



THE UNIVERSITY OF BRITISH COLUMBIA

Personalized Transplant Care

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BC Transplant Immunology Consultant

BC Kidney Day, November 2, 2018

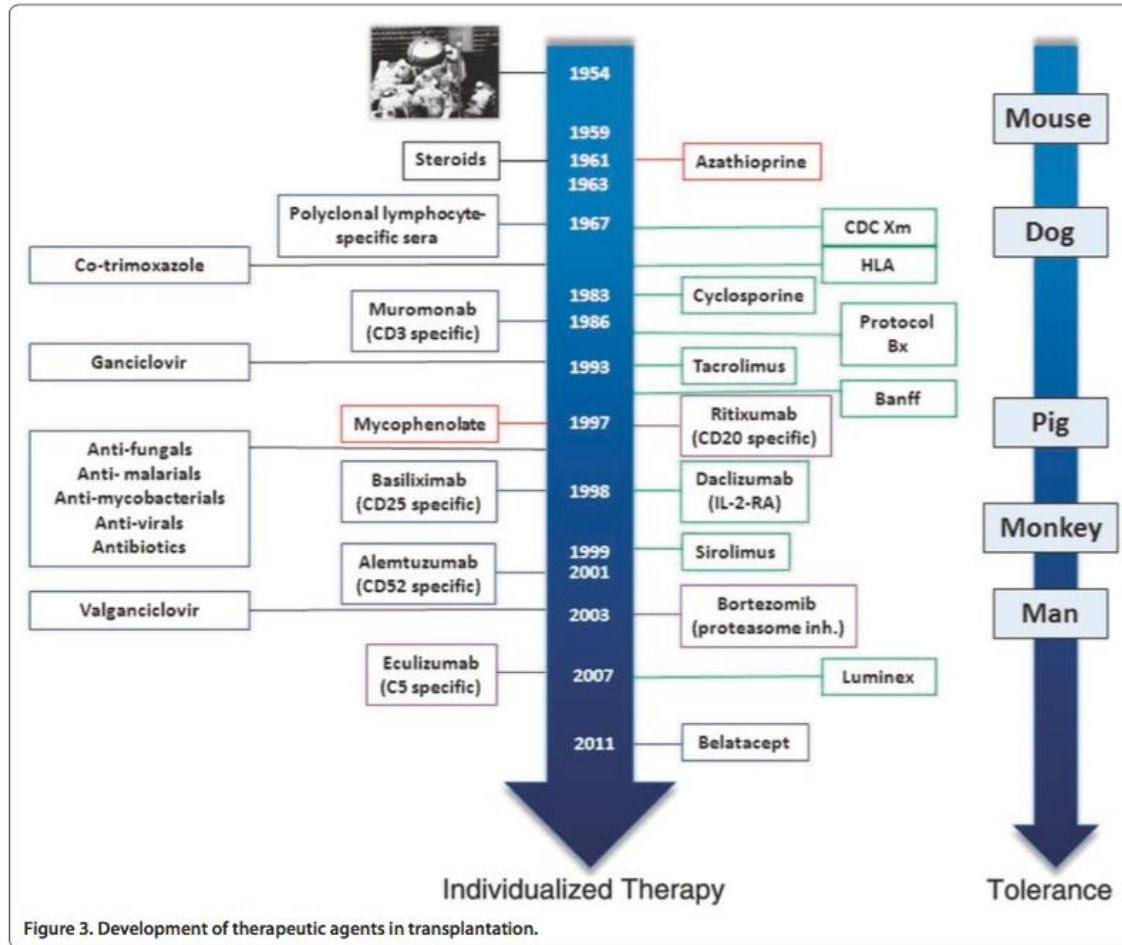
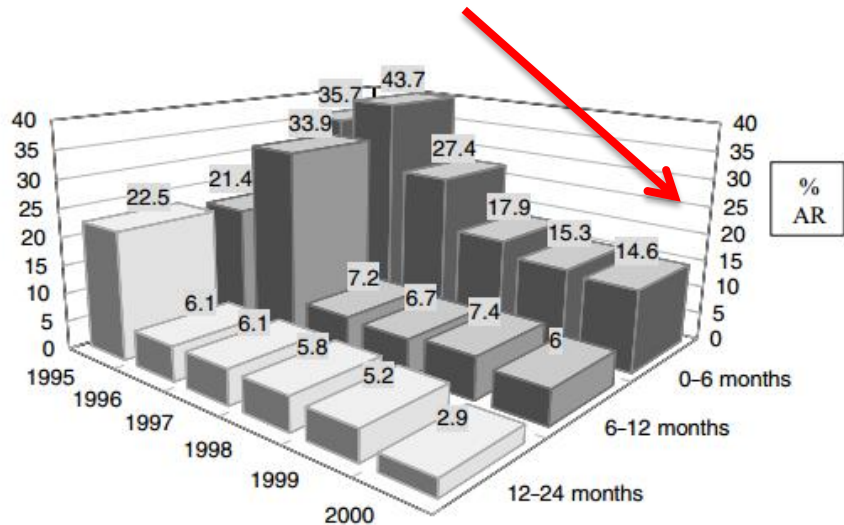


Figure 3. Development of therapeutic agents in transplantation.

Paradox of improvement in acute rejection but stagnant long-term outcomes

Incidence of Acute Rejection



Meier-Kriesche, AJT, 2004

Decreased donor kidney transplant attrition rates in the US (n=164,480)

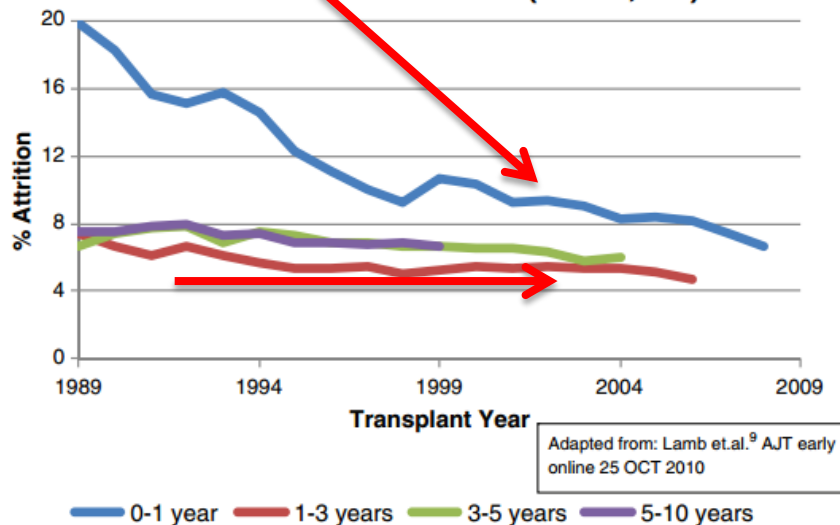
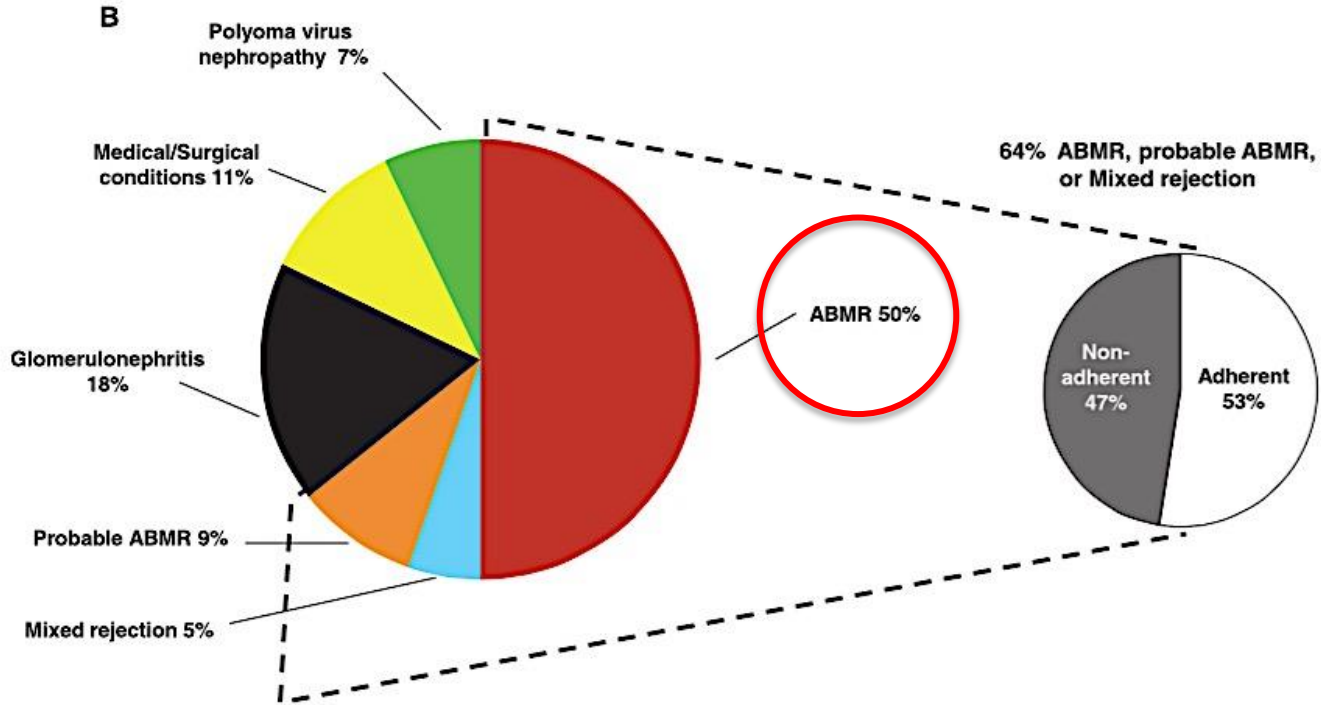


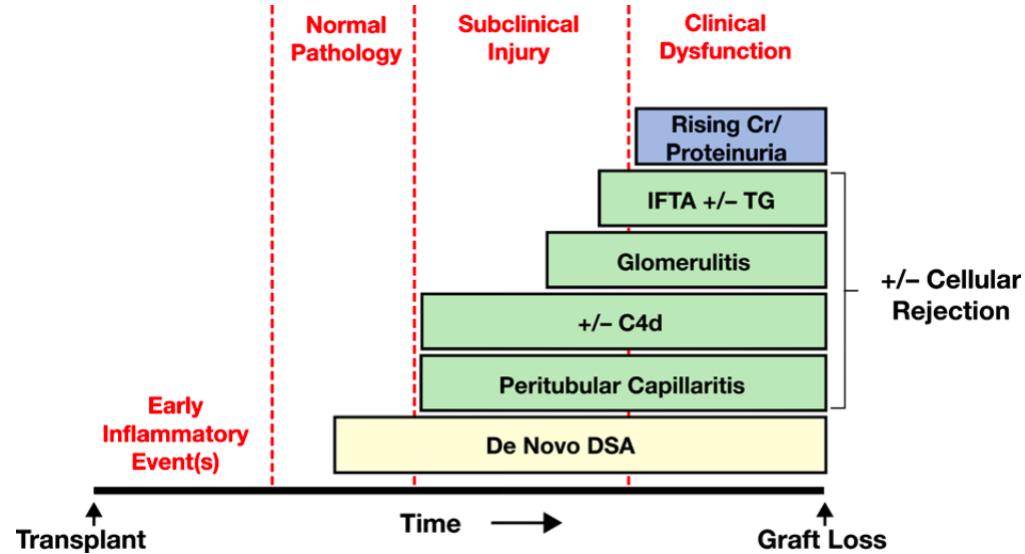
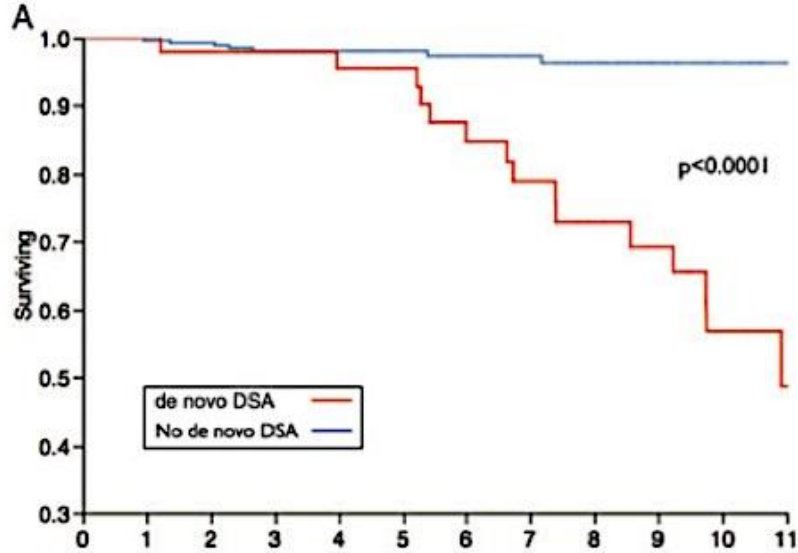
Fig. 2. Deceased donor kidney transplant attrition rates in the United States ($n = 164480$).

Lamb, AJT, 2011

Why do kidney transplants fail?

