CARE TEAM FORUM®

STRONGER FOR LONGER:
Managing Chronic Active ABMR in Renal Allograft Recipients

A Series of Expert Panel Discussions
Featuring an Experienced ABMR Patient

Taking Stock of New Findings in the Pathogenesis of Chronic Active ABMR in Kidney Transplantation

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Chair, Department of Medicine
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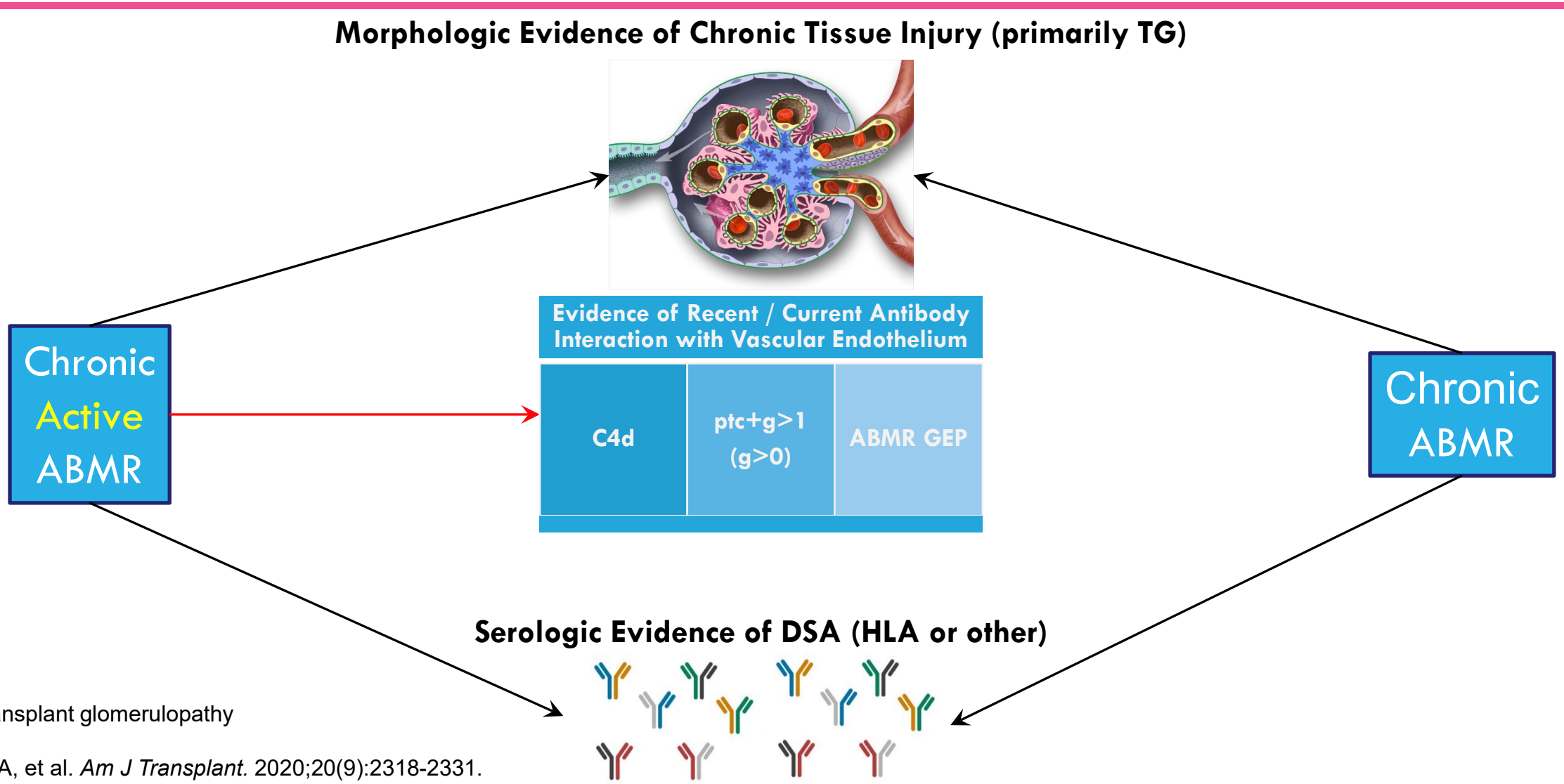
Chronic Active ABMR versus Chronic ABMR

