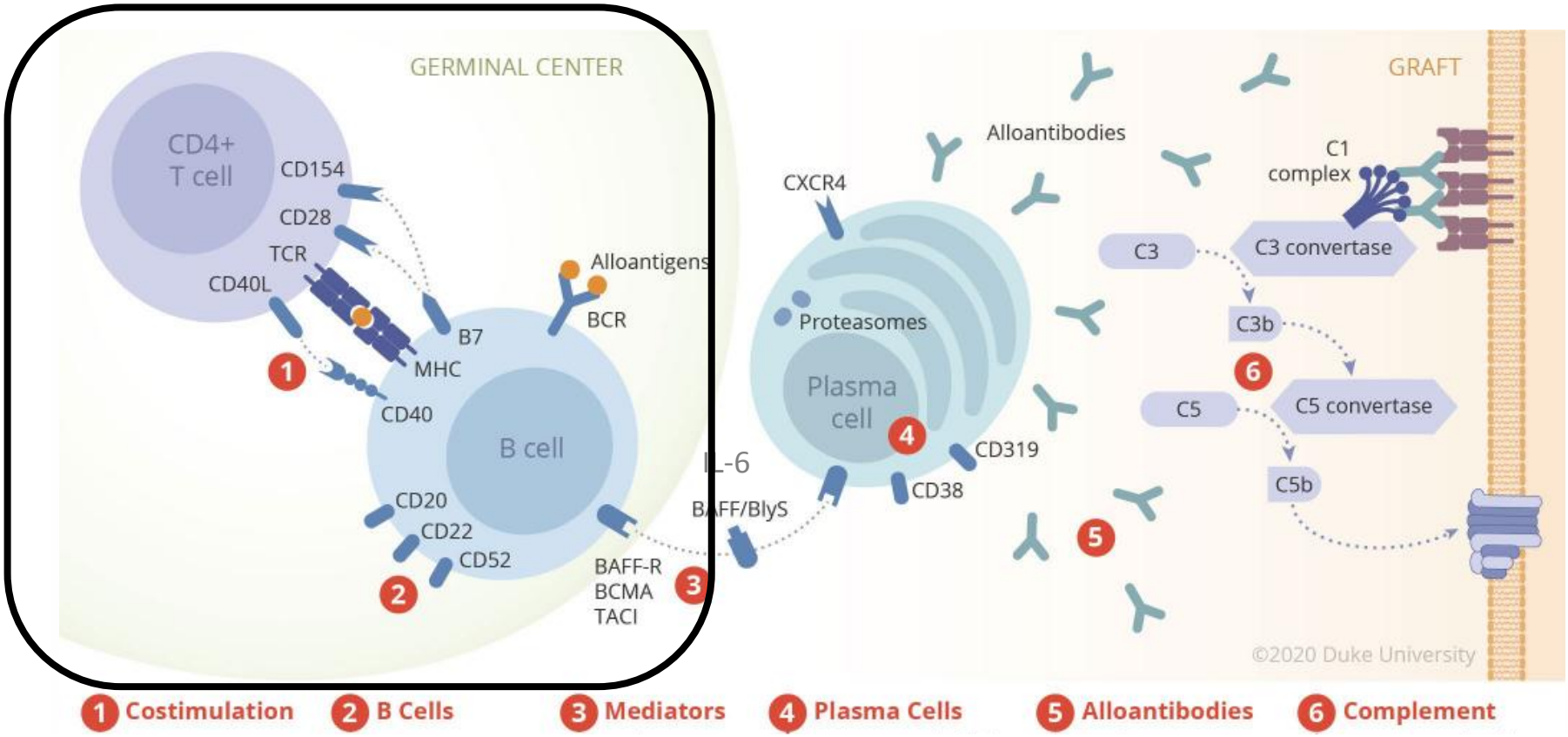


Kwun et al, JASN 2019

CD38 mAbs

- Waiting for results of phase I/II DARDAR study
- Other CD38 mABs targeting also NK and MN
  - Isatuximab
  - Elotuzumab

Costimulation blockade



Effect of costimulation blockade on B cells and humoral response

- **In vitro (belatacept)**
  - ↓ Plasmablasts differentiation
  - ↓ Ig production
  - ↓ Blimp 1
  - ↓ CD28-related activation of Tfh
- **In vivo (belatacept, anti-CD40)**
  - Alteration of GC reaction in primate models (↓ B clonal expansion, Tfh, IL21)
- **Clinical**
  - Decrease in de novo DSA (Benefit studies)

Leibler et al, JASN 2018
Kim et al, Am J Transpl 2014

Interest of combining costimulation blockade and PCs targeting

- **Humoral compensation**

Non human primate

↓

Fully mismatched Skin allosensitization→ donor specific antibodies

↓

Bortezomib

↓

↓PCs, → DSA

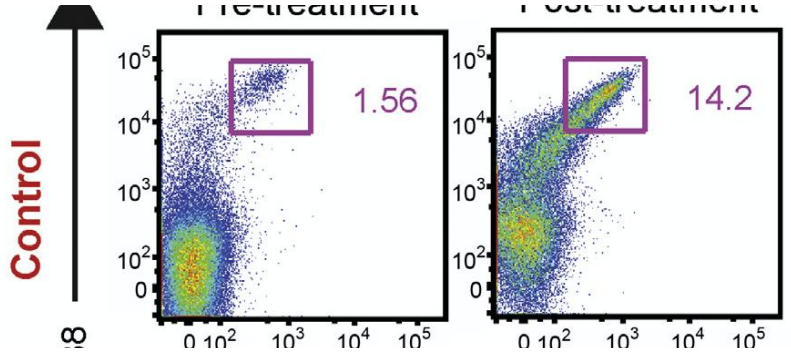
↓

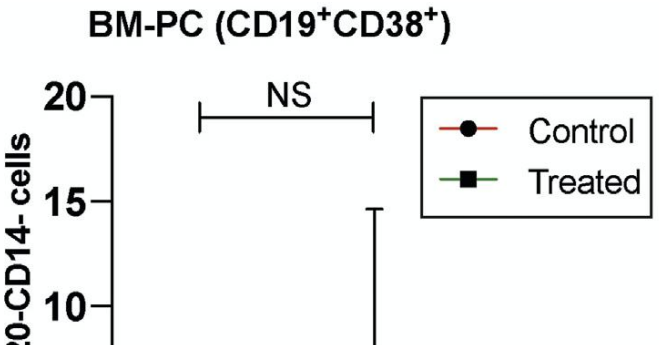
↑B cells in LN, ↑Tfh, ↑DSA : humoral compensation

Negative feedback

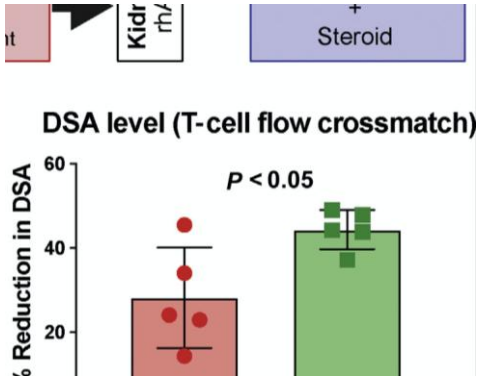
Kwun et al, JASN 2017

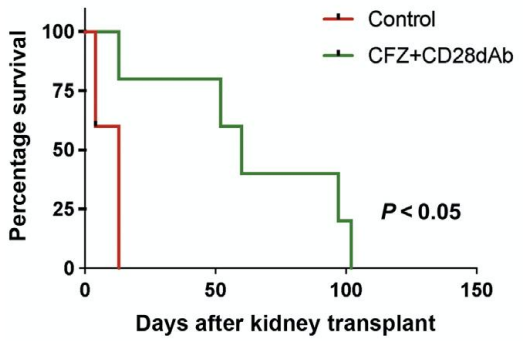
Costimulation blockade and PCs targeting

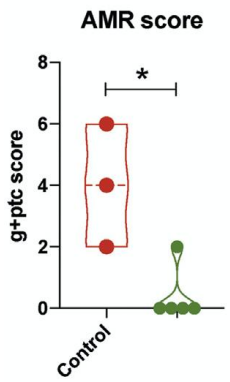




Lulizumab (anti-CD28), Carfilzomib (PI)







↓ Tfh, ↓ proliferative B cells in LN, ↑ naive B and T cells, → Treg

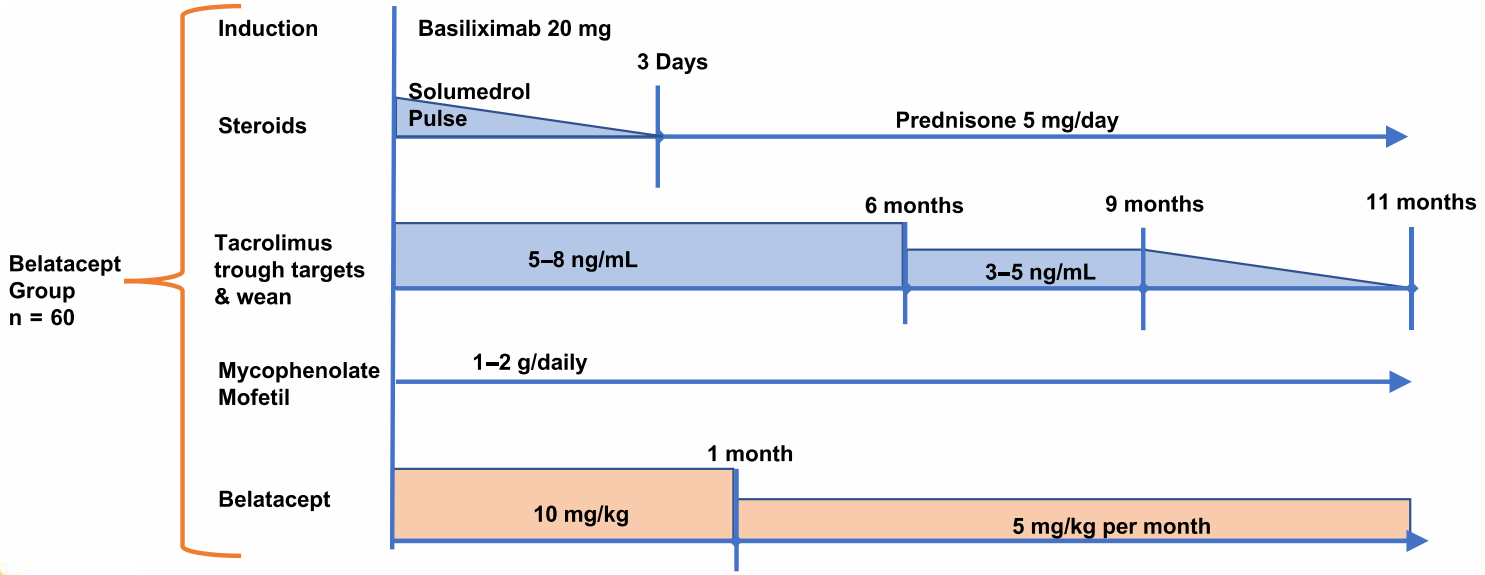
Schroder et al, Kidney int 2021

Effect of costimulation blockade on PRA

163 immunized patients cPRA [98-100%]