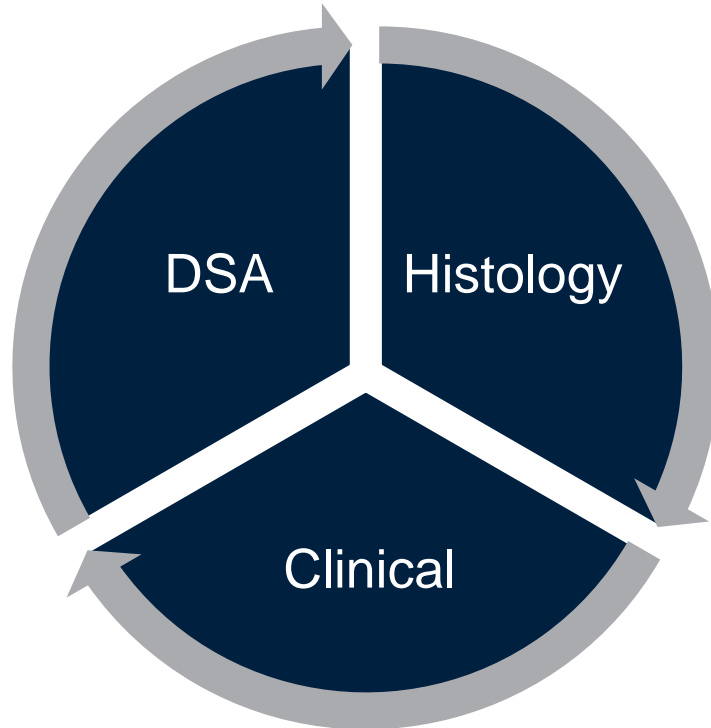


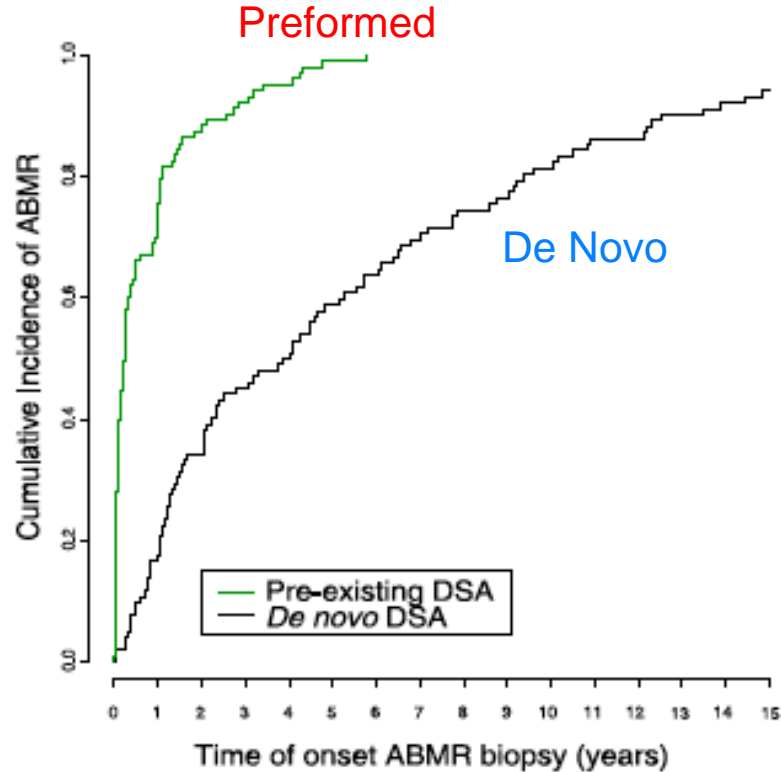
Deleterious impact of donor-specific antibodies



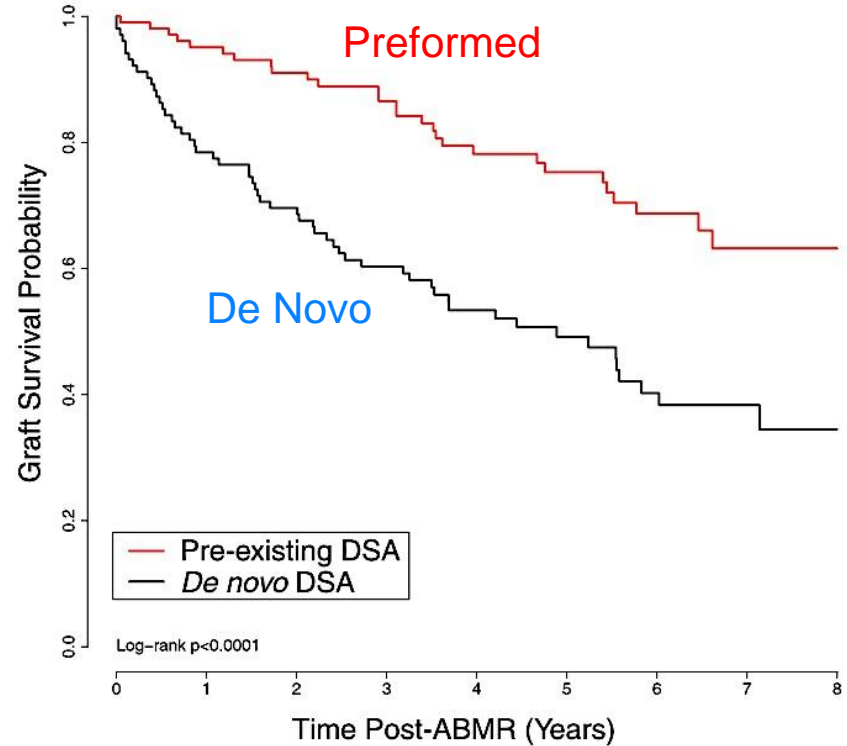
Who should be treated?

Due to the toxicity and cost of treatment, the decision to treat should be based on risk-stratification using available clinical, histologic, and DSA information





N at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pre-existing DSA	103	29	13	8	5	1										
De novo DSA	102	84	67	56	51	42	37	31	26	24	19	14	14	10	8	6



N at Risk	0	1	2	3	4	5	6	7	8
Pre-existing DSA	103	95	87	74	61	49	32	17	11
De novo DSA	102	80	70	56	43	31	22	10	4

De Novo DSA are Mainly Class II

	Willicombe Transplantation 2012	DeVos Kidney Int 2012	Musat AJT 2011	Smith AJT 2011	Palmer Transplantation 2002
Population	Renal	Renal	Liver	Heart	Lung
De Novo DSA	18.2% (92/502)	18% (62/347)	63% (27/43)	33% (57/173)	10% (9/90)
DQ DSA	54.3% (50/92)	53% (33/62)	81% (22/27)	72% (41/57)	56% (5/9)



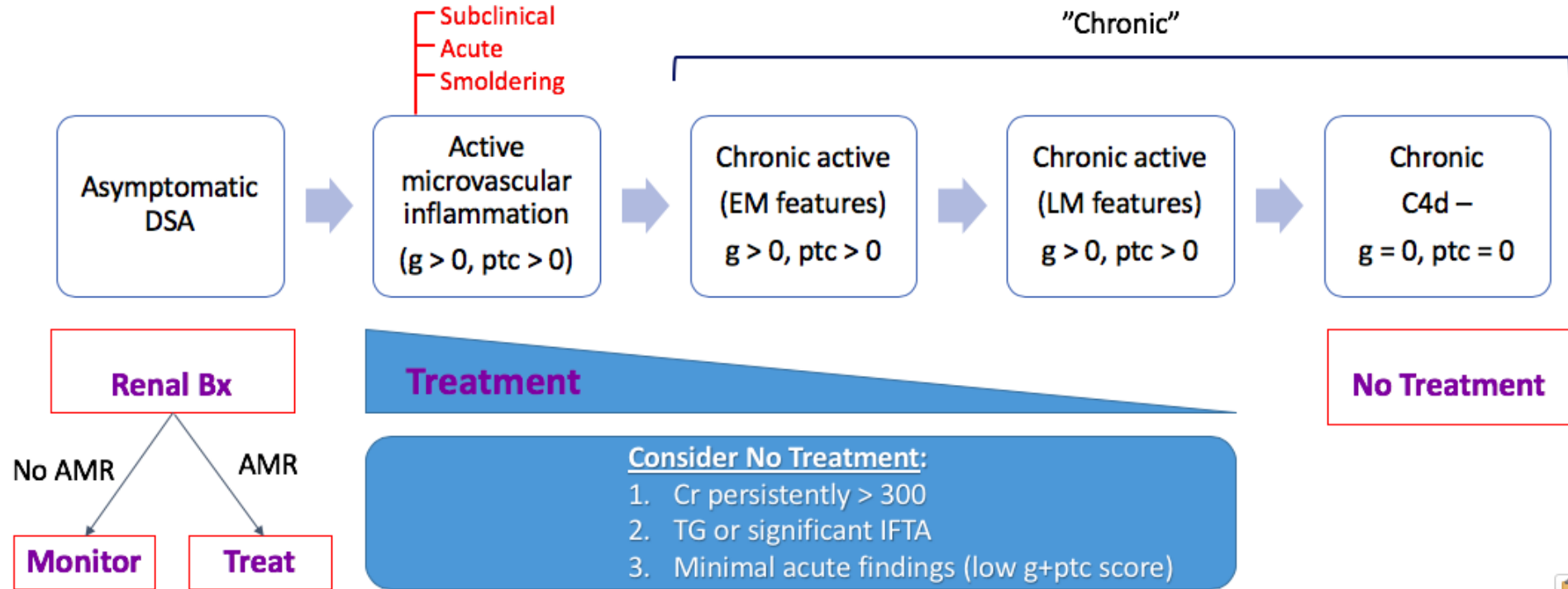
Clinical predictors of allograft loss outweigh C1q and DSA titering



Multivariate Model (n=70, 27 events)*		Hazard Ratio	p value
A)	C1q positive	1.06 (0.5-2.4)	0.88
	Non-Adherence	4.22 (1.4-14.4)	<0.01
	Clinical vs. Subclinical Phenotype	2.38 (1.0-6.9)	0.05
B)	dnDSA Titer \geq 1:64	1.41 (0.4-9.4)	0.65
	Non-Adherence	3.97 (1.2-14.0)	<0.01
	Clinical vs. Subclinical Phenotype	2.51 (1.0-6.9)	0.04
C)	dnDSA Titer \geq 1:1024	0.57 (0.2-1.4)	0.23
	Non-Adherence	5.17 (1.6-18.0)	<0.01
	Clinical vs. Subclinical Phenotype	3.04 (1.2-8.6)	0.02

*A multivariate model identified non-adherence and clinical phenotype as the only two significant predictors. The effect of C1q and dnDSA titer after adjustment for non-adherence and clinical phenotype are shown above.

General approach to patients with DSA and AMR



*Screen all patients for the cause of AMR **Optimize maintenance immunosuppression

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):

- **plasma exchange;**
- **intravenous immunoglobulin;**
- **anti-CD20 antibody;**
- **lymphocyte-depleting antibody.**

KDIGO, AJT, 2009

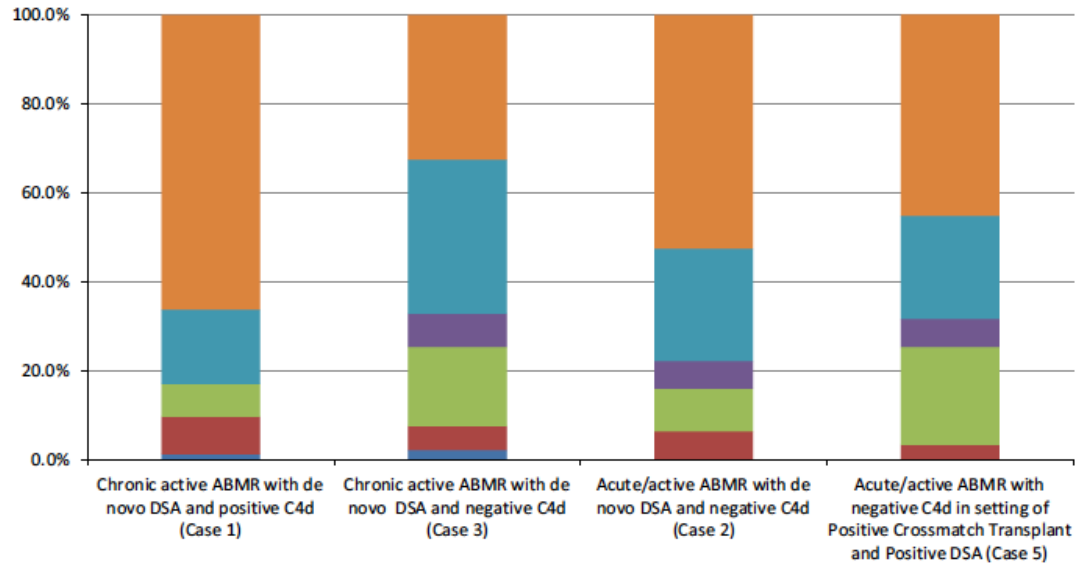
Standard of Care:



1. **PLEX + IVIG**
2. **High dose IVIG**

FDA AMR Workshop, Archdeacon, AJT, 2011

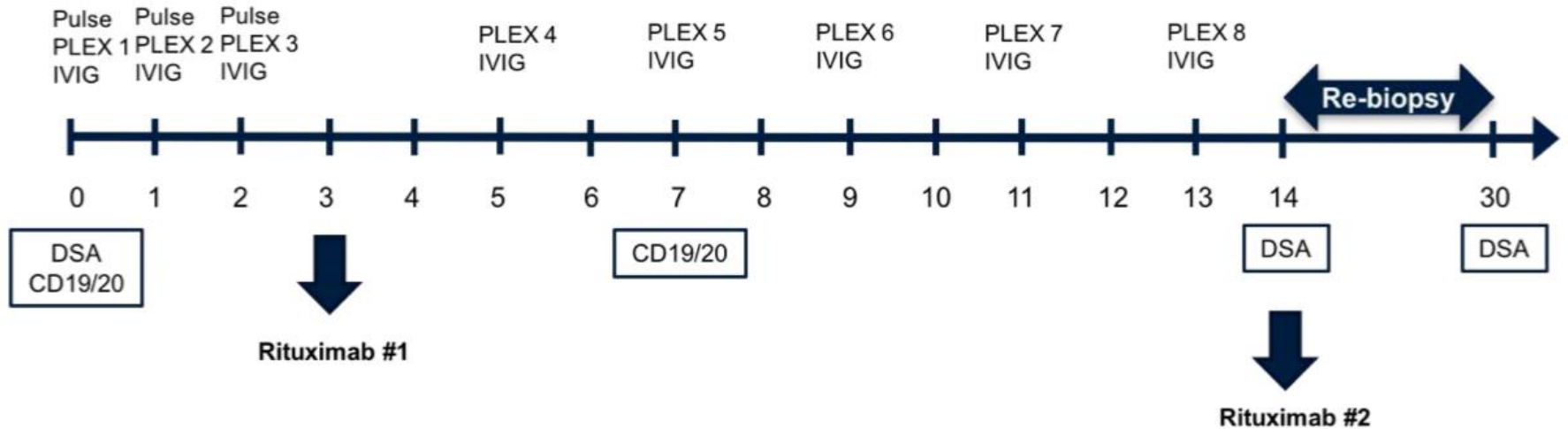
Heterogeneity of clinicians' treatment choices



Plasmapheresis, IVIG, +/- rituximab and/or bortezomib	66.3% (63)	32.6% (31)	52.6% (50)	45.3% (43)
IVIG +/- steroids	16.8% (16)	34.7% (33)	25.3%(24)	23.2% (22)
Steroids only	0.0% (0)	7.4% (7)	6.3% (6)	6.3% (6)
Conservative treatment only	7.4% (7)	17.9% (17)	9.5% (9)	22.1% (21)
Other	8.4% (8)	5.3% (5)	6.3% (6)	3.2% (3)
Unanswered	1.1% (1)	2.1(2)	0.0% (0)	0.0% (0)

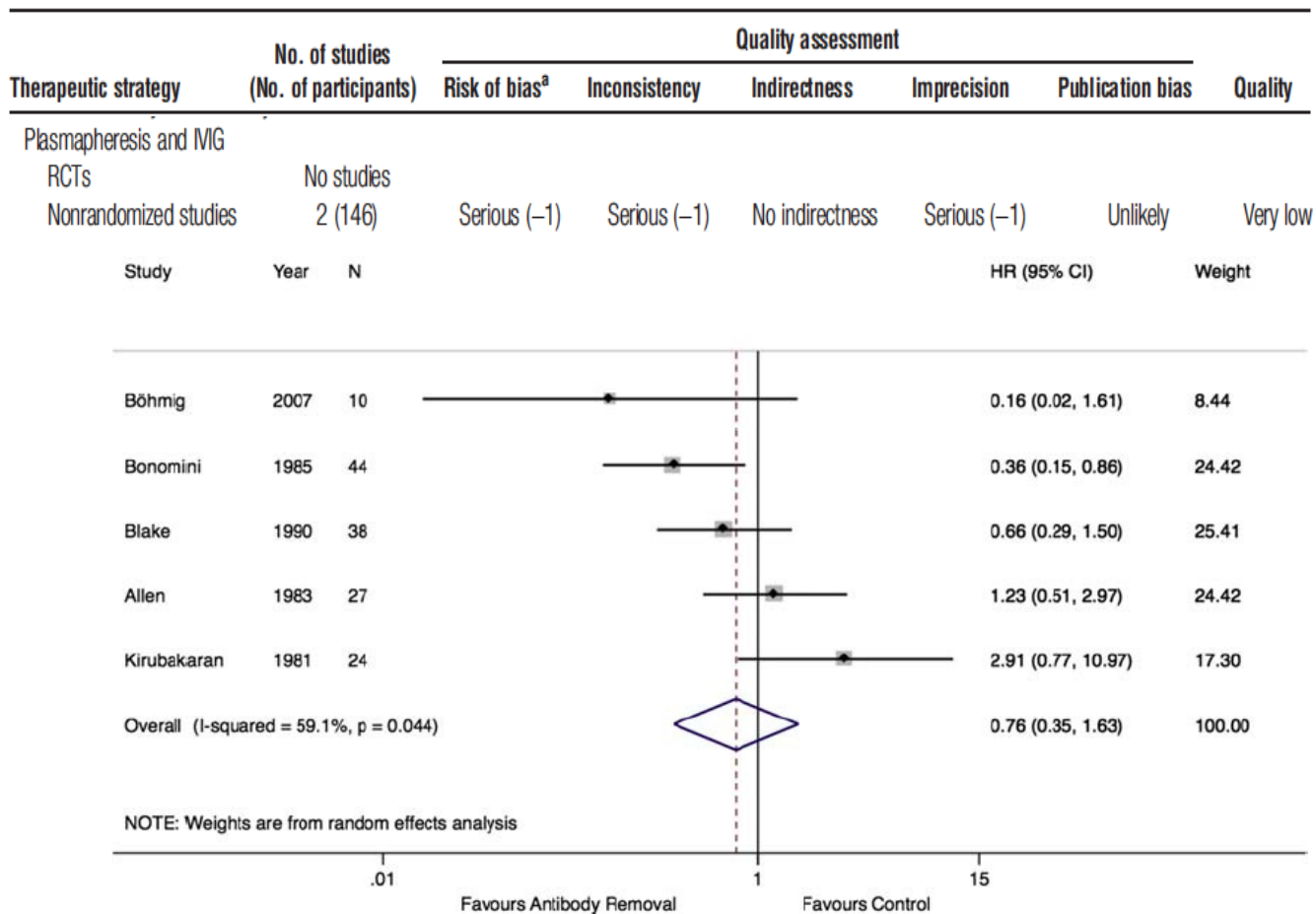
Schinstock, AJT 2018

AMR treatment protocol in BC



¹IVIG = 100 mg/kg
Pulse = methylpred 500 mg IV
Optimize MMF and Tacrolimus

²Rituximab dose #2 based on clinical indication and if CD19/20 ≥ 5 cells/mm²





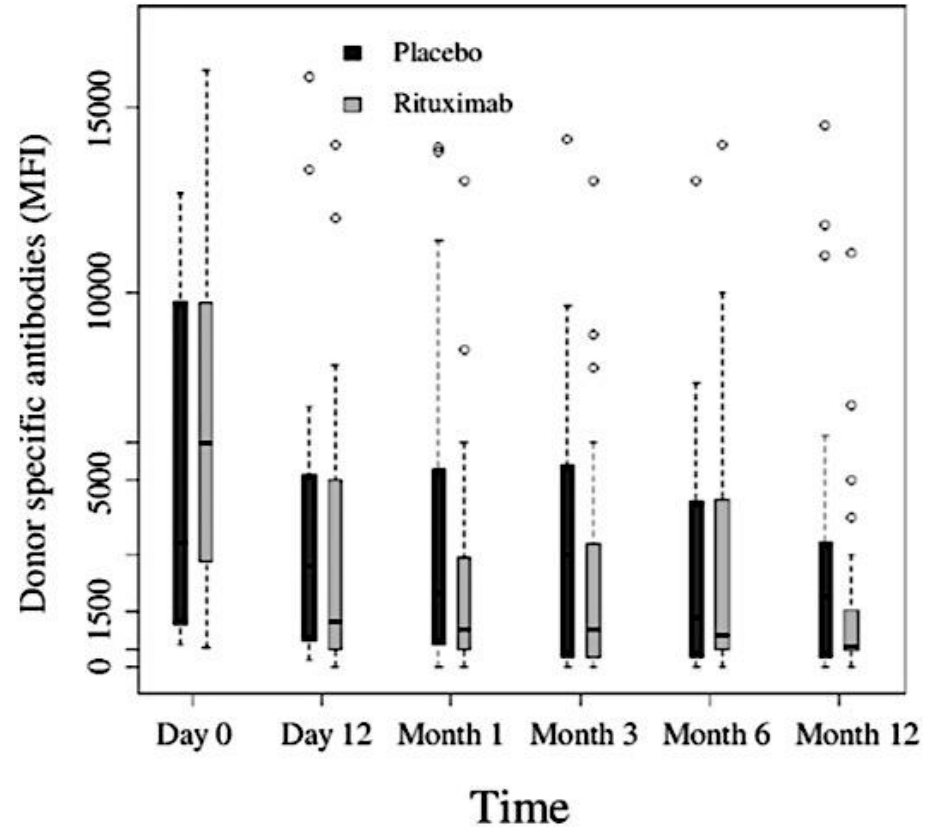
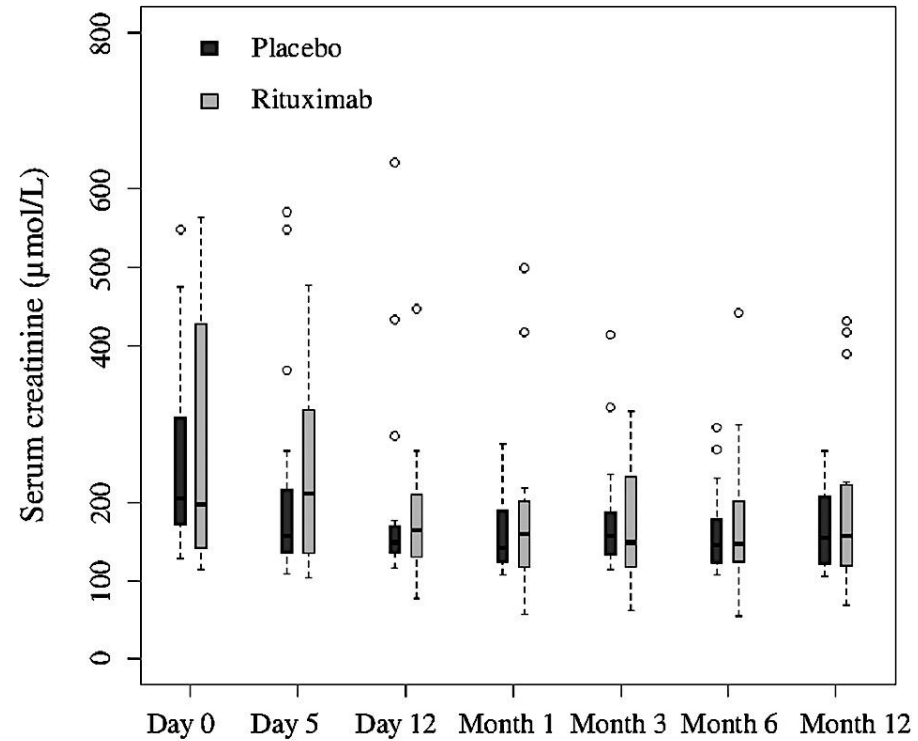
Rituximab

One-Year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation

*RITUX ERAH, a Multicenter Double-Blind Randomized
Placebo-Controlled Trial*

Bénédicte Sautenet, MD,^{1,2} Gilles Blancho, MD, PhD,³ Mathias Büchler, MD, PhD,^{1,2,4}
Emmanuel Morelon, MD, PhD,⁵ Olivier Toupance, MD,⁶ Benoit Barrou, MD, PhD,⁷ Didier Ducloux, MD, PhD,⁸
Valérie Chatelet, MD,⁹ Bruno Moulin, MD, PhD,¹⁰ Caroline Freguin, MD,¹¹ Marc Hazzan, MD, PhD,¹²
Philippe Lang, MD, PhD,¹³ Christophe Legendre, MD, PhD,¹⁴ Pierre Merville, MD, PhD,¹⁵
Georges Mourad, MD, PhD,¹⁶ Christine Mousson, MD, PhD,¹⁷ Claire Pouteil-Noble, MD, PhD,¹⁸ Raj Purgus, MD,¹⁹
Jean-Philippe Rerolle, MD,²⁰ Johnny Sayegh, MD,²¹ Pierre-François Westeel, MD,²² Philippe Zaoui, MD, PhD,²³
Hedia Boivin, PharmD,²⁴ Amélie Le Gouge, MSc,²⁵ and Yvon Lebranchu, MD, PhD^{1,2,4}

- **Acute C4d+ AMR** with HLA-DSA within 1st year
- N = 19 (Placebo)
- N = 19 (Rituximab)
- Usual Care: Methylpred pulse x 3 days
PLEX x 6 + low dose IVIG over 12 days
- Rituximab (375 mg/m²) at Day 5 (option for 2 additional doses)
- Primary endpoint: treatment failure = composite graft loss or no improvement in Cr (<30% decrease of peak Cr) at Day 12