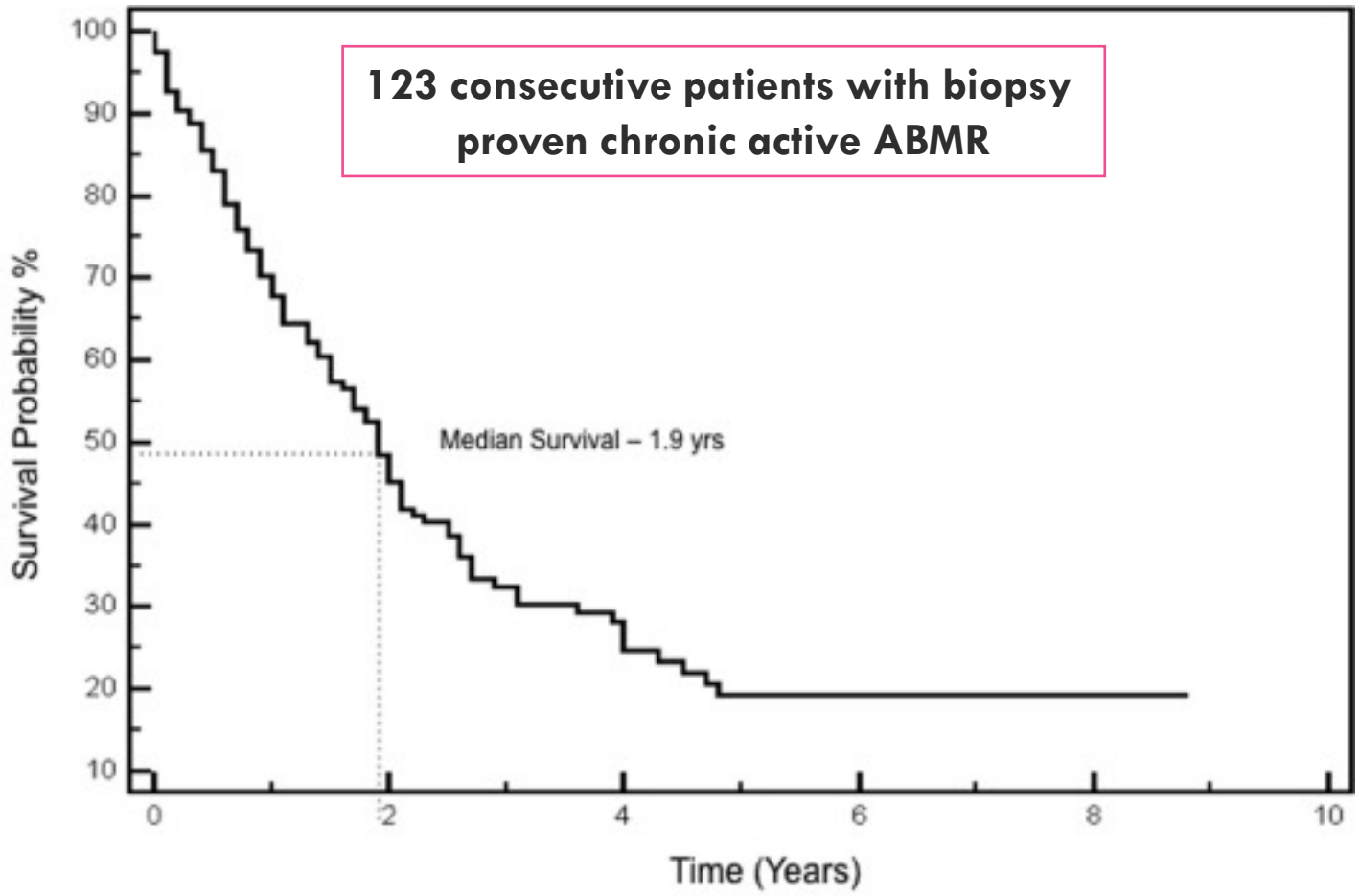


TG, transplant glomerulopathy

Loupy A, et al. *Am J Transplant.* 2020;20(9):2318-2331.

How Bad is Chronic Active ABMR?