↓

60 patients transplanted with belatacept > 6 Mo., 44 control



Parsons et al, Am J Transplant 2019

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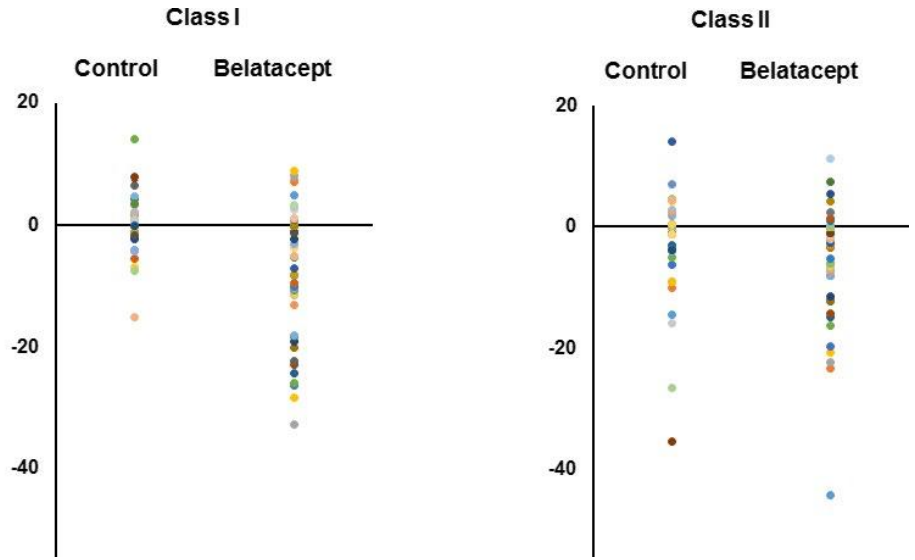
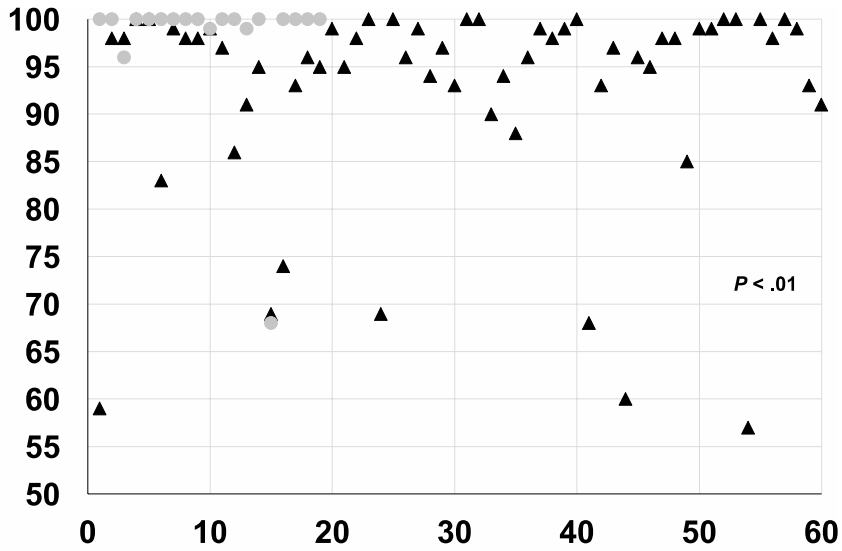