- *No difference in SCr improvement at 1 yr*
- *Only 1 graft loss in each arm*
- *Trend towards greater DSA reduction at 1 yr with Ritux*


Five-Year Outcomes after Randomized Treatment by Rituximab in Early Acute Antibody-Mediated Rejection in Renal Transplantation: Long Term Outcomes of the RITUX ERAH Study

ATC 2017

E. Bailly,¹ G. Blanco,² S. Ville,² E. Morelon,³ J. Bamoulid,⁴ S. Caillard,⁵ V. Chatelet,⁶ P. Malvezzi,⁷ J. Tourret,⁸ V. Vuiblet,⁹ D. Anglicheau,¹⁰ D. Bertrand,¹¹ P. Grimbert,¹² F. Haidar,¹³ M. Hazzan,¹⁴ N. Kamar,¹⁵ P. Merville,¹⁶ C. Mousson,¹⁷ V. Pernin,¹⁸ C. Pouteil-Noble,¹⁹ R. Purgus,²⁰ J. Sayegh,²¹ P. Westeel,²² M. Büchler.¹

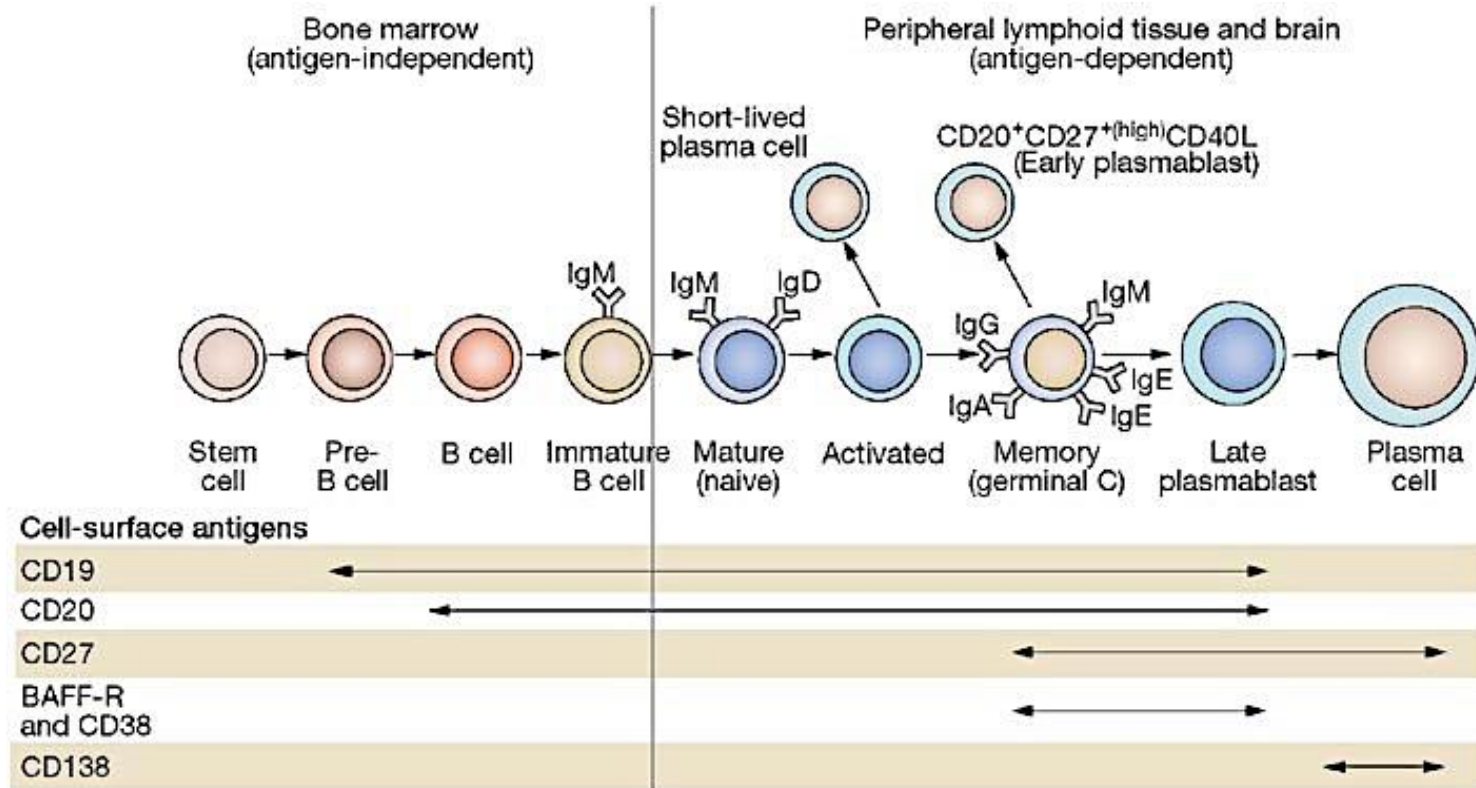
- 38 patients: 11 placebo vs. 27 Rituximab
- At 5 years after AMR:
 - No difference in DCGF (55% in placebo vs 57% in Ritux)
 - No difference in renal function, proteinuria, incidence of infections and neoplasms
- *Overall, no benefit 5 years after AMR of rituximab in addition to PLEX/IVIg/Steroids*

Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial

Francesc Moreso¹ | Marta Crespo² | Juan C. Ruiz³  | Armando Torres⁴ |
Alex Gutierrez-Dalmau⁵ | Antonio Osuna⁶ | Manel Perelló¹ | Julio Pascual² |
Irina B. Torres¹ | Dolores Redondo-Pachón² | Emilio Rodrigo³ | Marcos Lopez-Hoyos⁷ |
Daniel Seron¹

- Randomized, placebo-controlled trial for **chronic AMR** (TG + DSA)
- Treatment group: **IVIg (0.5 g/kg) x 4 + Rituximab x 1 (375 mg/m²)** vs. **placebo**
- Planned sample size of 50 but only 25 patients randomized (13 treatment, 12 placebo)
- Outcomes:
 - No difference in eGFR decline (primary outcome) or change in proteinuria
 - No difference in Banff scores at 1 year
 - No difference in DSA MFI
- **Overall, no benefit of IVIg + Rituximab in patients with chronic AMR (presence of TG)**

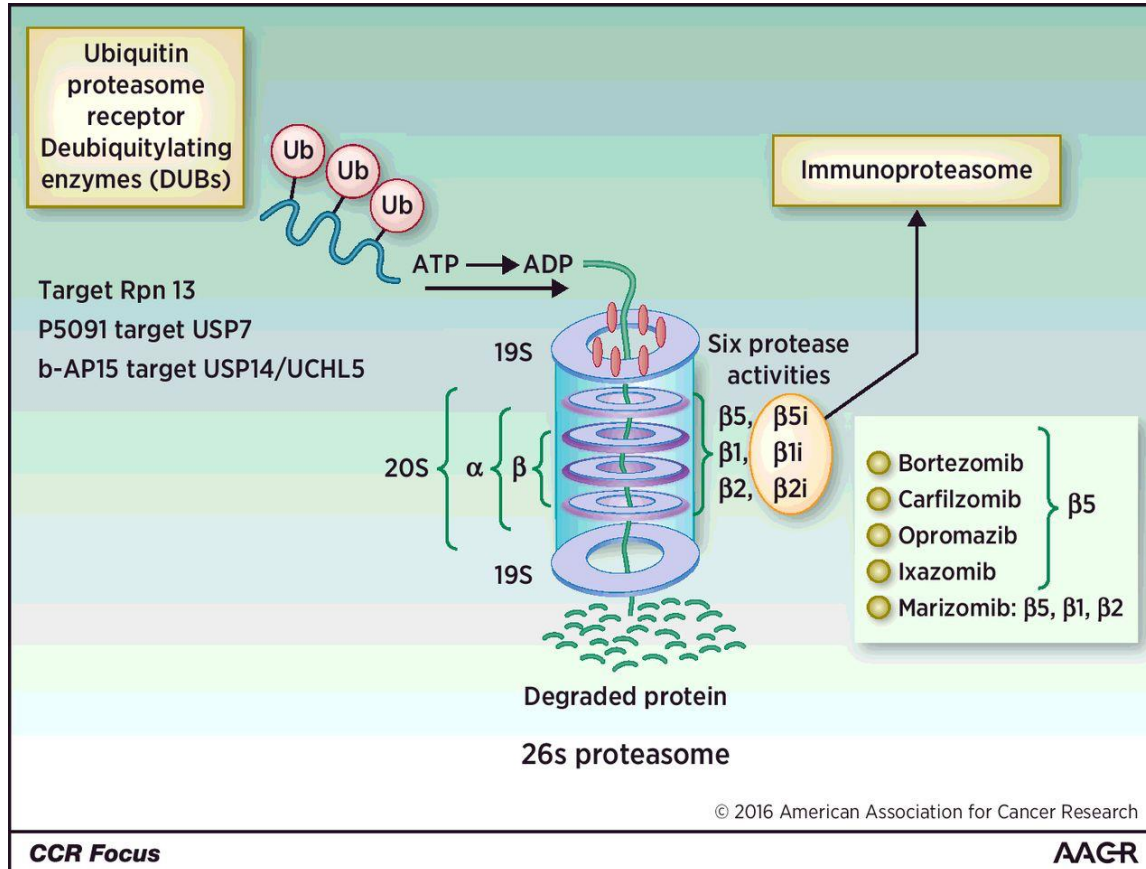
B Cell Maturation






Novel Therapeutics for AMR

Bortezomib: proteasome inhibitor

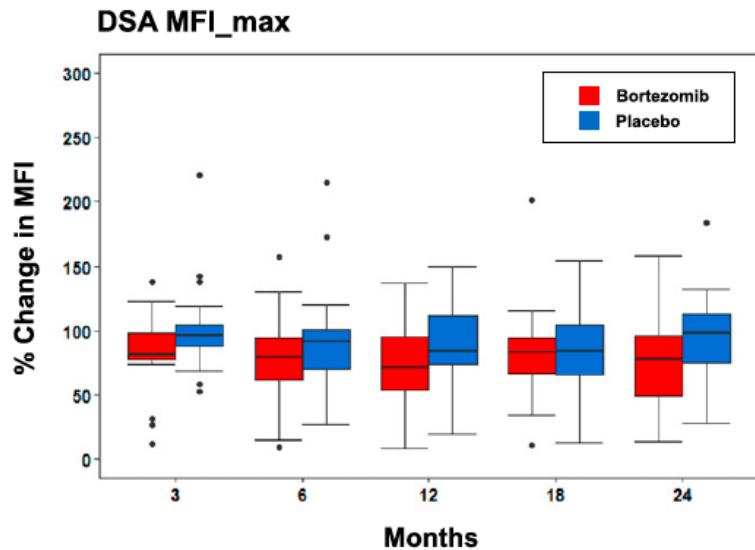
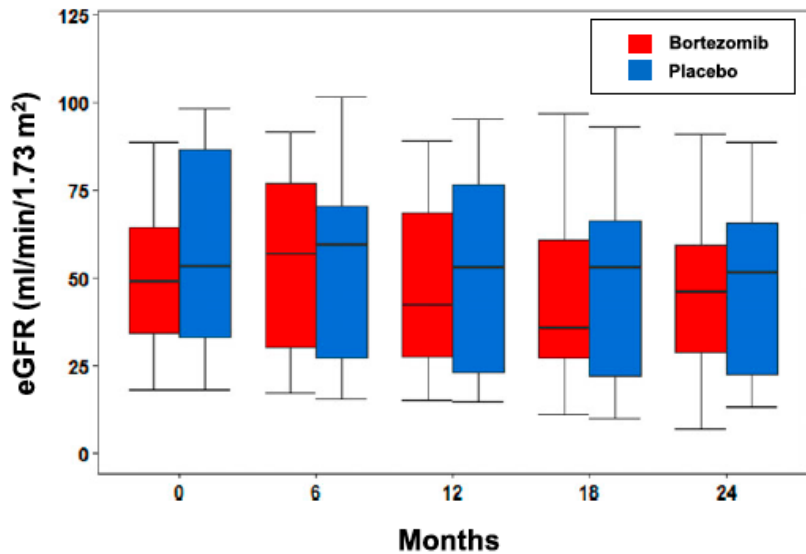


A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection

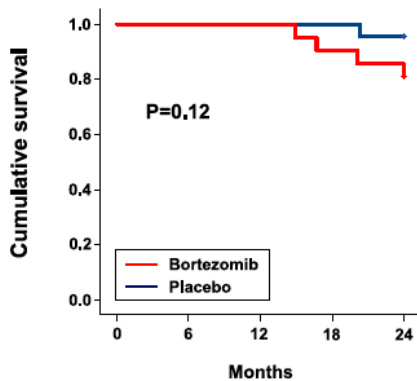
JASN 2018

Farsad Eskandary,¹ Heinz Regele,² Lukas Baumann,³ Gregor Bond,¹ Nicolas Kozakowski,² Markus Wahrmann ,¹ Luis G. Hidalgo,⁴ Helmuth Haslacher,⁵ Christopher C. Kaltenecker,¹ Marie-Bernadette Aretin,⁶ Rainer Oberbauer,¹ Martin Posch,³ Anton Staudenherz,⁷ Ammon Handisurya,¹ Jeff Reeve,⁸ Philip F. Halloran,⁸ and Georg A. Böhmig¹