Chronic Active ABMR: Median Graft Survival After Diagnosis

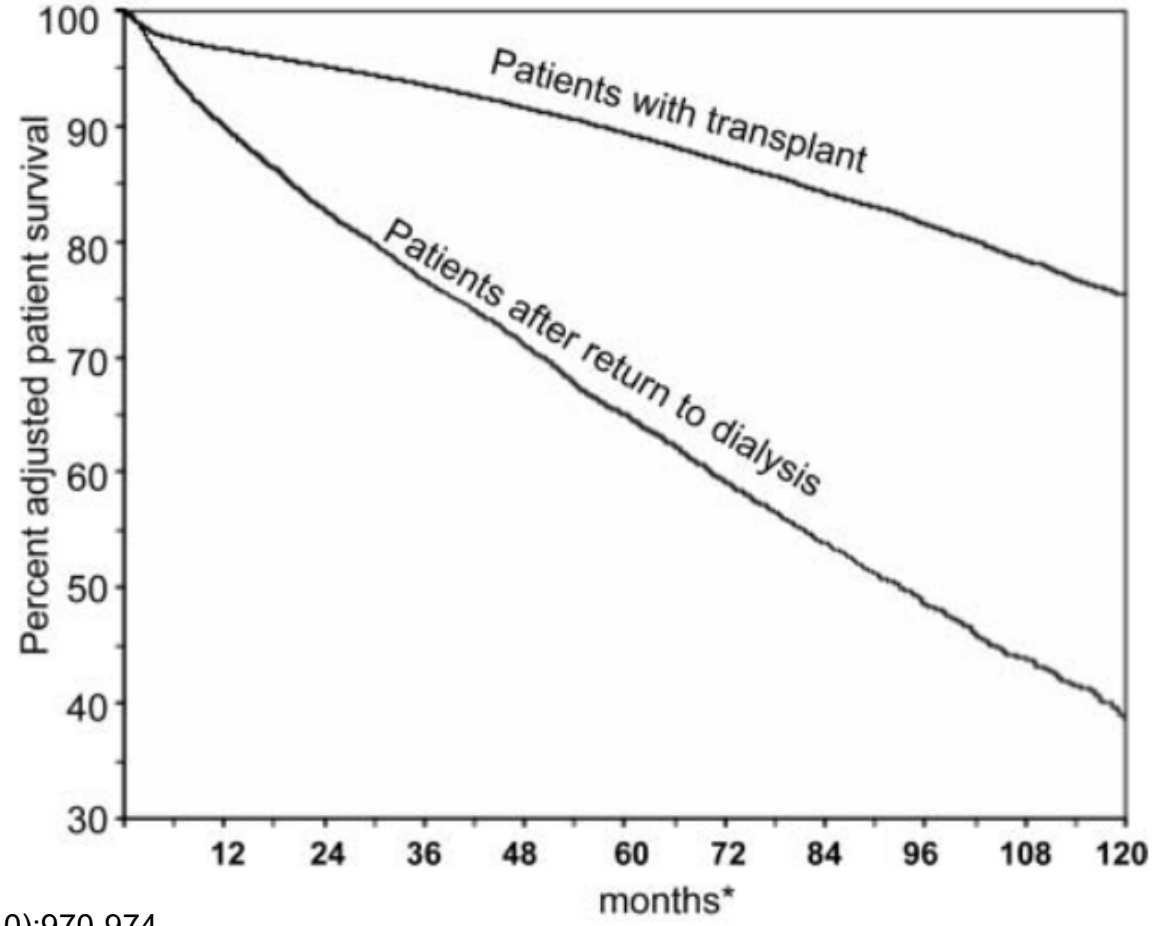


Median graft survival after diagnosis: ~2 years

Redfield RR, et al. *Hum Immunol.* 2016;77(4):346-352.

Patient Death Rate After Graft Failure

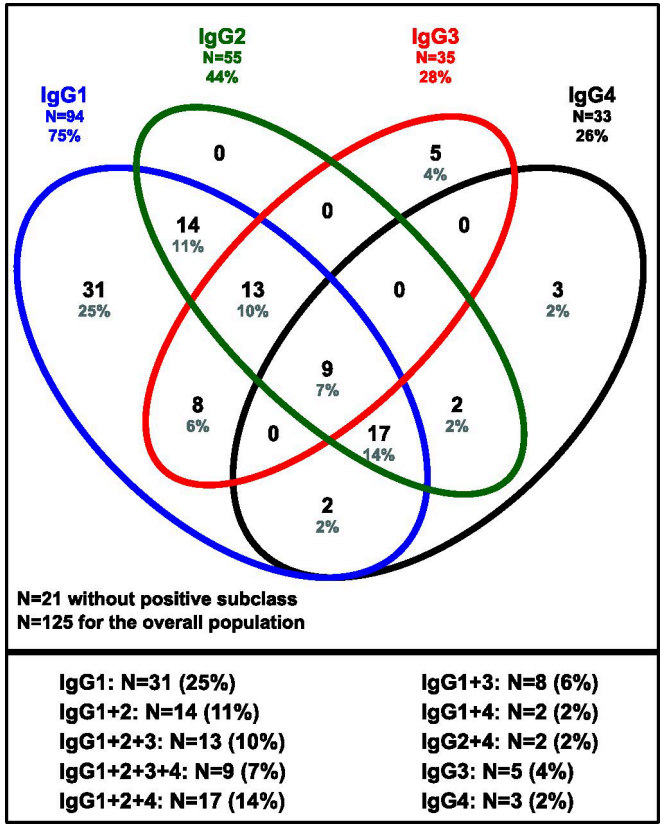
Adjusted Annual Patient Death Rate After Graft Failure is >3X Higher



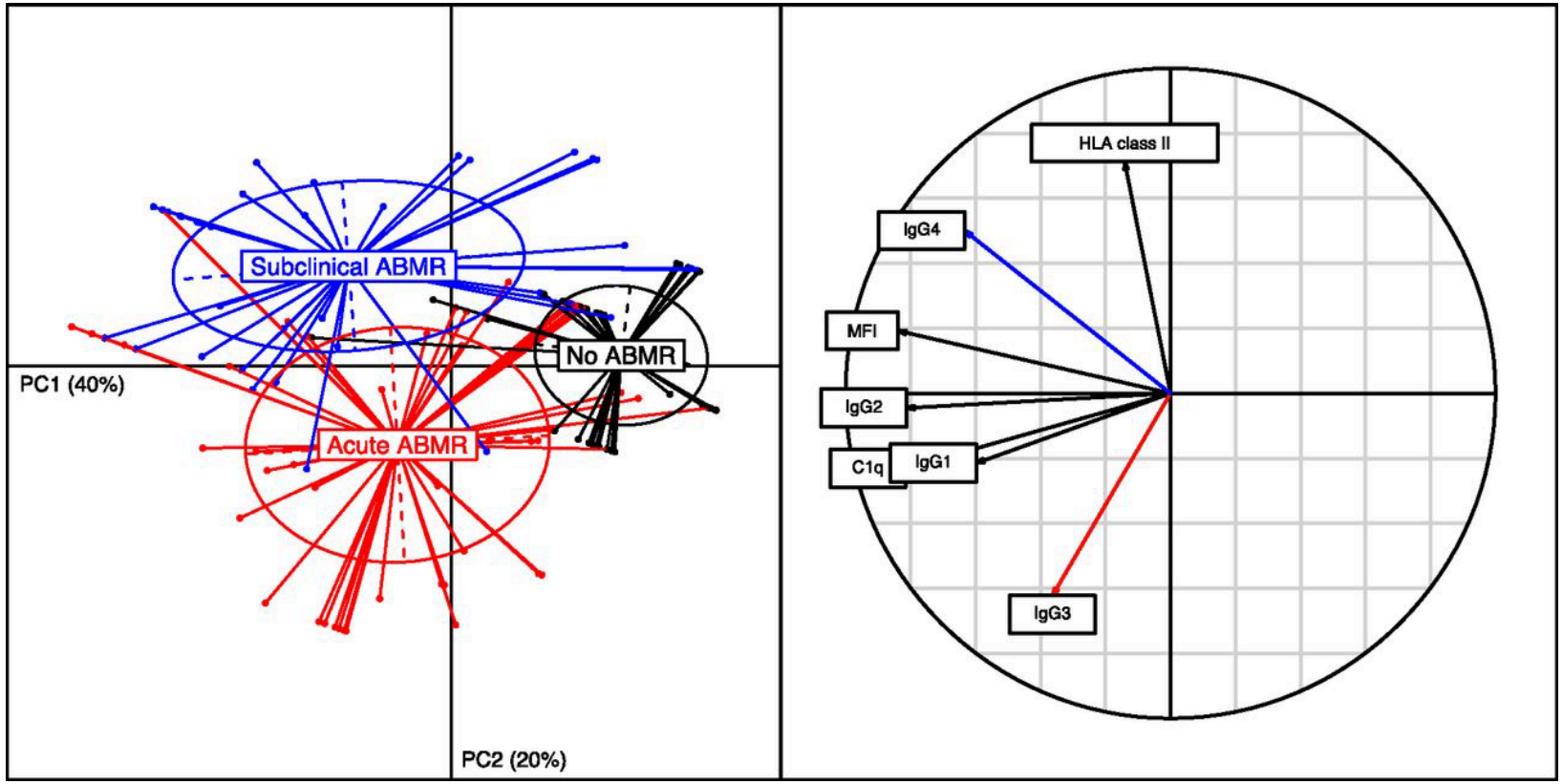
Kaplan B, et al. *Am J Transplant.* 2002;2(10):970-974.