P<0.0009

P=0.4

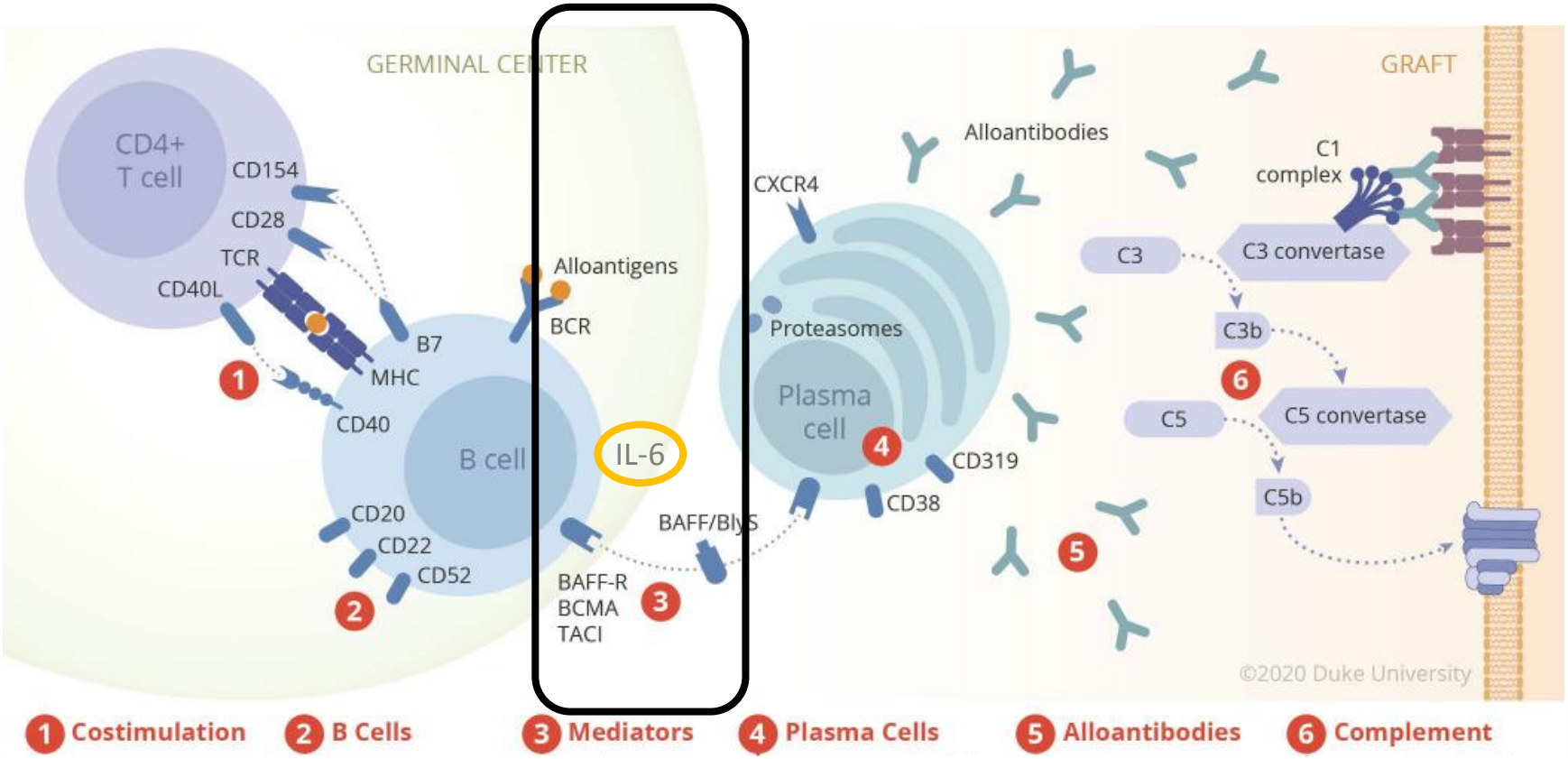
Flow PRA reduction



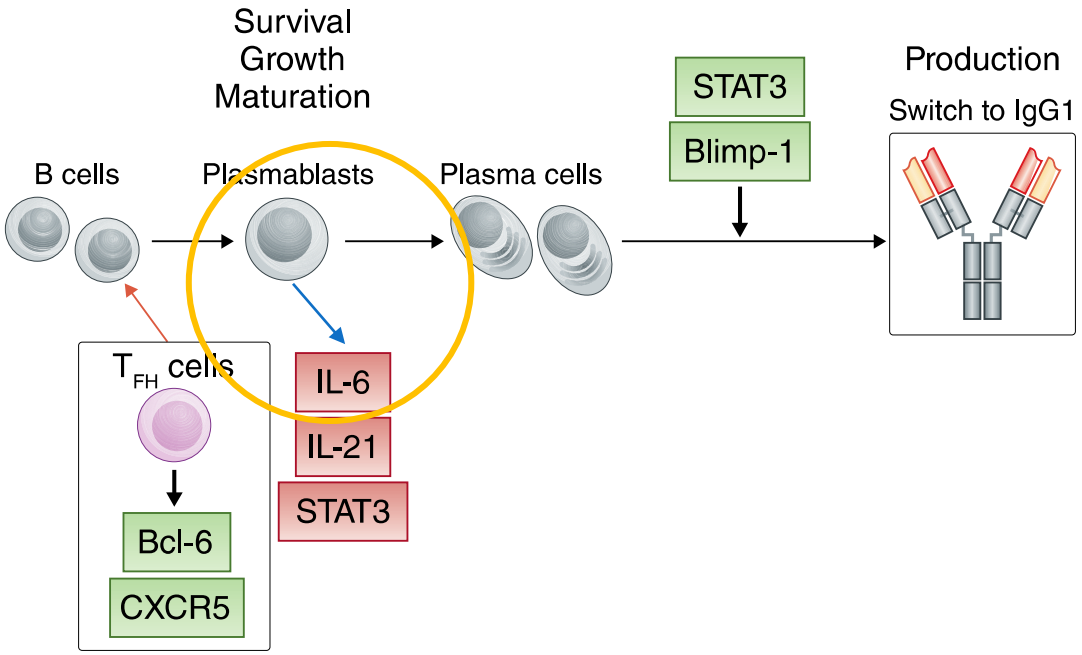
cPRA reduction

Parsons et al, Am J Transplant 2019

Mediators IL-6



Targeting IL-6



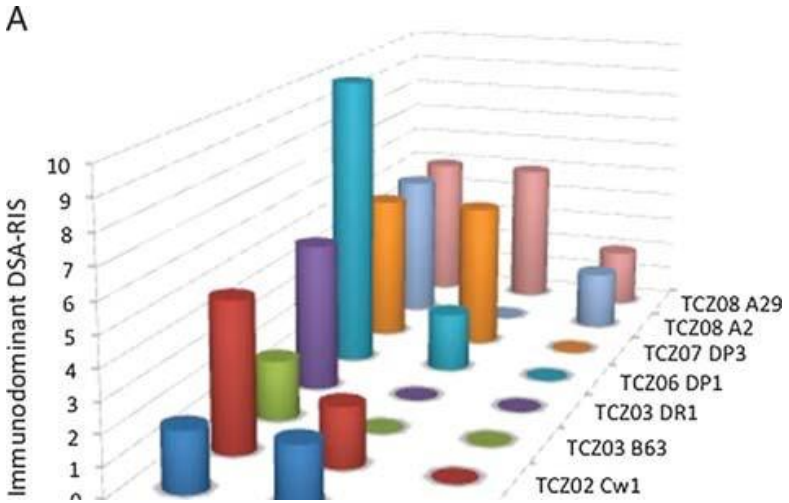
Critical role in initiation of adaptative humoral response,
progression of naive B cells to PB and production of high affinity antibodies
Activation of Th17, inhibition of Tregs

→ Tocilizumab : anti-IL6 R
→ Clazakizumab : anti-IL6

Chavele et al, J Immunol 2015

Targeting IL-6

- **Tocilizumab**, phase I-II in 10 immunized patients resistant to IVIG/RTX desensitization
  - **IVIg** : D0/D30
  - **TCZ** : D15, M1→6
  - 5/10 transplanted patients (negative CDC XM, MFI < 10000)
  - No ABMR on 6-Mo biopsy
  - GFR 60+/- 25 ml/min

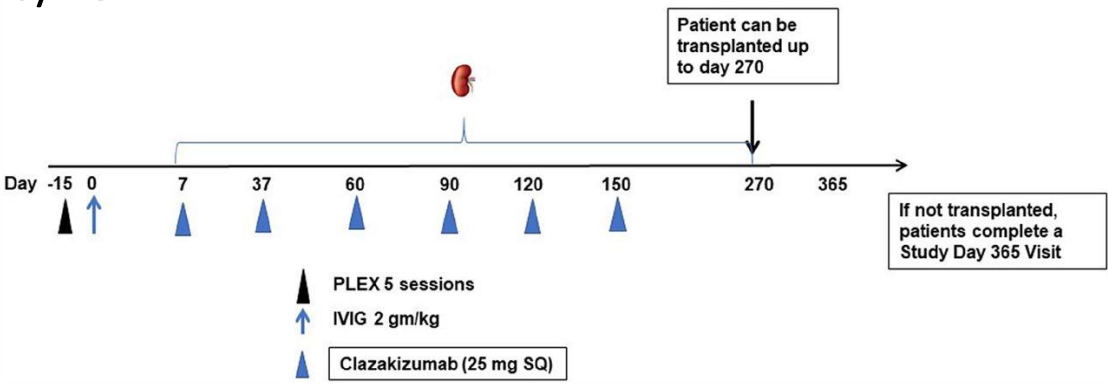


Course of DSA

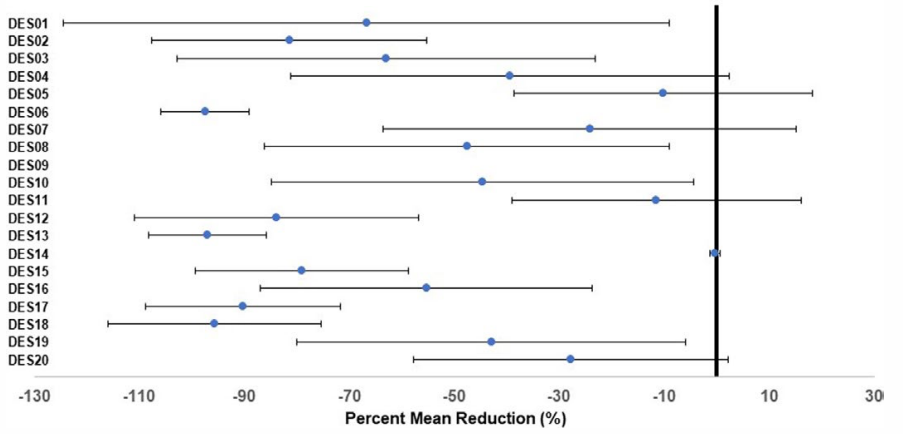
Vo et al, Transplantation 2015

Targeting IL-6

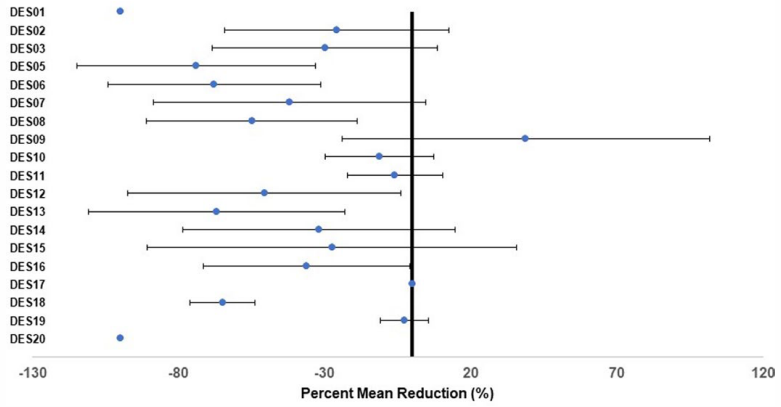
- **Clazakizumab**, phase II pilot study in 20 immunized reTx patients, 6 monthly injections pre and post Tx
- cPRA >85%, DSA 14/18, FXM + 10/18
- 18 patients transplanted



CLASS I Ab

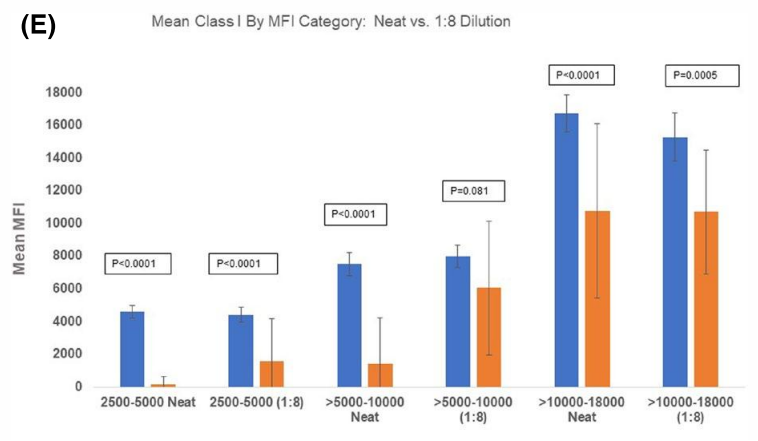


CLASS II Ab



Vo et al, Am J Transplant 2021

Targeting IL-6



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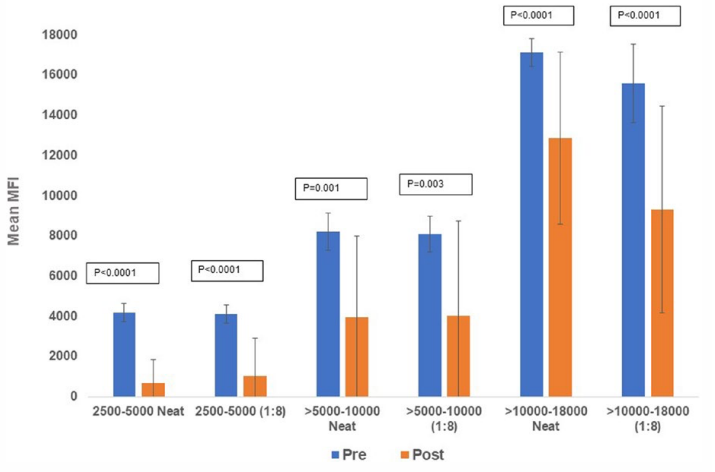