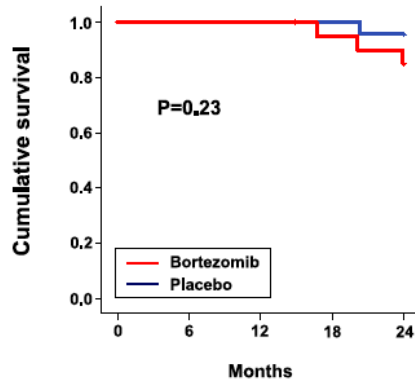
- Randomized, placebo-controlled trial of bortezomib in **late AMR**
- Inclusion: > 6m post-Tx, acute or chronic AMR features on biopsy, presence of DSA
- Treatment = **2 cycles of Bortezomib (each cycle 4 IV doses)**
- n=21 bortezomib vs. n=23 placebo
- Primary endpoint: eGFR slope



A
Overall graft survival



B
Death-censored graft survival



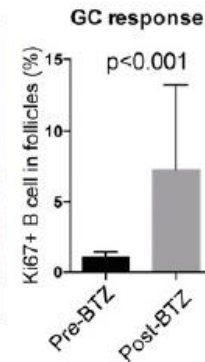
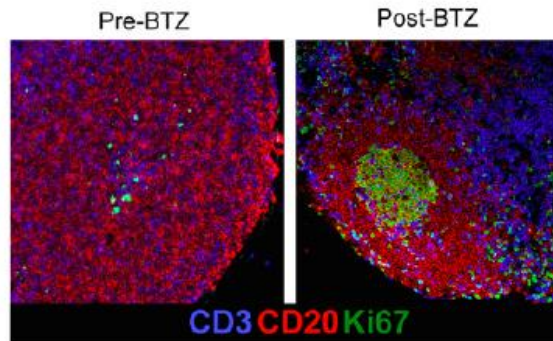
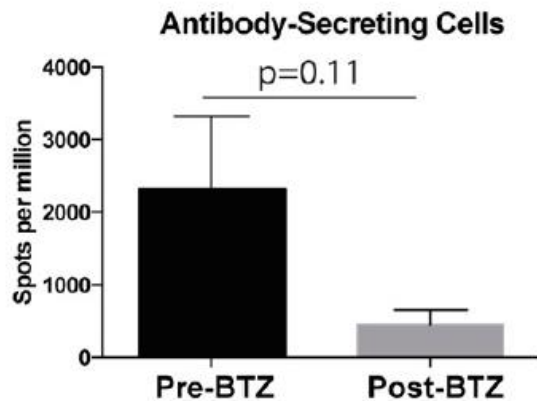
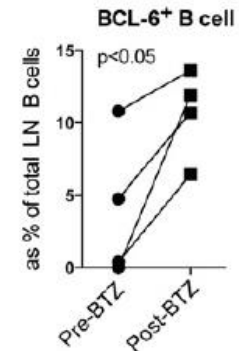
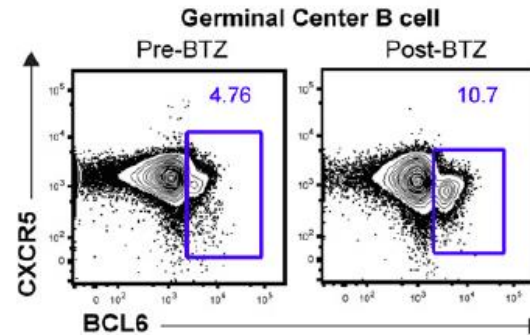
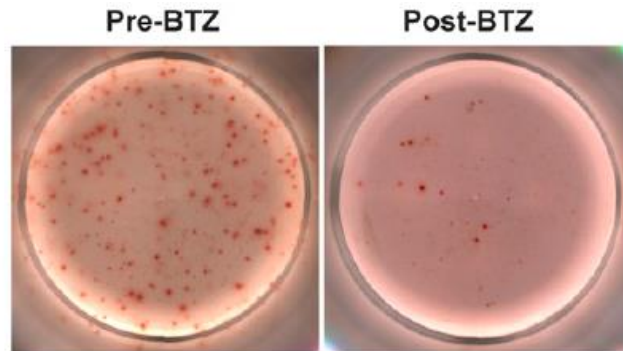
- Overall, bortezomib did not prevent GFR loss, reduce DSA or improve histologic or molecular features despite significant GI and hematologic toxicities

Humoral Compensation after Bortezomib Treatment of Allosensitized Recipients

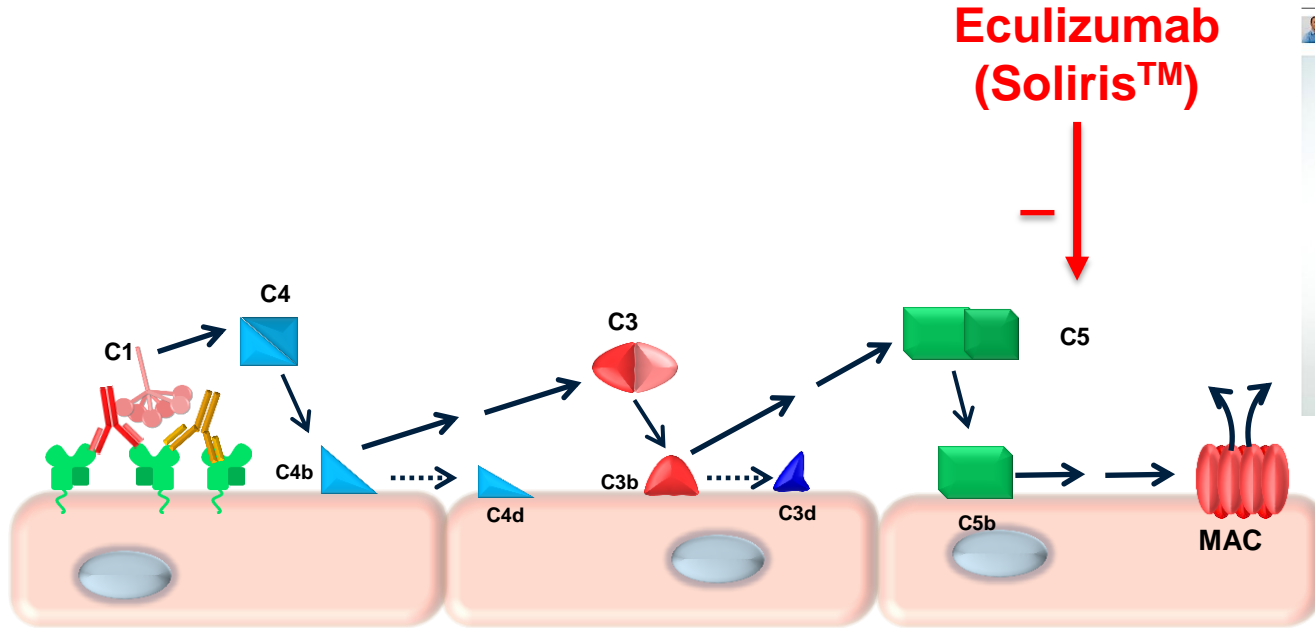
JASN 2017

Jean Kwon,^{*†} Christopher Burghuber,^{†‡} Miriam Manook,^{*} Neal Iwakoshi,[†] Adriana Gibby,[†] Jung Joo Hong,[§] and Stuart Knechtle^{*†}

- *Compensatory B cell proliferation in germinal center*



Complement inhibitors (extinguishing the fire)



World's most expensive drug — which costs up to \$700,000 per year — too expensive, Canada says

TOM BLACKWELL | February 3, 2015 | Last Updated: Feb 3 1:47 AM ET
More from Tom Blackwell | @tomblackwellNP



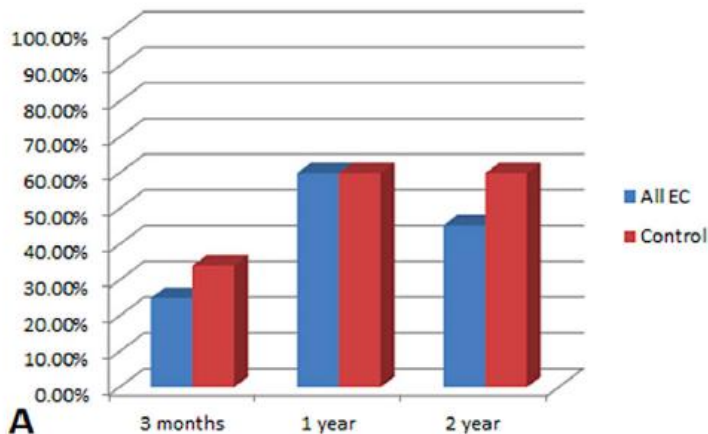
Courtesy of Nicole Venezuela

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell¹, C. A. Schinstock²,
M. J. Gandhi³, W. K. Kremers² and
M. D. Stegall^{2,*}

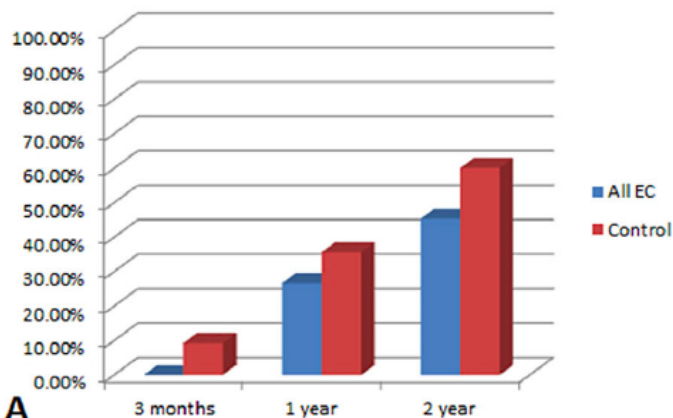
AJT, 2015

- Eculizumab did not prevent microcirculatory damage and TG



A

Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	25.0% (7/28)	60.0% (18/30)	45.4% (10/22)
Control	34.1% (14/41)	60.0% (21/35)	60.0% (15/25)
p-value (control vs. EC)	P= 0.59	P=1.00	P=0.39



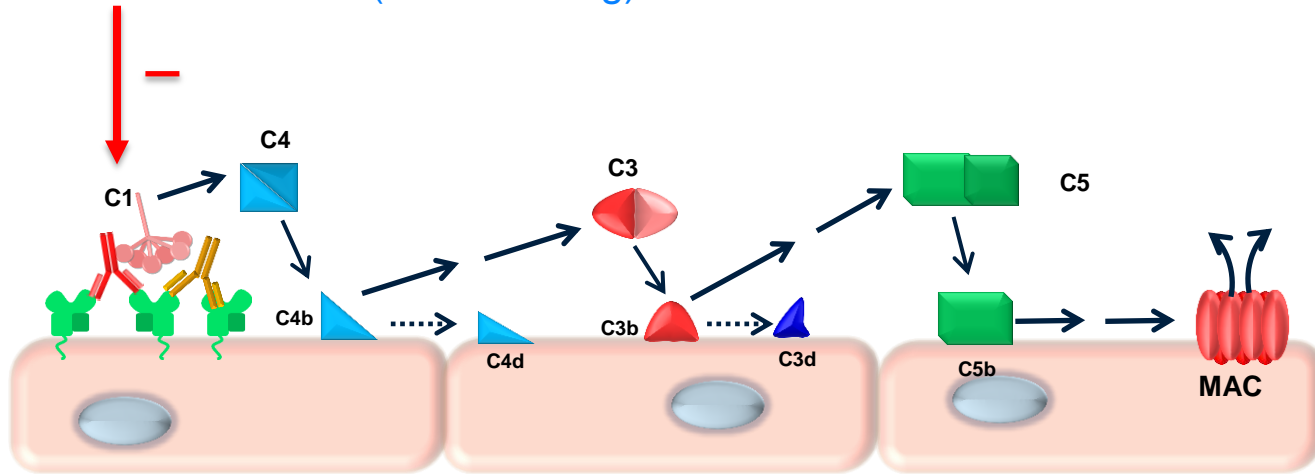
A

Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

Complement inhibitors (extinguishing the fire)

C1 INH

- Cinryze (Shire)
- Berinert (CSL Behring)