Pathophysiology of Chronic Active ABMR

IgG Donor-Specific Anti-Human HLA Antibody Subclasses and Kidney Allograft Antibody-Mediated Injury



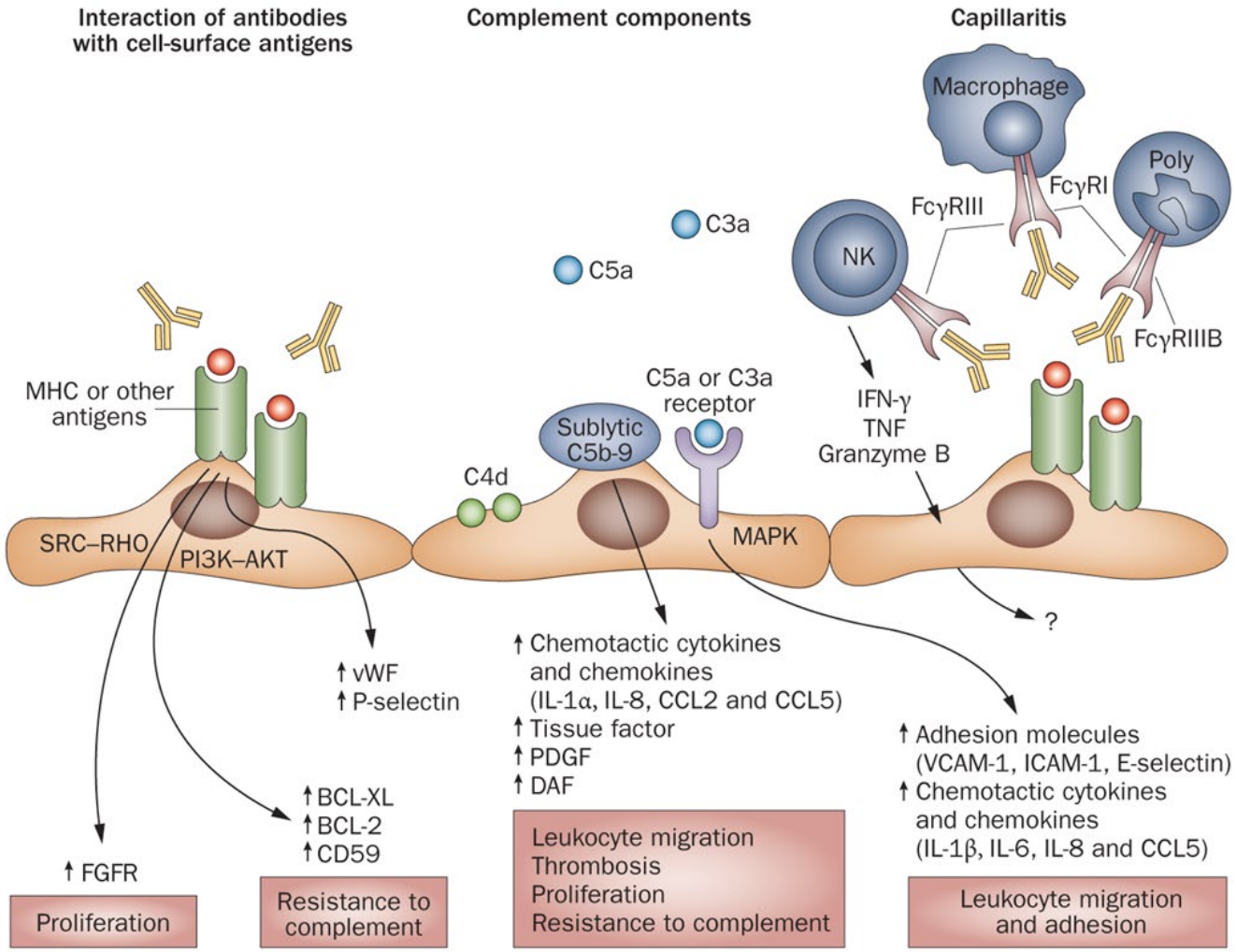
Distribution of IgG1-4 iDSA subclasses



Identification of the 3 distinct rejection phenotypes according to the characteristics of the dominant donor-specific anti-HLA antibody (MFI, HLA class specificity, C1q-binding capacity, and IgG1-4)