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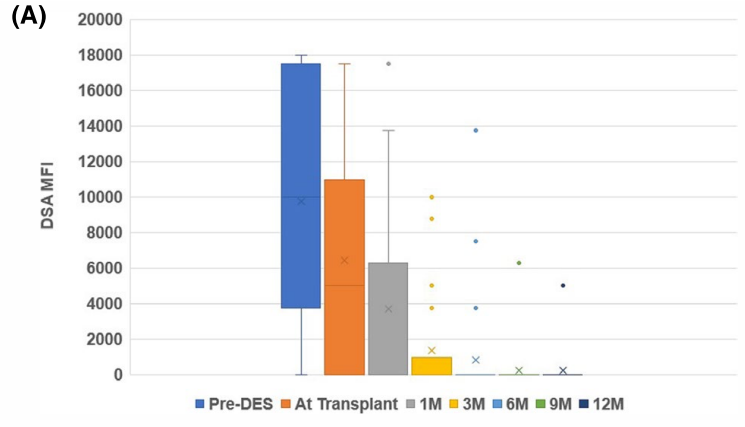
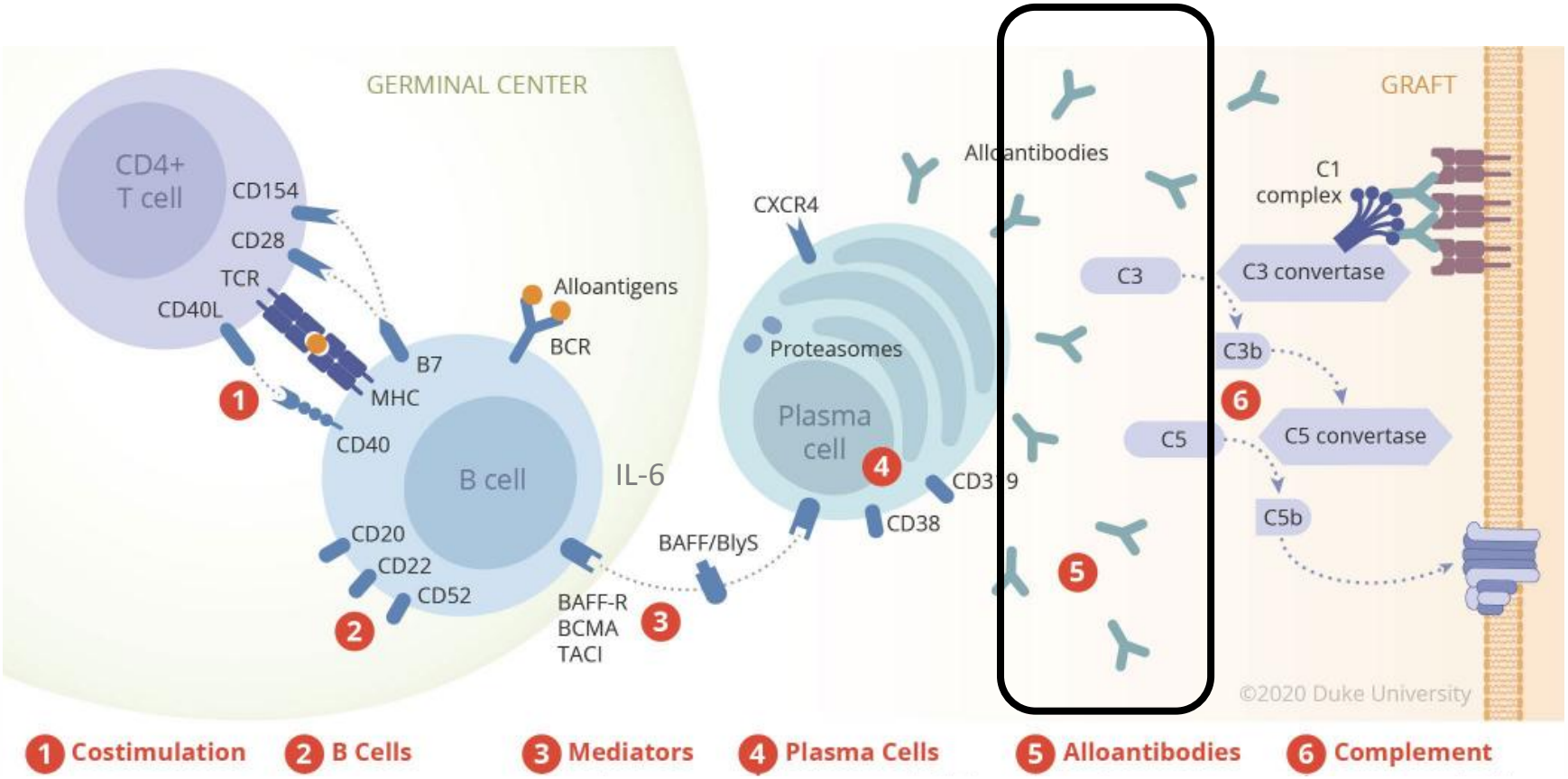


DSA

13/14 no DSA at 6Mo
AMR n=2
Patient Survival 100%
Graft survival 94% at 1-yr

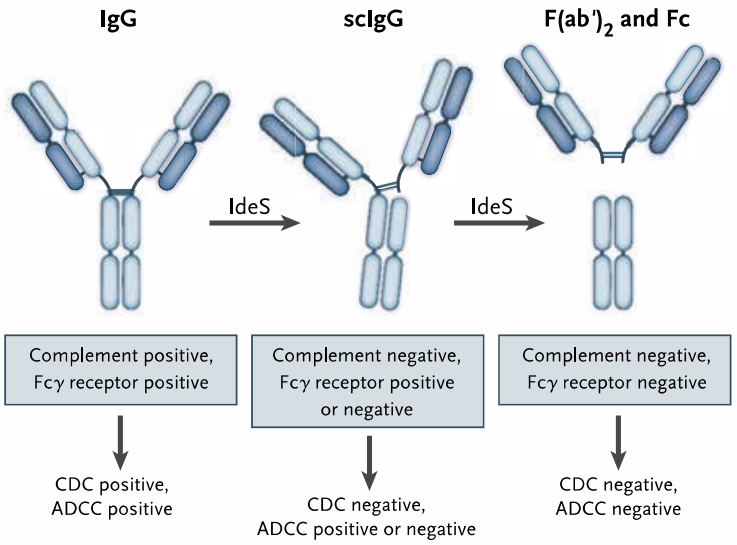
Vo et al, Am J Transplant 2021

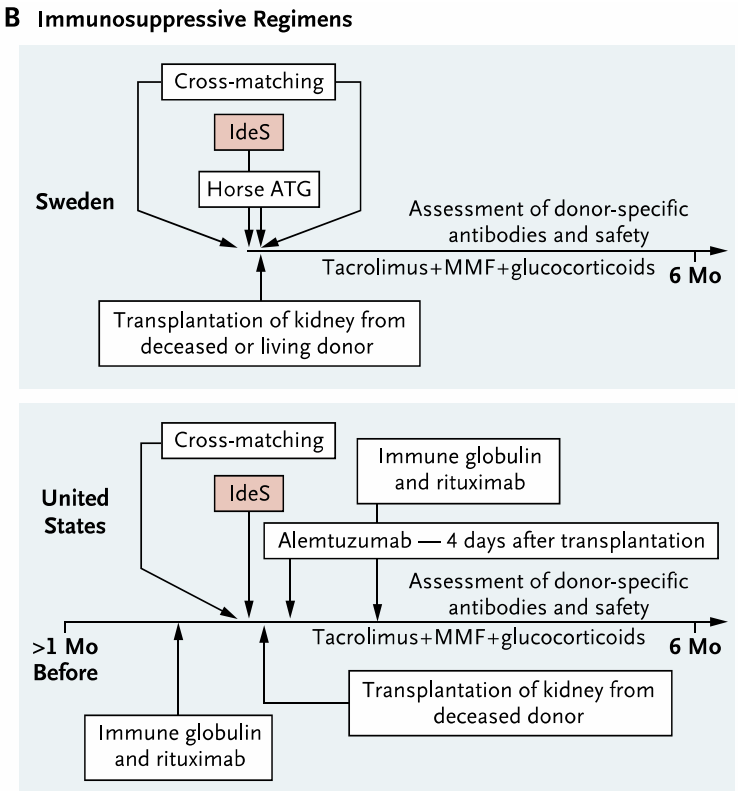
Alloantibodies



IdeS : IgG endopeptidase / Imlifidase

- Cleavage of IgG
- Inhibition of Complement and Antibody-dependant cytotoxicity
- Cleavage of BCR in memory B cells (Jarnum JI 2015)