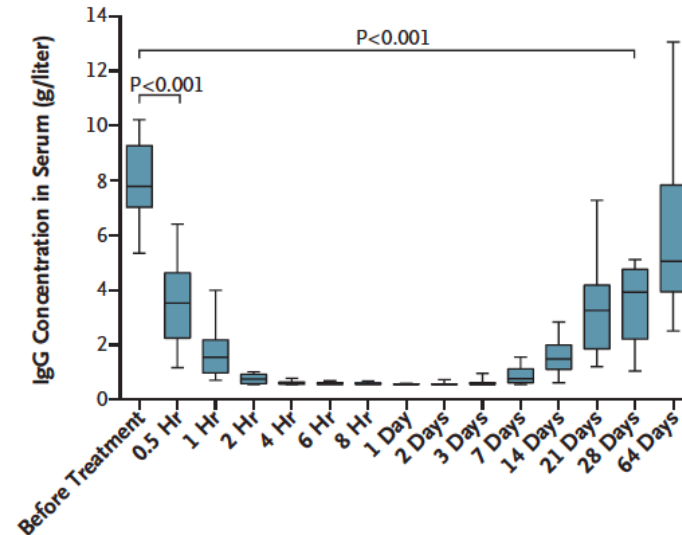
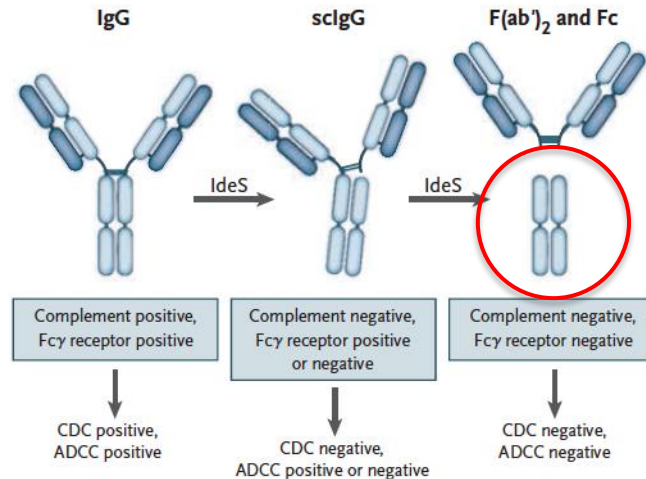


IdeS (IgG-degrading enzyme derived from *Streptococcus pyogenes*)

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

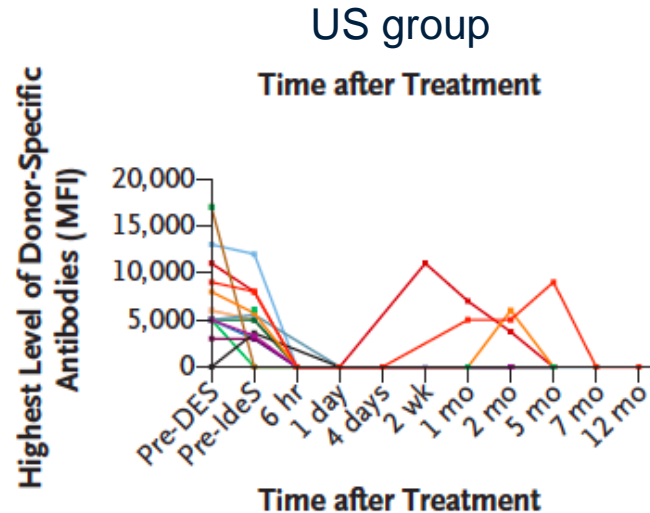
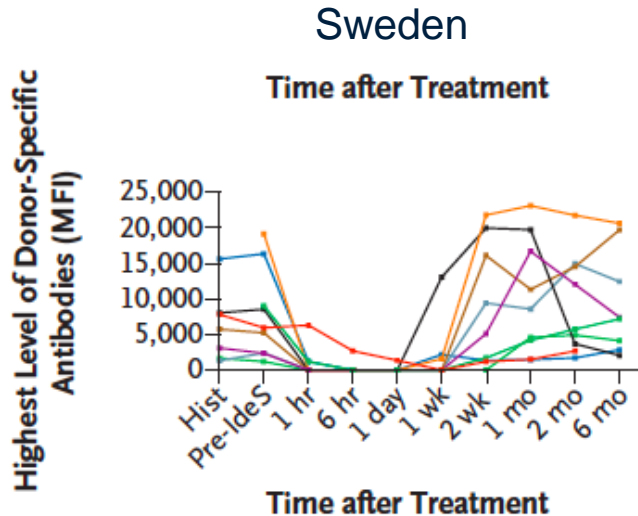
NEJM, 2017

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson



Ides (IgG-degrading enzyme derived from *Streptococcus pyogenes*)

- Open-label, phase 1-2, desensitization trial (US, Sweden)
- N=25 highly sensitized patients, cPRA $\geq 95\%$
- All IgG-DSA eliminated at time of transplantation
- N=10/25 with AMR, 1 patient with hyperacute rejection (non-HLA) – **rebound phenomenon**



Challenges with AMR treatment

1. Rituximab: *does not target plasma cells, incomplete penetration of B cells in lymphoid organs*
2. Bortezomib: *humoral compensation in germinal center*
3. Complement inhibitors: *non-complement-mediated pathways*
4. IdeS: *rebound antibody production*

All of these medications have significant treatment-related toxicities

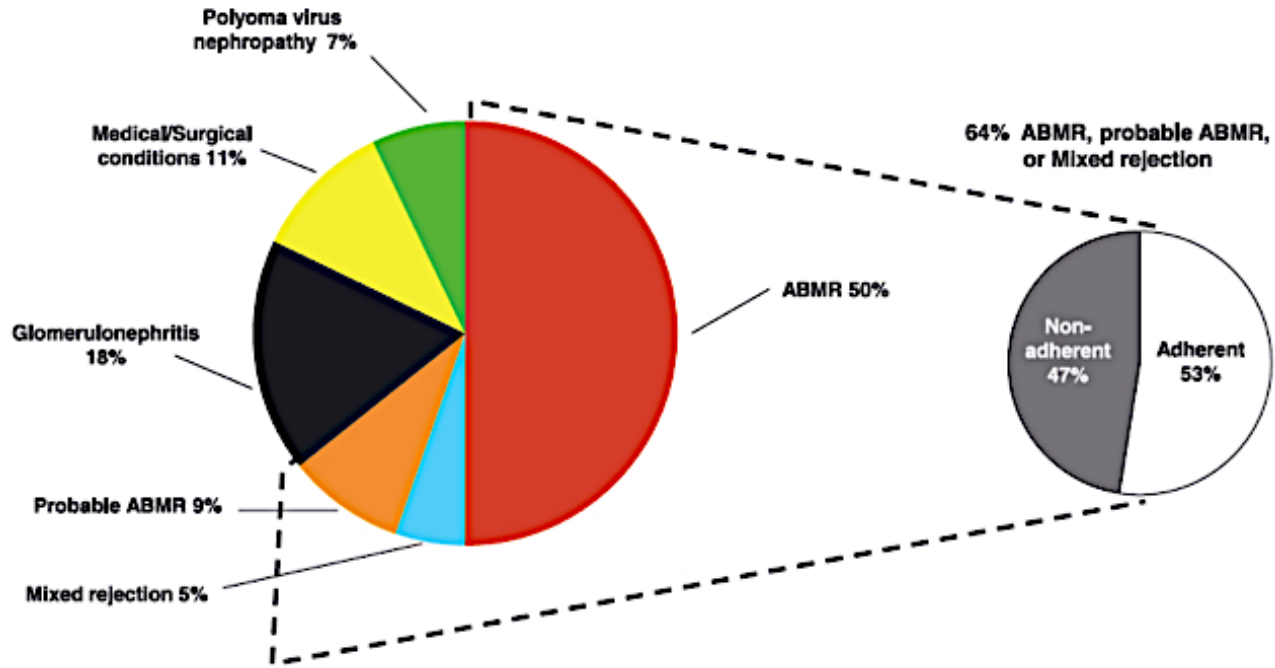
When B cells are out of the gate...



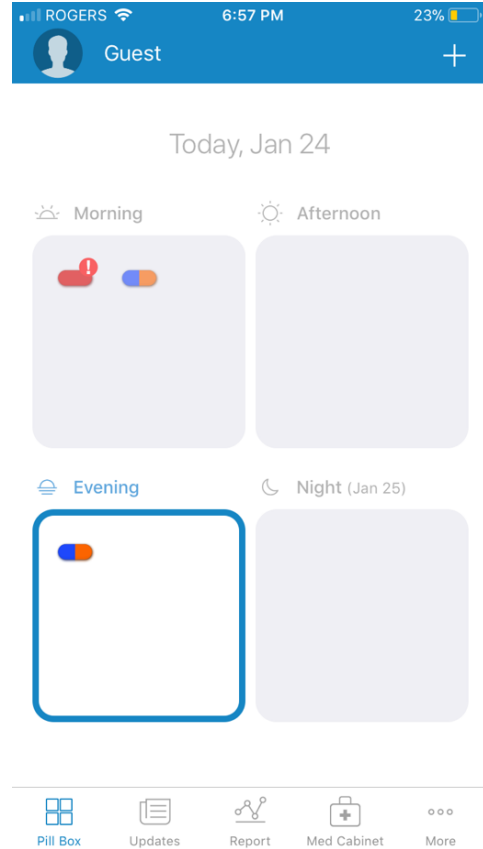
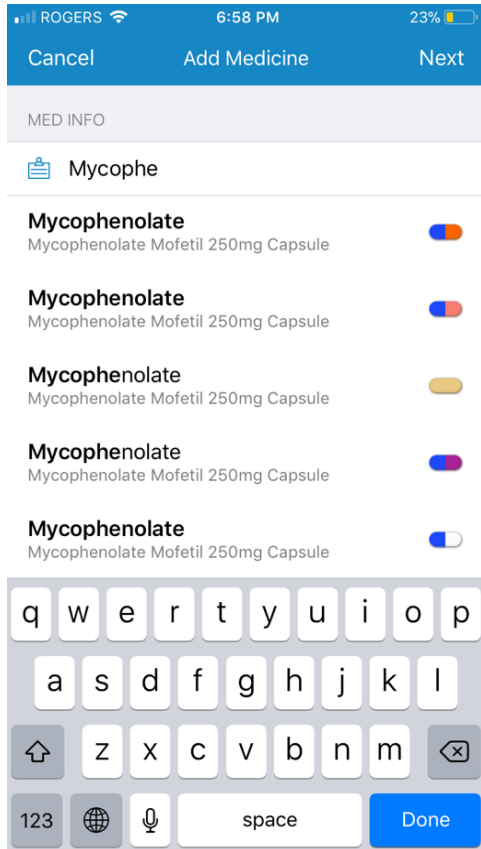
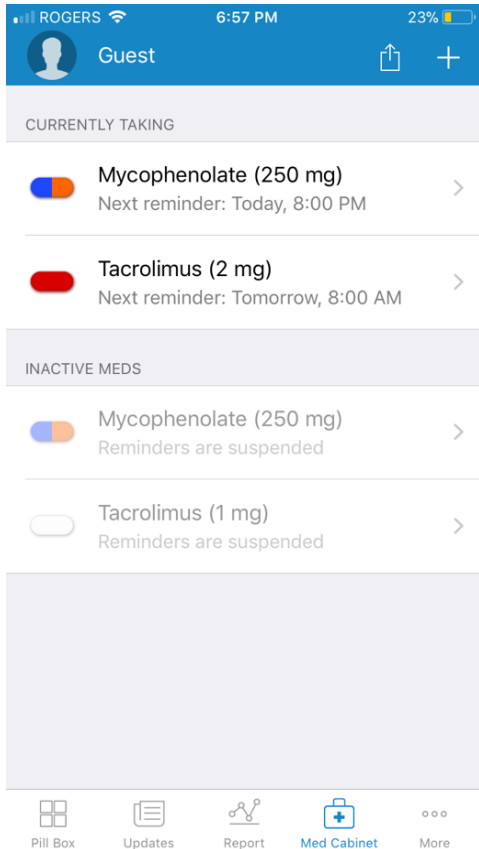
An ounce of prevention is worth a pound of cure

1. Multidisciplinary approach to target non-adherence
2. Optimize immunosuppression
3. A better way of matching using epitope?