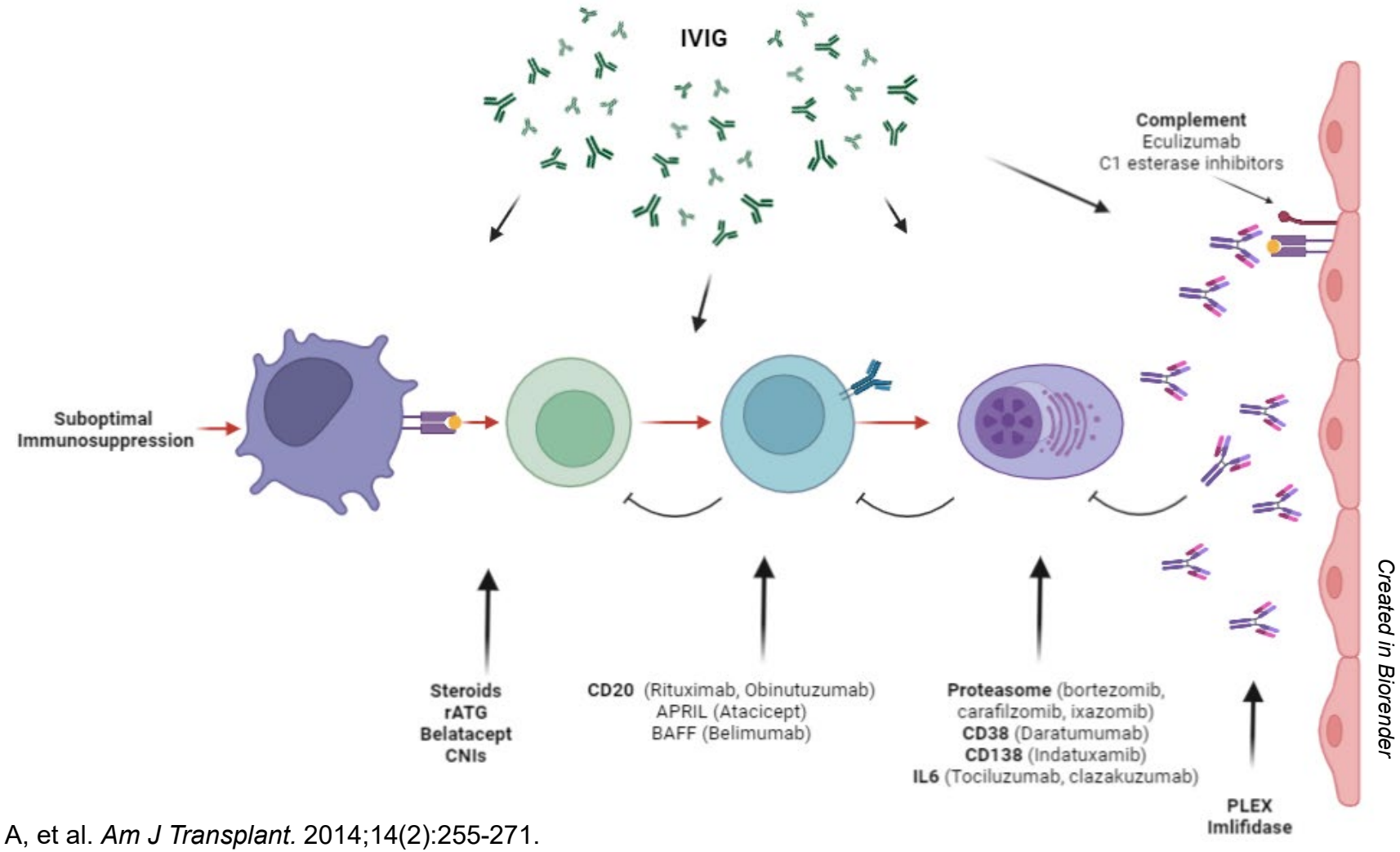
LeFaucheur C, et al. *J Am Soc Nephrol.* 2016;27(1):293-304.

Direct and Indirect Pathways of Endothelial Cell Injury



Farkash EA, et al. *Nat Rev Nephrol.* 2012;8(5):255-257.