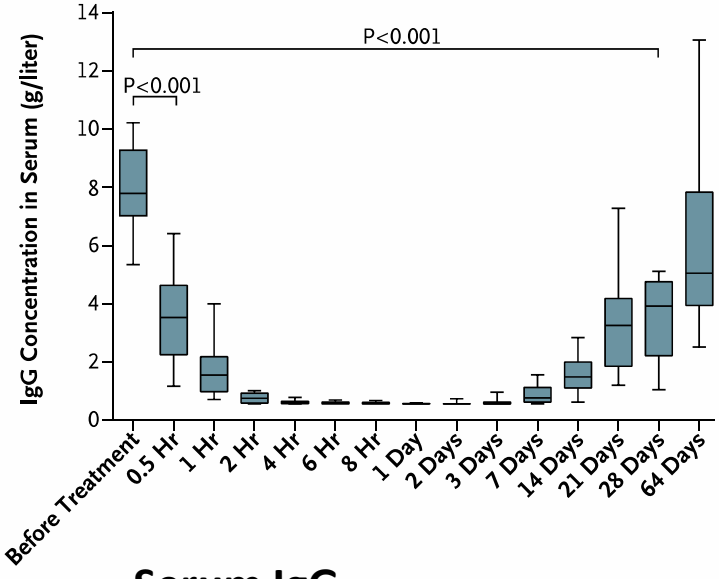




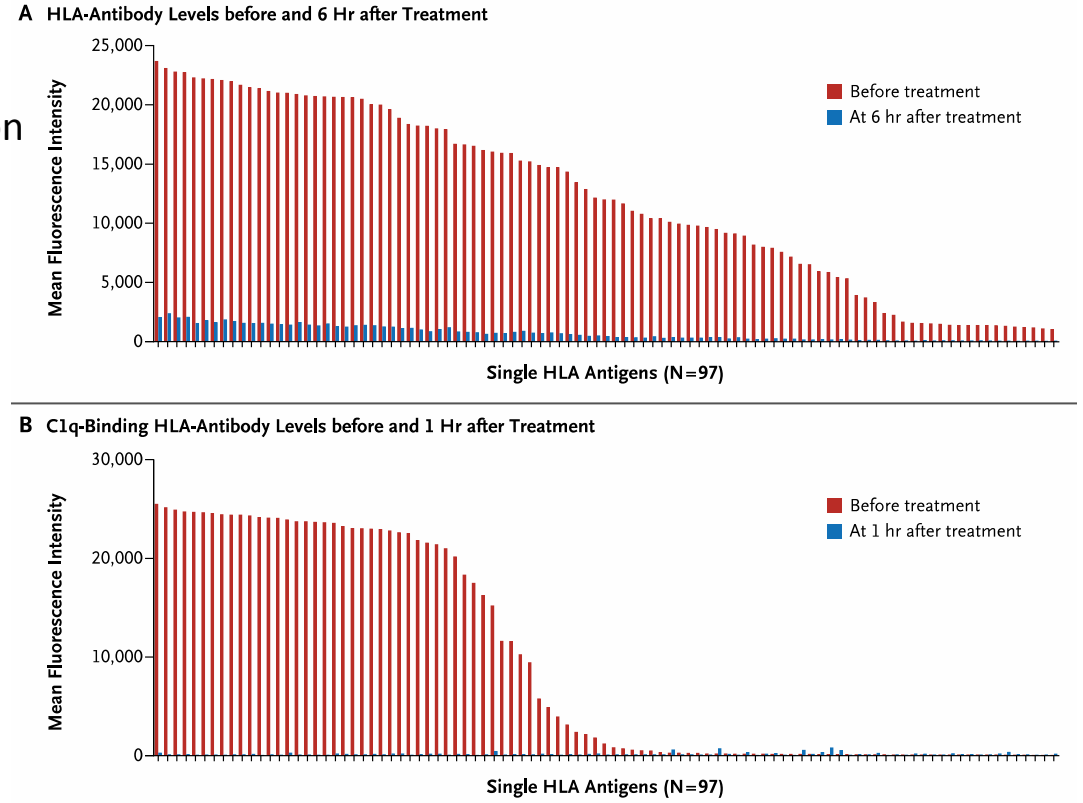
Jordan, NEJM, 2017

Imlifidase – 6 months results

- 2 centers (US/Sweden)
  - 22/25 DSA+ at Tx
  - Mean MFI 5660(cl1) 8200(cl2)
  - 20/25 positive Flow XM
- 5 patients : ABMR
- 1 graft loss due to acute ABMR
- 16 patients with microvascular inflammation



Serum IgG



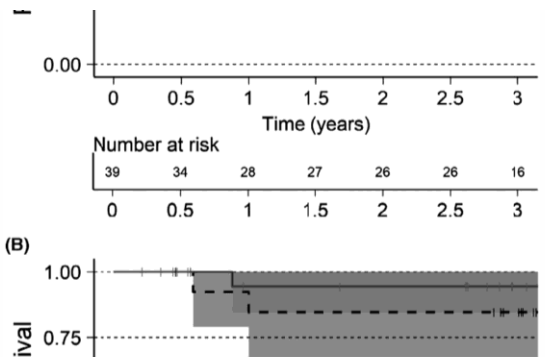
Jordan, NEJM, 2017

Outcome at 3 years

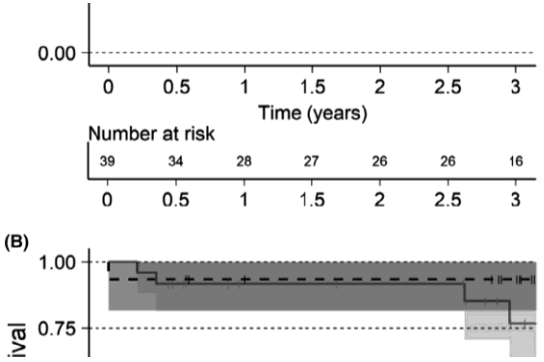
46 patients in 4 studies

→ 7 patients excluded (neg XM)

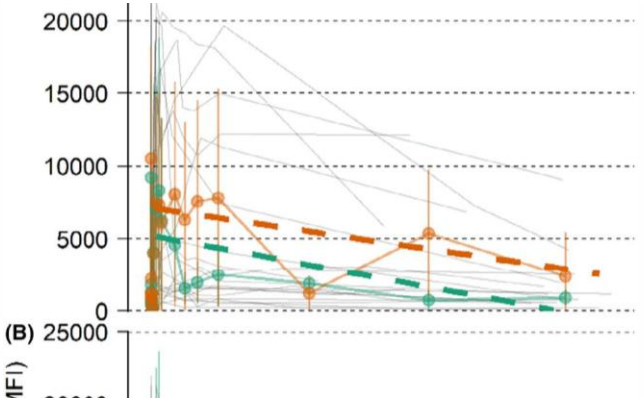
39 patients → **AMR n=15 (38%)**



90% patient survival
(3 deaths)



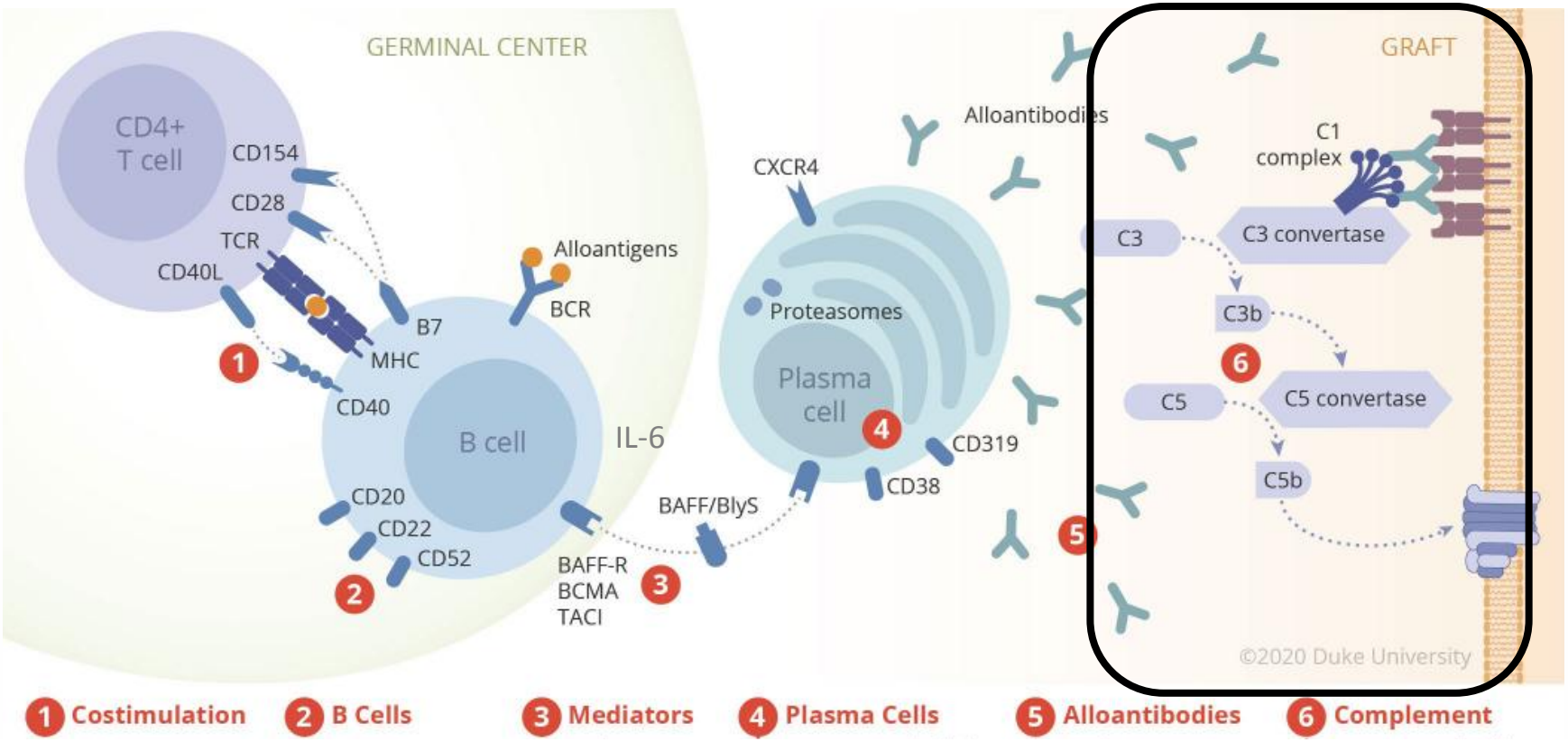
84% graft survival
(9 graft losses)