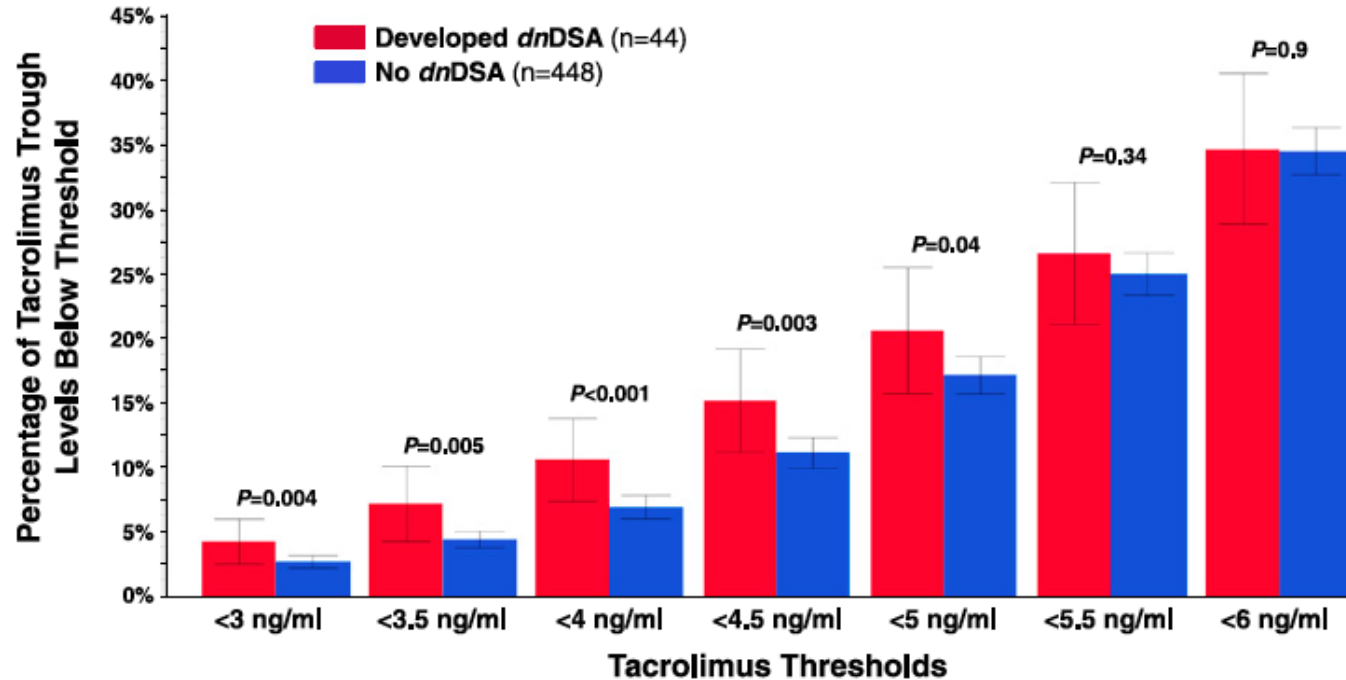
Non-adherence in AMR



Modernized tools to address non-adherence

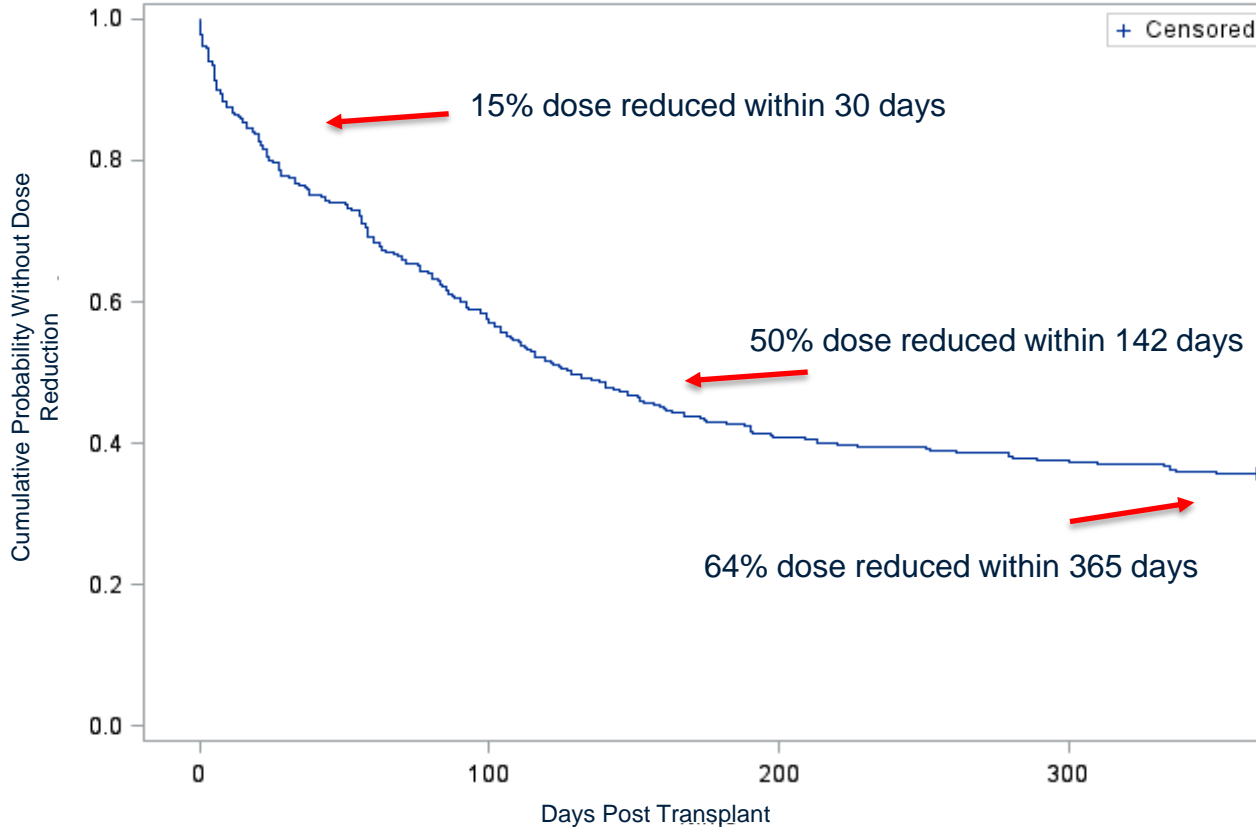


Optimizing CNI Level

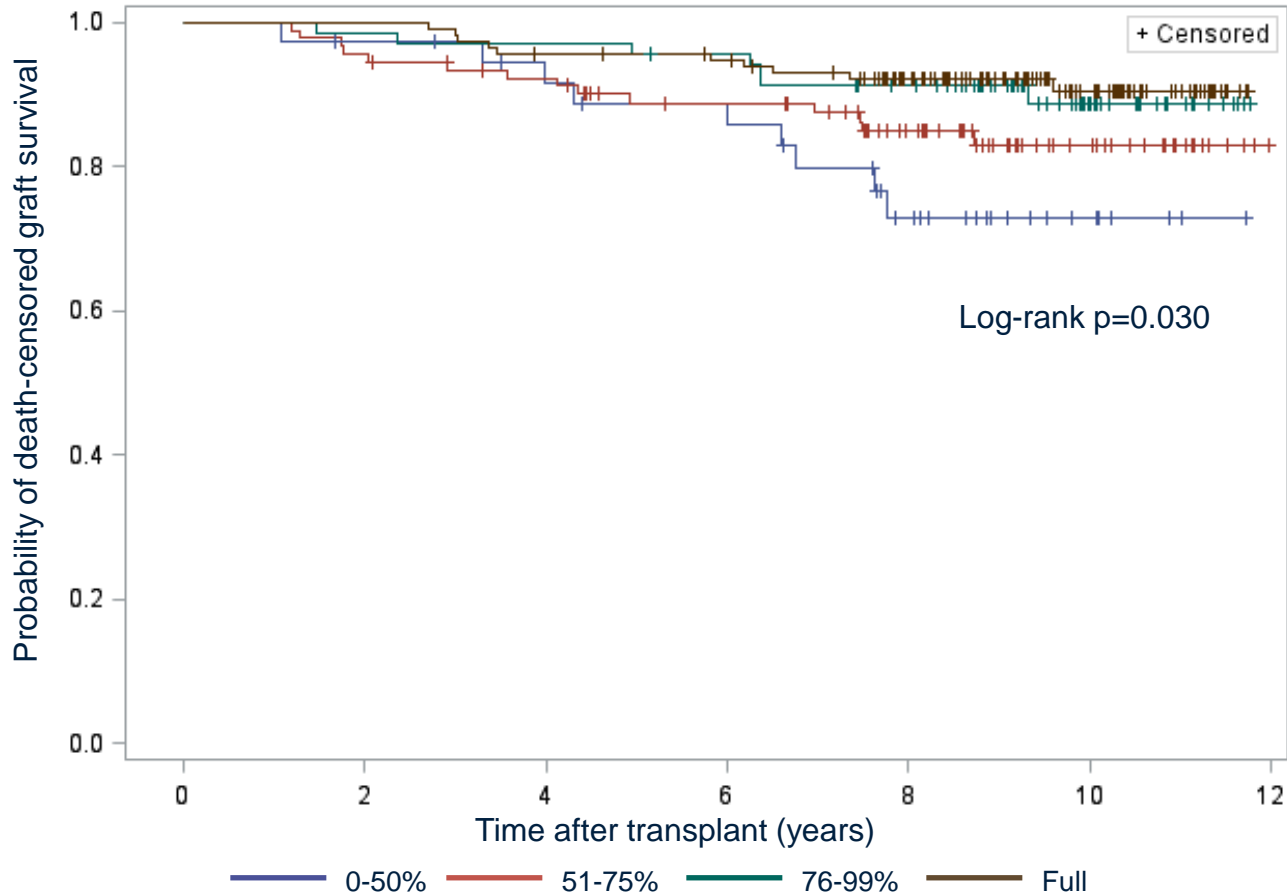


Impact of MMF dose reduction on long-term outcomes

Likelihood of reduction-free MMF dose maintenance in the first year posttransplant



Impact of MMF dose reduction on long-term outcomes



Impact of MMF dose reduction on long-term outcomes

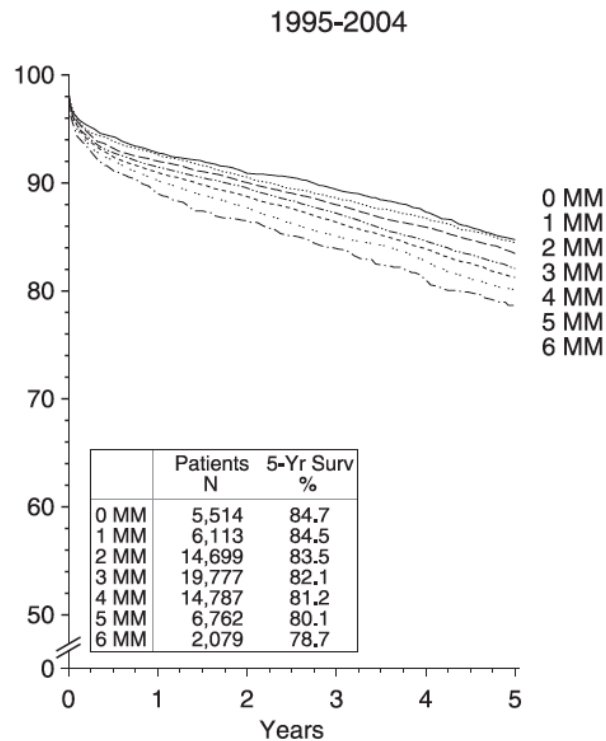
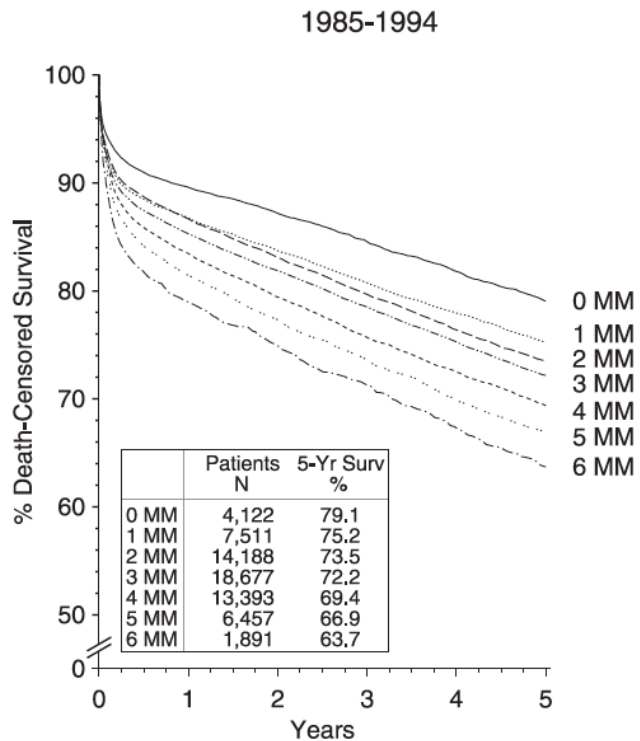
	Full Dose MMF N=119	76-99% MMF Dose N=70	51-75% MMF Dose N=92	0-50% MMF Dose N=38
Model 1: HR (95% CI) Unadjusted	1 (referent)	1.17 (0.45-3.08)	2.04 (0.91-4.60)	3.33 (1.35-8.20)
Model 2: HR (95% CI) Adjusted for recipient factors: Age, sex, race, BMI, PRA, cause of ESRD	1 (referent)	1.08 (0.40-2.94)	2.20 (0.96-5.02)	4.08 (1.60-10.38)
Model 3:HR (95% CI) Model 2 and: donor age, repeat transplant, donor type, HLA mismatch, CIT	1 (referent)	0.99 (0.36-2.73)	2.39 (1.00-5.72)	4.04 (1.42-11.47)
Model 4: HR (95% CI) Model 3 and: CNI use, ATG, prednisone	1 (referent)	0.92 (0.32-2.62)	2.25 (0.89-5.58)	3.28 (1.10-9.76)
Model 5:HR (95% CI) Model 4 and: DGF	1 (referent)	0.93 (0.32-2.65)	2.25 (0.89-5.69)	3.29 (1.10-9.83)

BMI = body mass index, PRA = panel reactive antibody, ESRD = end-stage renal disease, HLA = human leukocyte antigen, CIT = cold ischemic time, CNI = calcineurin inhibitor, ATG = antithymocyte globulin, DGF = delayed graft function, AR = acute rejection