Cellular Pathways Resulting in Allo-Antibody Generation

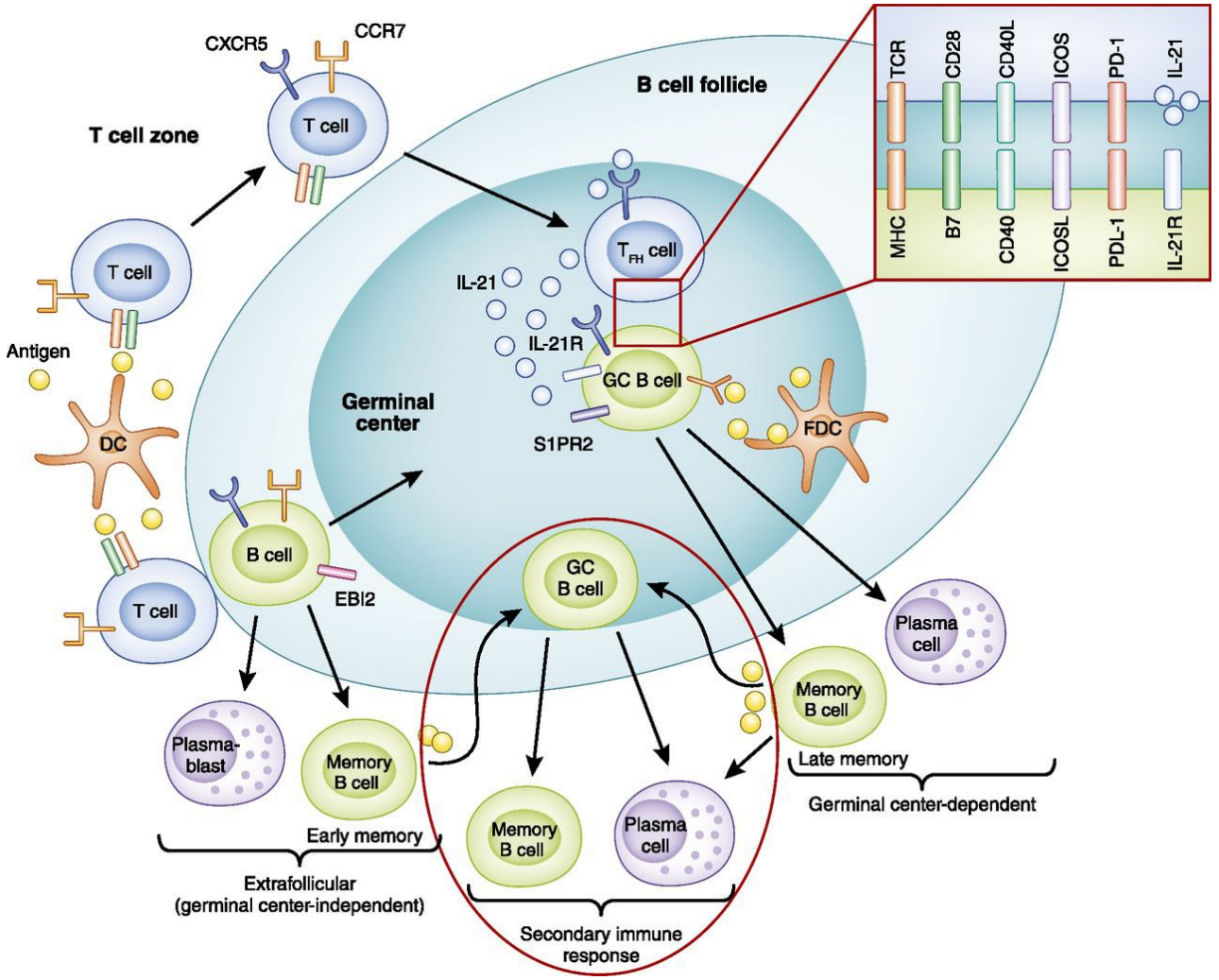


Modified from: Djamali A, et al. *Am J Transplant.* 2014;14(2):255-271.

Secondary Lymphoid Organ

Initial interaction occurs here:

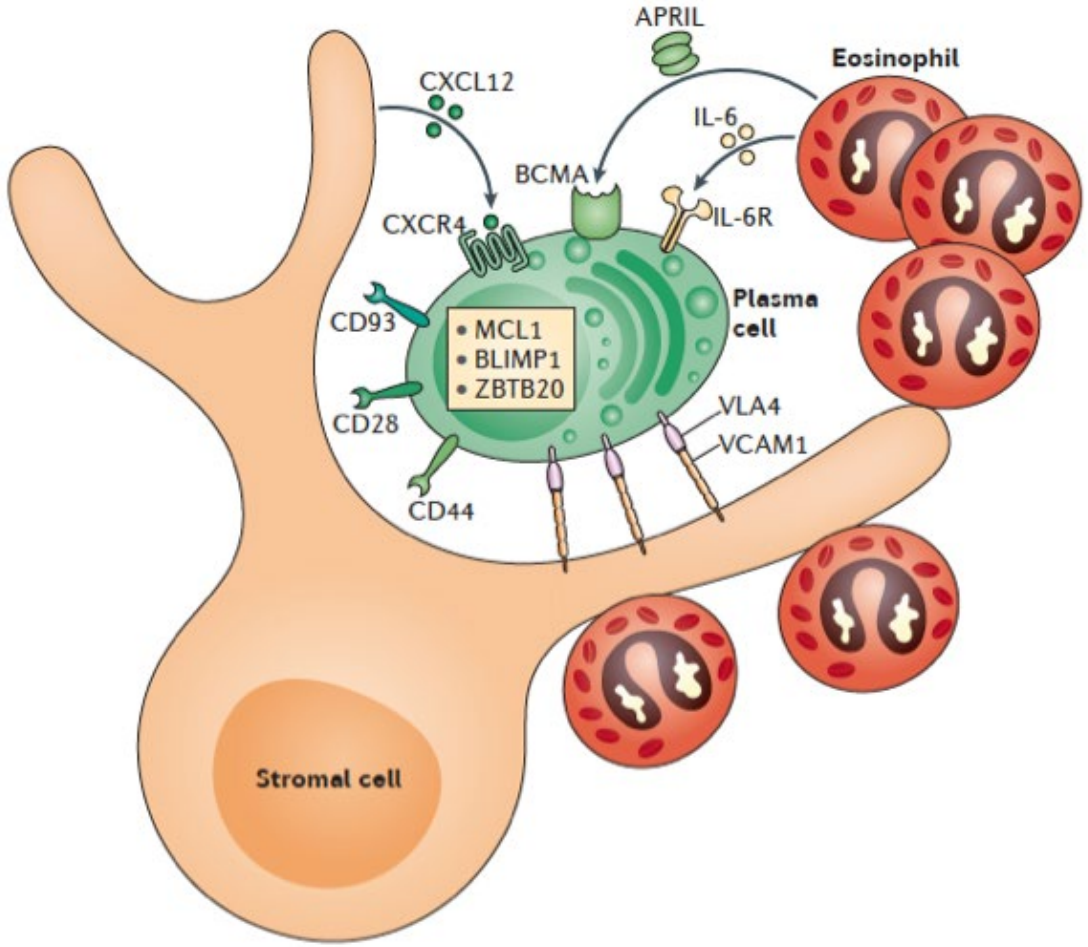
- T-helper cell interacts with B-cell
- B-cell activation and differentiation into memory B cells or plasma cells
- Recirculate to secondary lymph nodes or to tertiary or primary organs



Hoffman W, et al. *Clin J Am Soc Nephrol.* 2016;11(1):137-154.