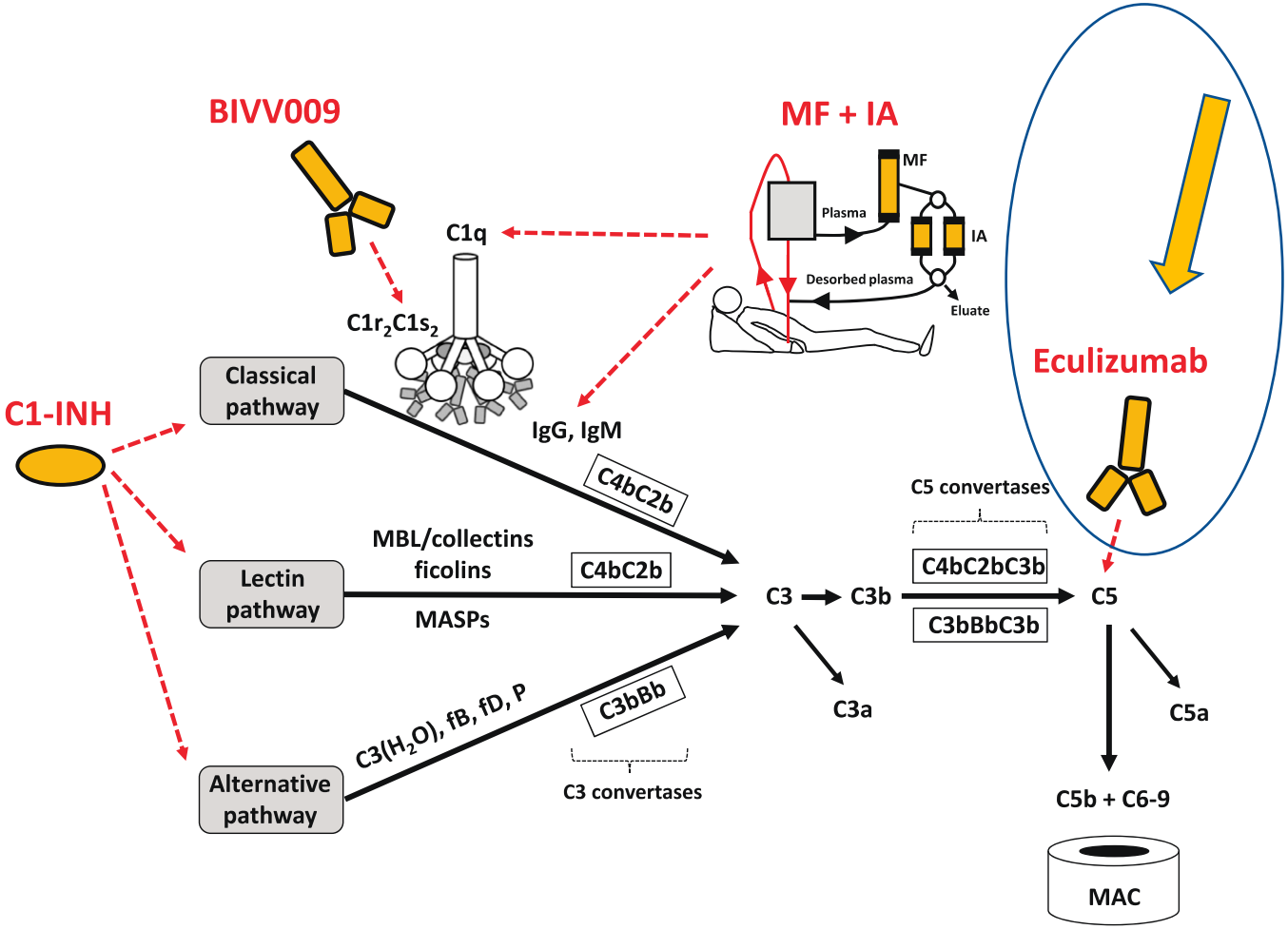
	AMR + n=15	AMR – n=24
Predose DSA (MFI median)	**13009 [6515-21580]**	**5727 [2699-9470]**
PreTranspl DSA (MFI median)	**1584 [903-3303]**	**576 [193-1397]**

Kjellman, Am J Transplant, 2021

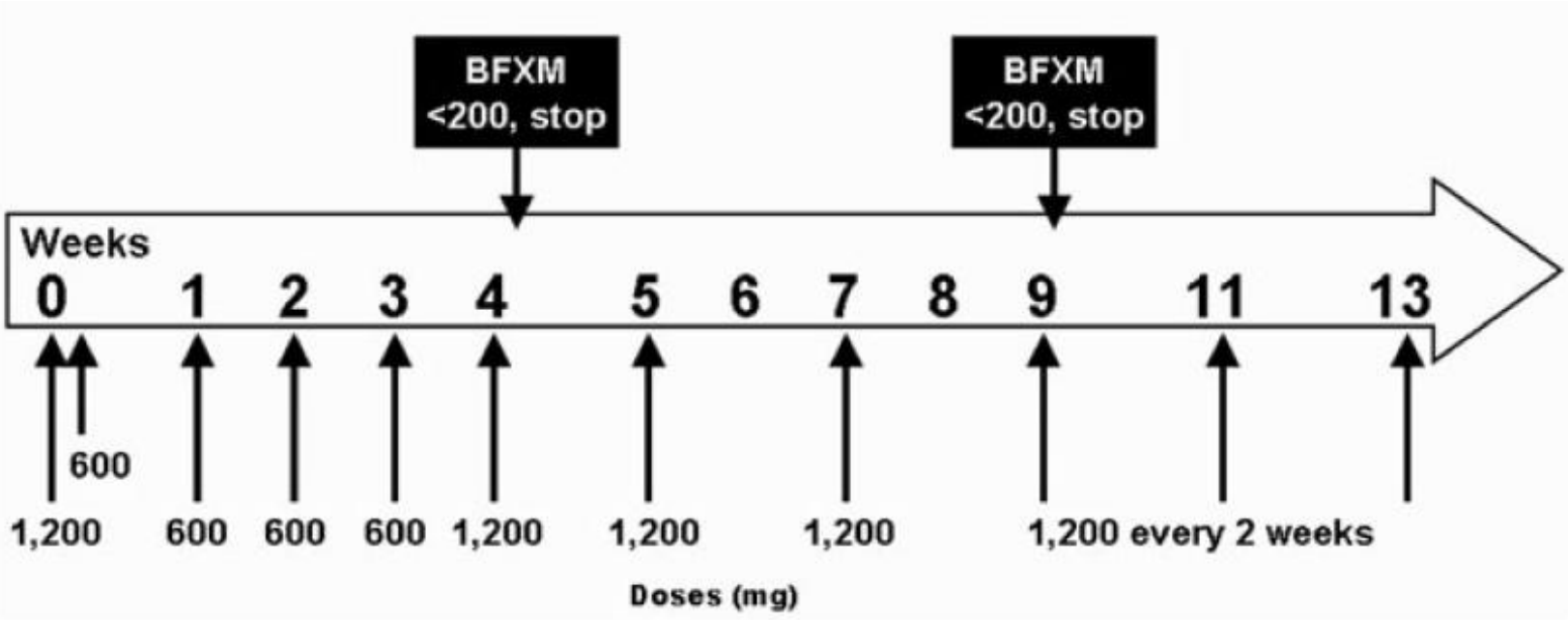
Complement blockade



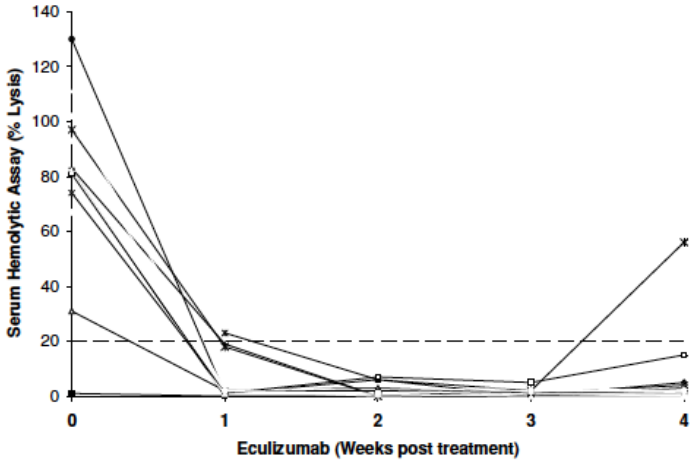
3 targets


BIVV009
MF + IA
MF
Plasma
IA
Desorbed plasma
Eluate
C1q
C1r2C1s2
Eculizumab
C1-INH
Classical pathway
IgG, IgM
C4bC2b
MBL/collectins
ficolins
Lectin pathway
C4bC2b
MASPs
C5 convertases
C4bC2bC3b
C3
C3b
C5
C3bBbC3b
C3a
C5a
C3(H2O), fB, fD, P
C3bBb
Alternative pathway
C3 convertases
C5b + C6-9
MAC

Mayo Clinic experience with eculizumab



MAYO CLINIC



MD Stegall et al, Am J Transplant 2011

Mayo Clinic experience with eculizumab : 1 yr

Table 2: Posttransplant outcomes in the eculizumab-treated and control groups

Category	Eculizumab group (n = 26)	Control group (n = 51)	p-Value
Follow-up (mean months ± SD, range)	11.8 ± 6.3 (3.0–27.5)	48.8 ± 14.1 (7.8–69.8)	
Graft survival at 1 year (n, %)	16/16 (100%)	49/51 (96%)	1.00
Antibody-mediated rejection ≤ 3months (n, %)	2 (7.7%)	21 (41%)	0.0031
Number of PE treatments (mean ± SD)	0.35 ± 1.1	7.9 ± 7.5	<0.0001
Splenectomy (n, %)	0 (0%)	9 (18%)	0.025
Graft dysfunction in first month (mg/dL) (maximum	0.45 ± 0.37	0.93 ± 1.15	0.05
Ct score (mean ± SD)	1.13 ± 0.74	0.91 ± 0.80	0.33
Cv score (mean ± SD)	0.80 ± 0.68	0.59 ± 0.74	0.23

[1]B flow crossmatch channel shift >350 at any time point in the first 3 months.