Back to the beginning



Effect of HLA matching over time



1985-1994

1995-2004

Towards better HLA matching

1954-2018

Rejection

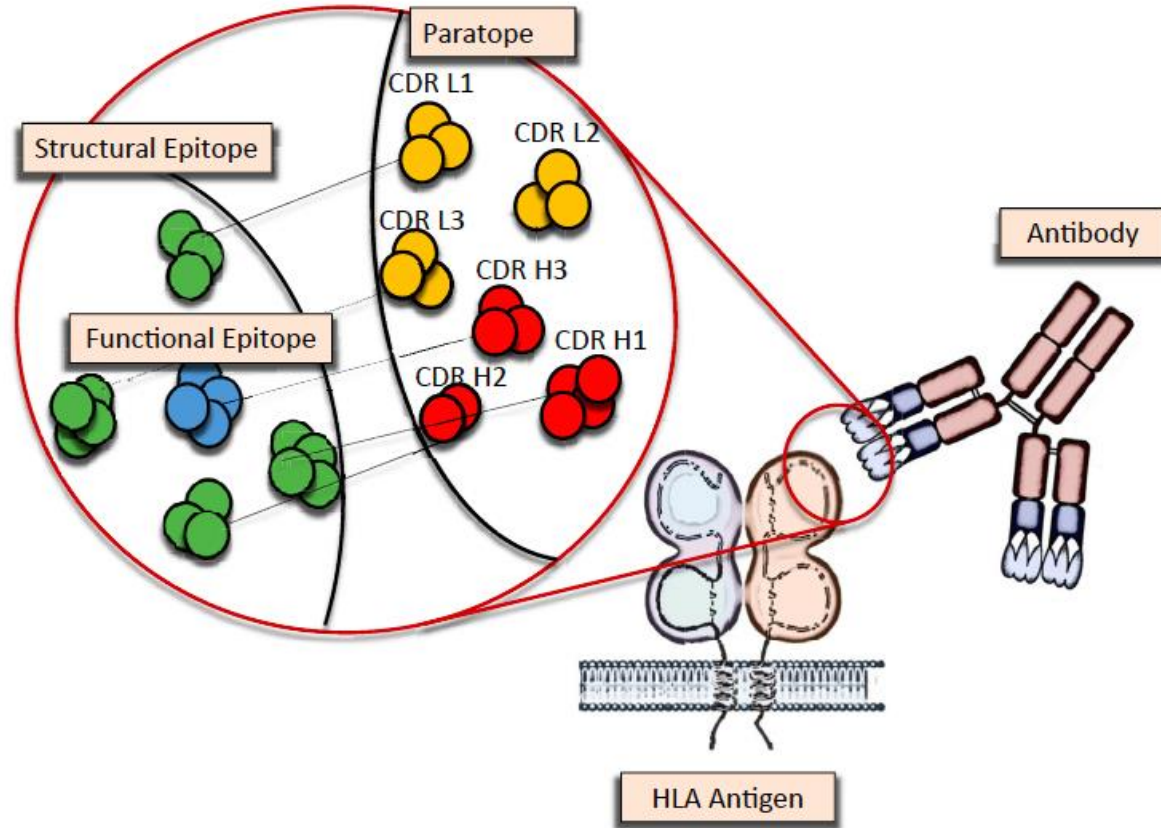
Infection
Malignancy
Med toxicities



2018-2028: improved HLA matching



Epitope analysis: a new way of HLA matching



Epitope analysis: not all mismatches are created equal

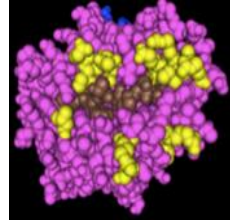
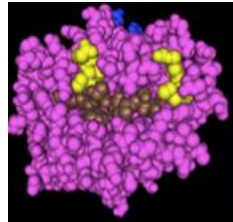
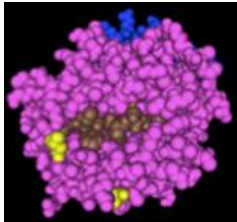
Recipient:

B7

Donor 1

Donor 2

Donor 3



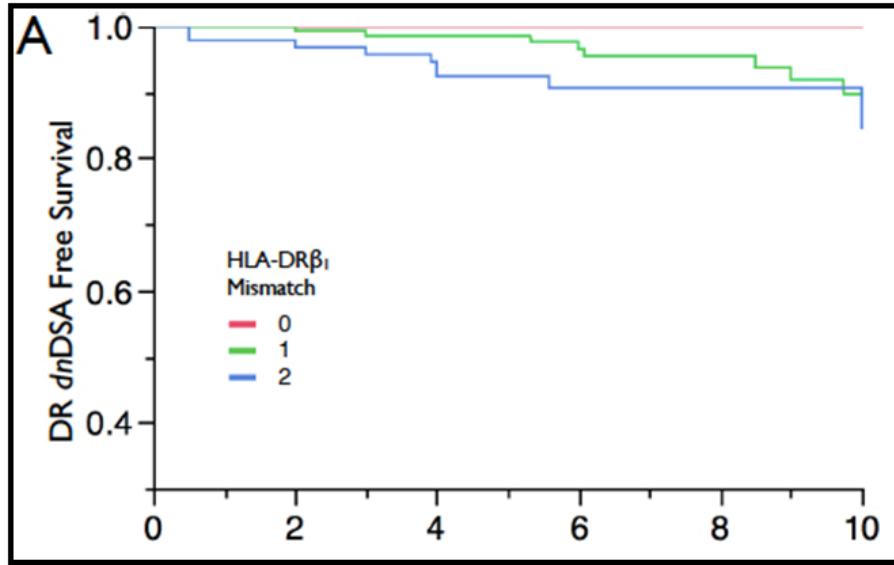
B8

B35

B44

	AA Pos.	80	90
Recipient	B*07:02:01:01	AQTDRESLRN	LRGYYNQSEA
Donor 1	B*08:01:01:01	T-----	-----
Donor 2	B*35:01:01:01	T--Y-----	-----
Donor 3	B*44:02:01:01	T--Y--N--T	ALR-----

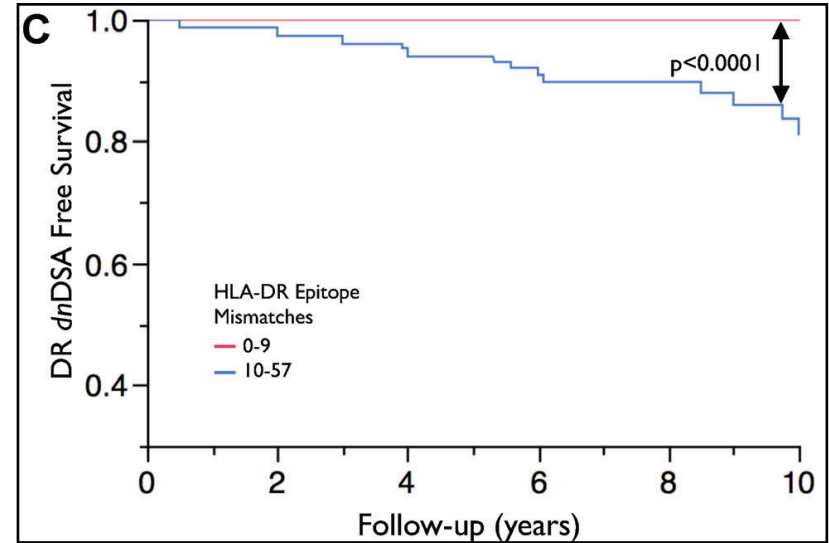
Epitope analysis: not all mismatches are created equal



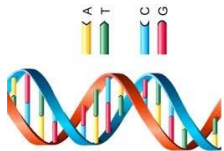
0 mm

1 mm

2 mm

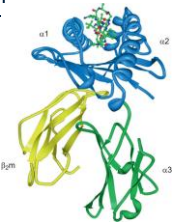


Workflow of epitope-based analysis



HLA-A*02:01

HLA matchmaker



Epitope analysis: easy as 1, 2, 3

Patient Name:	x	Donor Name	x	#####	Sort by DRB Eplets	Sort by DQB Eplets	Sort by DQA Eplets	Sort by DPB Eplets
Locus	Patient HLA	Donor HLA	mmEp	Mismatched Donor Eplets				
DRB1	DRB1*0101	DRB1*0401	11	,,12VKH,14HEH,,26RF,32FYH,34HQ,,,,,71QKA,,,96YL,98EN,104AK,120N,,,,,180LT,,				
DRB1	DRB1*0301	DRB1*1101	5	,,,,26RF,32FYN,,,57DE,,67FR,71DRA,,,,,,,,,,,,,				
DRB345	x	x	-	...				
DRB345	x	x	-	...				
DQB	DQB1*0501	DQB1*0301	14	,14AM,,26Y,30YYA,45EV,46EVY,52PL,55PPP,57PD,,70RT,74EL,77DT,,,,,,,,,,,,,140T,167HG,182N,,,,,				
DQB	DQB1*0201	DQB1*0301	14	,14AM,,26Y,30YYA,45EV,46EVY,52PL,55PPP,57PD,,70RT,74EL,77DT,,,,,,,,,,,,,140T,167HG,182N,,,,,				
DQA	x	x	-	...				
DQA	x	x	-	...				
Suggested 1st DQA?	DQA1*0101	DQA1*0302						
Suggested 2nd DQA?	DQA1*0501	DQA1*0501						

Era of Precision Medicine

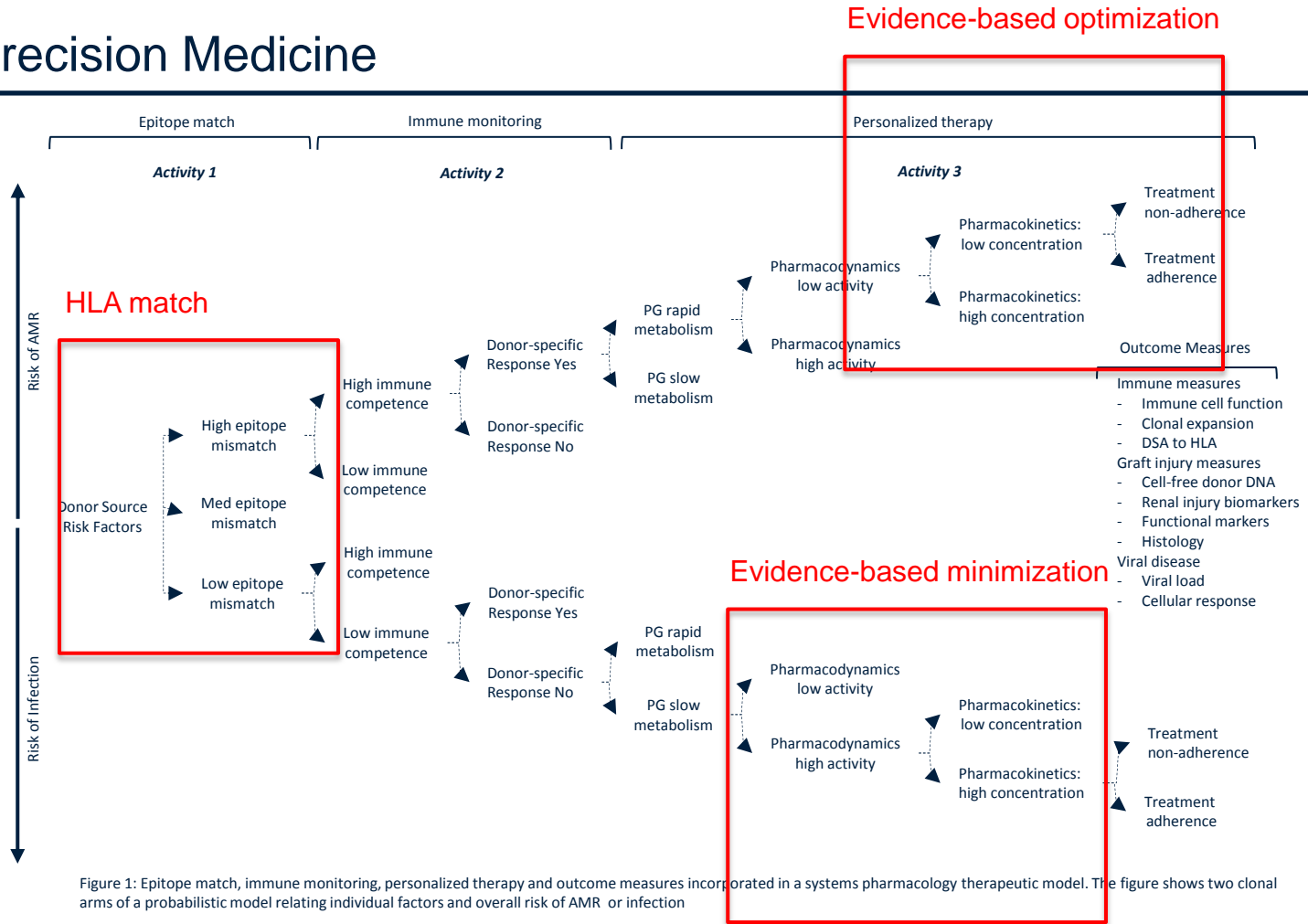


Figure 1: Epitope match, immune monitoring, personalized therapy and outcome measures incorporated in a systems pharmacology therapeutic model. The figure shows two clonal arms of a probabilistic model relating individual factors and overall risk of AMR or infection

THANK YOU



Questions?

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