Primary Lymphoid Organ

- Long-lived plasma cells find their niche in the bone marrow
- Plasma cells obtain high level of specificity and high-level generation of antibodies
- Difficult to reach and treat



Nutt SL, et al. *Nat Rev Immunol.* 2015;15(3):160-171.

Tertiary Lymphoid Organ: Ectopic Germinal Center in Kidney

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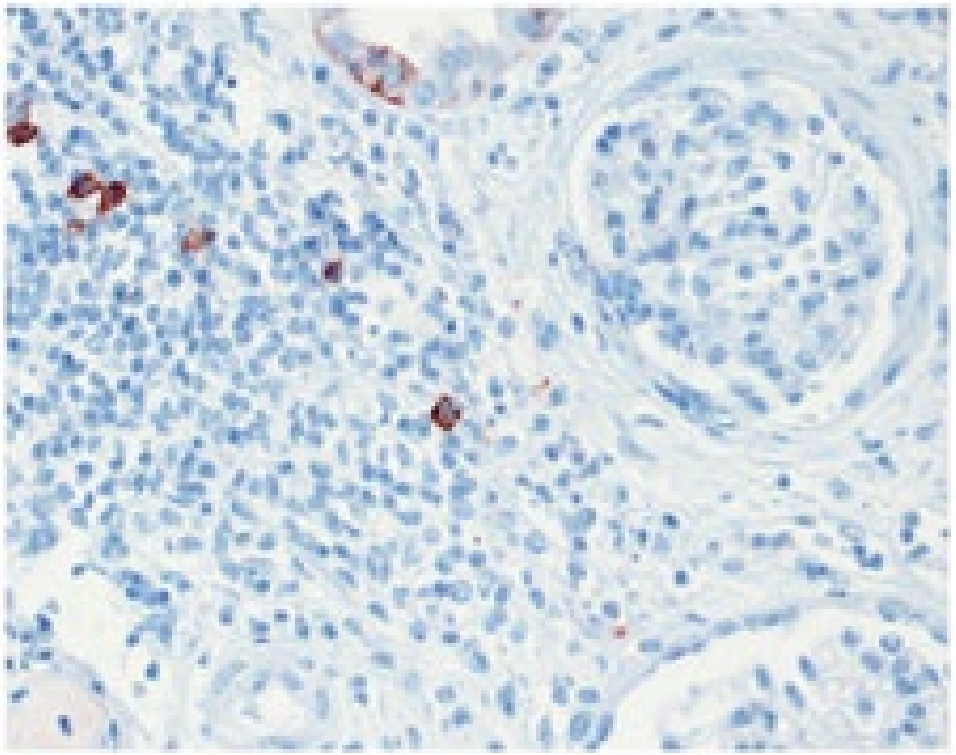
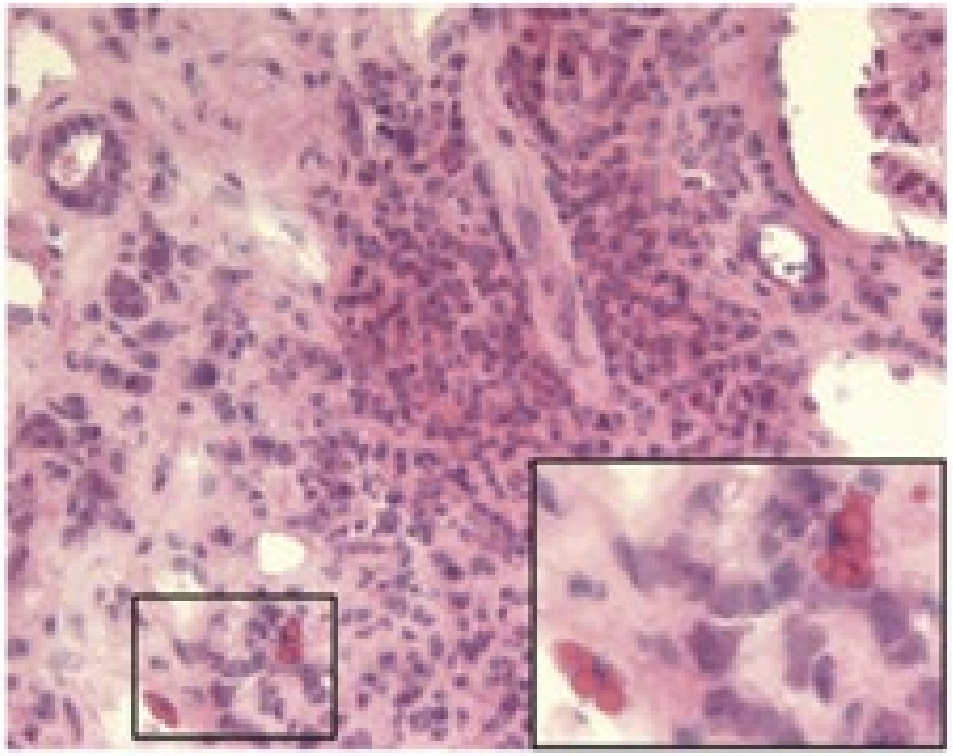
Ectopic Germinal Centers and Tertiary Lymphoid Organs