16/16 (100%) **One year graft survival** 49/51 (96%)

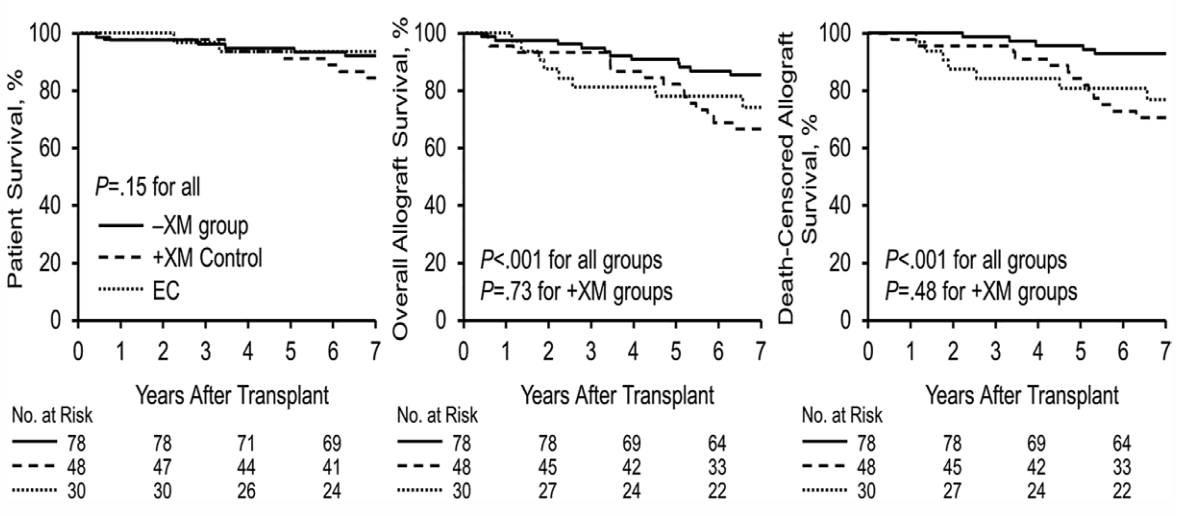
2 (7.7%) **Acute AMR** 21 (41%)

1/15 (6.7%) **1 year Transplant Glom** 15/42 (36%)

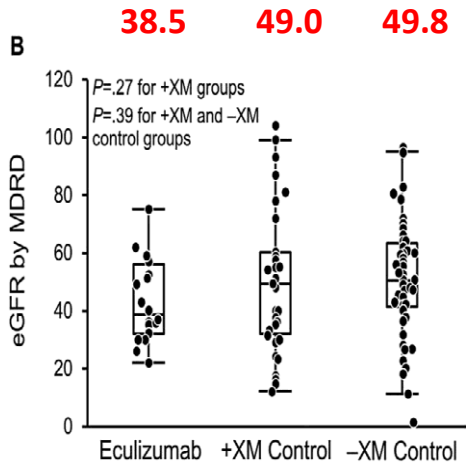
MD Stegall et al, Am J Transplant 2011

Mayo Clinic experience with eculizumab : 5 yrs

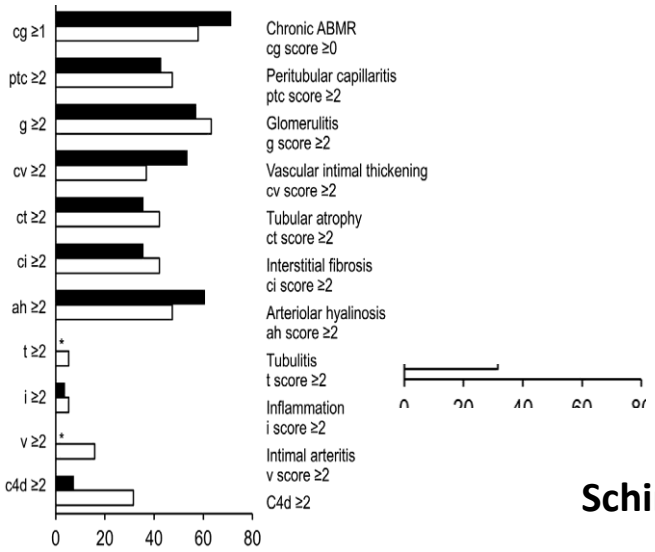
- 30 flow XM + treated with eculizumab
- 48 patients XM+ CTRL
- Plasmapheresis → XM -
- 78 patients XM- CTRL
- Eculizumab 1x/week



91%
77%
71%



38.5 49.0 49.8



- Similar Graft survival
- Similar renal function
- Similar Histology

Schinstock et al, Am J Transplant 2019

Complement blockade with eculizumab C10-002

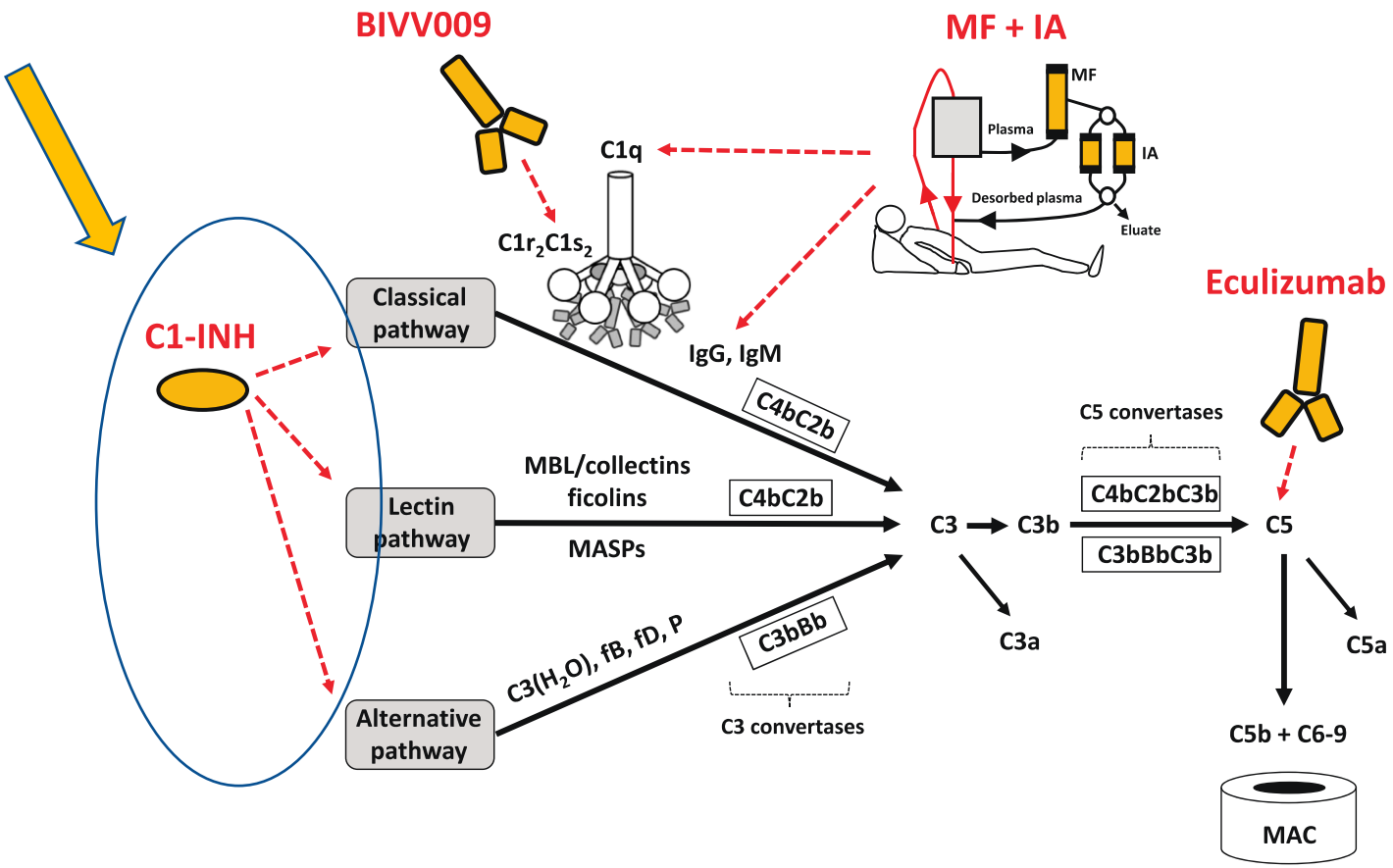
End point	Week 9 (N = 80)		Month 12 (N = 80)	
	Treated patients, n (%)	Exact 95% CI, *P* value[c]	Treated patients, n (%)	Exact 95% CI
Central pathology				
Treatment failure				
Yes	7 (8.8)	3.6-17.2, <.001	15 (18.8)	10.9-29.0
No	73 (91.3)		65 (81.3)	
Composite end point component[a]				
Biopsy-proved acute AMR[d]	3 (3.8)		5 (6.3)	
Graft loss	4 (5.0)		10 (12.5)	
Death	1 (1.3)		2 (2.5)	
Loss to follow-up[b]	0 (0.0)		0 (0.0)	

- **Open trial**
- **Prevention of AMR with eculizumab in deceased donors recipients**
- **1200 mg D0, 900 mg D7, 14, 21, 28, 1200 mg W5, 7 , 9**
- **80 patients**
- **No PEx**

- **Wk 9 : 4 non immunologic graft losses and 3 ABMR → 8.8 % failure (expected 40%)**
- **Wk 9 - M12 : 6 immunologic failures (5 AMR, 1 TCMR)**
- **M12 - M36 : 4 immunologic failures (3 AMR, 1 TCMR)**
- **3 years Graft survival 83%**

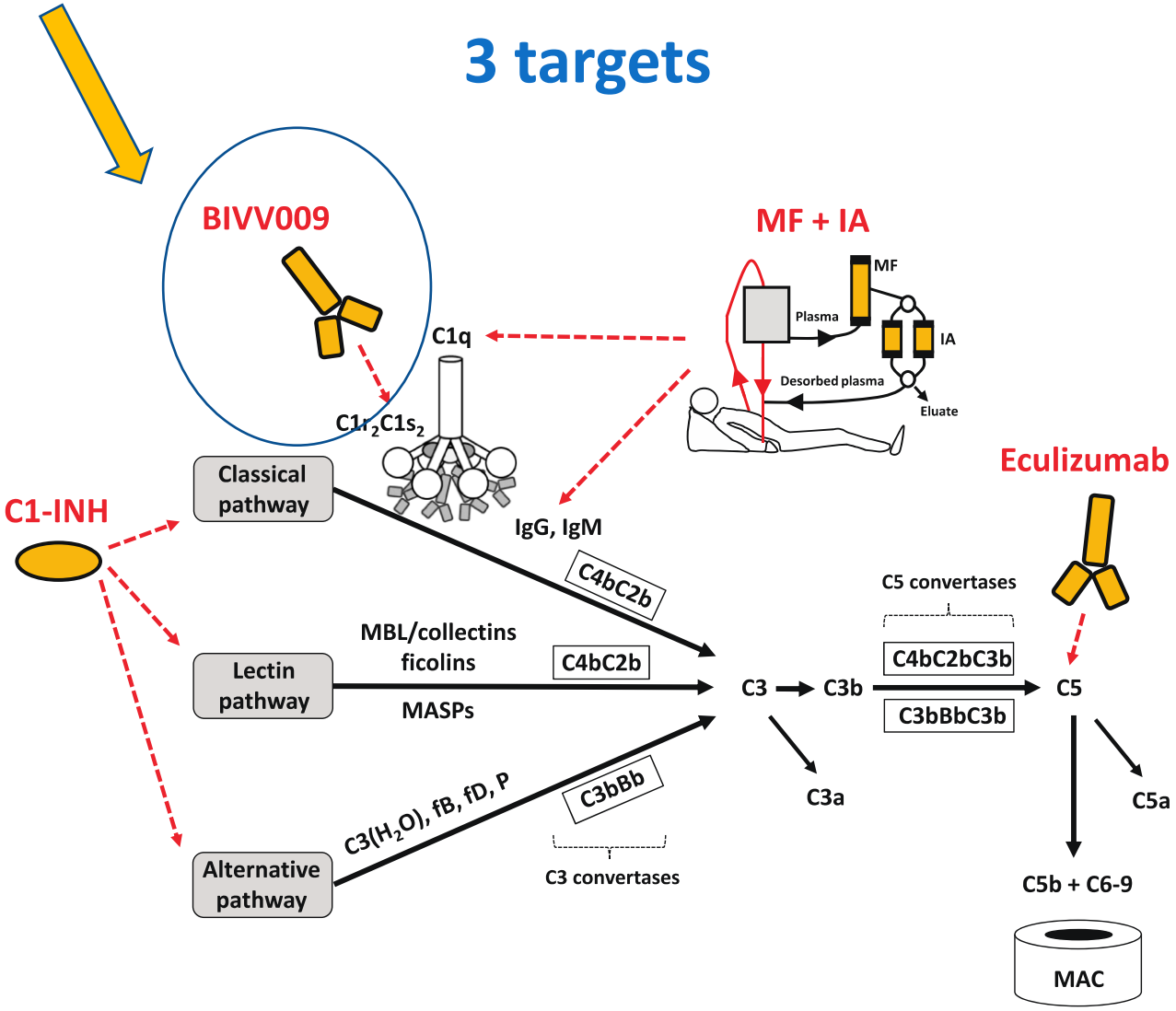
Glotz et al, Am J Transplant 2019

3 targets



Interest in IRI prevention

3 targets


BIVV009
MF + IA
MF
Plasma
IA
Desorbed plasma
Eluate
C1q
$C1r_2C1s_2$
C1-INH
Classical pathway
IgG, IgM
C4bC2b
Lectin pathway
MBL/collectins
ficolins
MASPs
C4bC2b
Alternative pathway
$C3(H_2O)$, fB, fD, P
C3bBb
C3 convertases
C3
C3b
C3a
C5 convertases
C4bC2bC3b
C3bBbC3b
C5
C5a
Eculizumab
C5b + C6-9
MAC

C1 blockade

- **C1 inhibitor** : 20 immunized patients, treated with PEX +/- RTX +/- IVIg randomized to receive C1 –INH versus placebo
  - 4 DGF versus 1
  - AMR 2 versus 3

- **Anti-C1s** : 4 weekly doses (60 mg/ kg) of BIVV009 in 10 patients with late ABMR
  - Negativation or reduction of C4d staining
  - no change in mi- crocirculation inflammation, gene expression patterns, DSA levels, or kidney function.

Vo et al, Transplantation 2015
Eskandary et al, Am J Transplant 2017

Conclusion 1….

American Journal of Transplantation 2011; 11: 1131–1139
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03581.x

Meeting Report

Antibody-Mediated Rejection—An Ounce of Prevention Is Worth a Pound of Cure

J. A. Bradley[a], W. M. Baldwin[b], A. Bingaman[c], C. Ellenrieder[d], H. M. Gebel[e], D. Glotz[f] and A. D. Kirk[g,*]

Key words: Alloantibody, antibody-mediated rejection, desensitization, immune monitoring, kidney paired donation

…remains true

Current protocols associated with an uncertain benefit in terms of patients and kidney survival

Conclusion 2….Promising tools

- Immunized patients are a « niche » and studies are mostly little sized uncontrolled, but

- ***ANTI-IL6*** : block the activation of TFh cells and plasmablasts, induce T Regs
- ***ANTI-PCs daratumumab*** : inhibition of high affinity Abs production
- ***Costimulation blockade*** interesting combination with PCs targeting

- ***IMLIFIDASE*** in case of failure to reduce sufficiently DSA titers – dramatic but transitory reduction in MFI Available in France since April 2022
- ***COMPLEMENT BLOCKADE*** temporary inhibition of effector function

Conclusion 3 towards a multimodal approach to desensitization

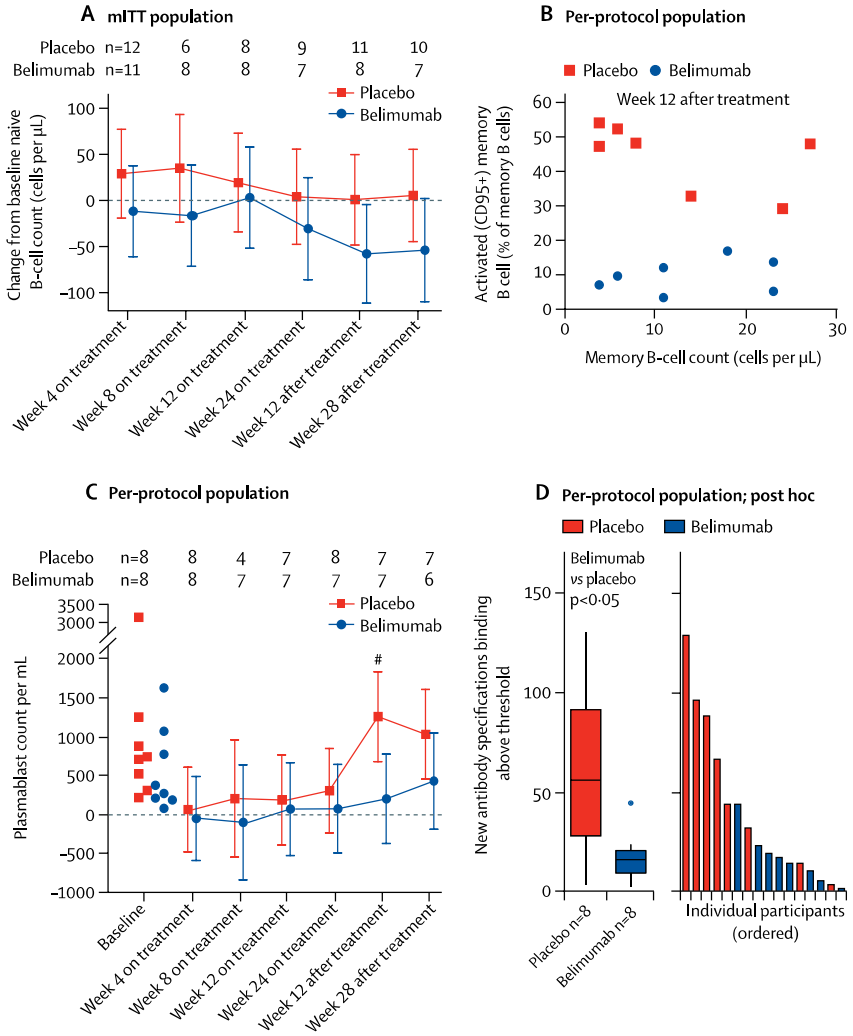
Removal of preformed antibodies : allows transplantation but without longlasting effect on humoral alloimmunity

No treatment will be sufficient alone to promote a long term control

Need for developing strategies targeting multiple steps from B cell activation to Ab effector functions

Belimumab in kidney transplantation: an experimental medicine, randomised, placebo-controlled phase 2 trial

Gemma D Banham, Shaun M Flint*, Nicholas Torpey, Paul A Lyons, Don N Shanahan, Adele Gibson, Christopher J E Watson, Ann-Marie O'Sullivan, Joseph A Chadwick, Katie E Foster, Rachel B Jones, Luke R Devey, Anna Richards, Lars-Peter Erwig, Caroline O Savage, Kenneth G C Smith, Robert B Henderson*, Menna R Clatworthy**



Belimumab vs placebo in addition to standard-of-care (basiliximab, mycophenolate mofetil, tacrolimus, and prednisolone)

10 mg per kg or placebo, day 0, 14, and 28, and then every 4 weeks for a total of seven infusions

EP safety and naive B cells

Banham Lancet 2018