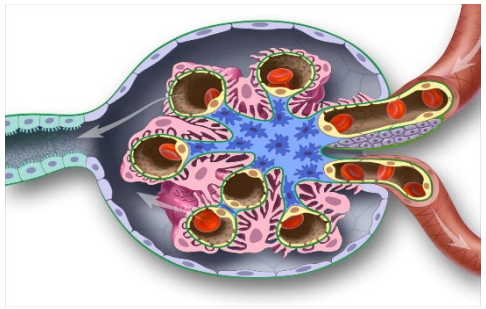




Thaunat O, et al. *J Immunol.* 2010;185(1):717-728.

What is ABMR Without Detectable HLA DSA?

Morphologic Evidence of Chronic Tissue Injury (primarily TG)



Evidence of Recent/Current Antibody Interaction with Vascular Endothelium

C4d	ptc+g>1 (g>0)	ABMR GEP

Chronic Active ABMR

Chronic ABMR

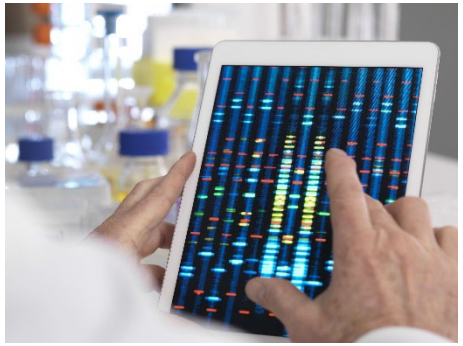
Serologic Evidence of DSA (HLA or other)

C4d staining or validated transcripts/classifiers may **substitute** for DSA; however thorough DSA testing, including testing for non-HLA antibodies, if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

Loupy A, et al. *Am J Transplant.* 2020;20(9):2318-2331.

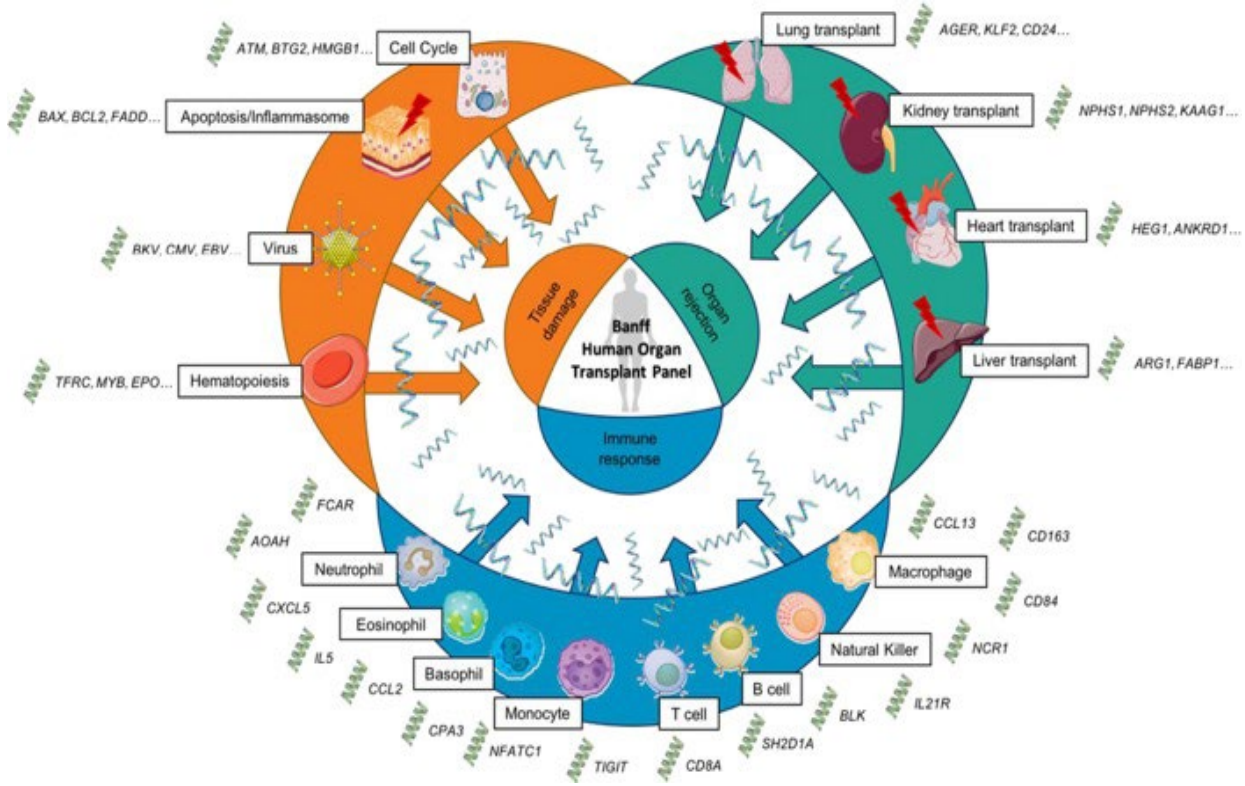
Molecular Diagnostics in Chronic Active ABMR

Biopsy tissue



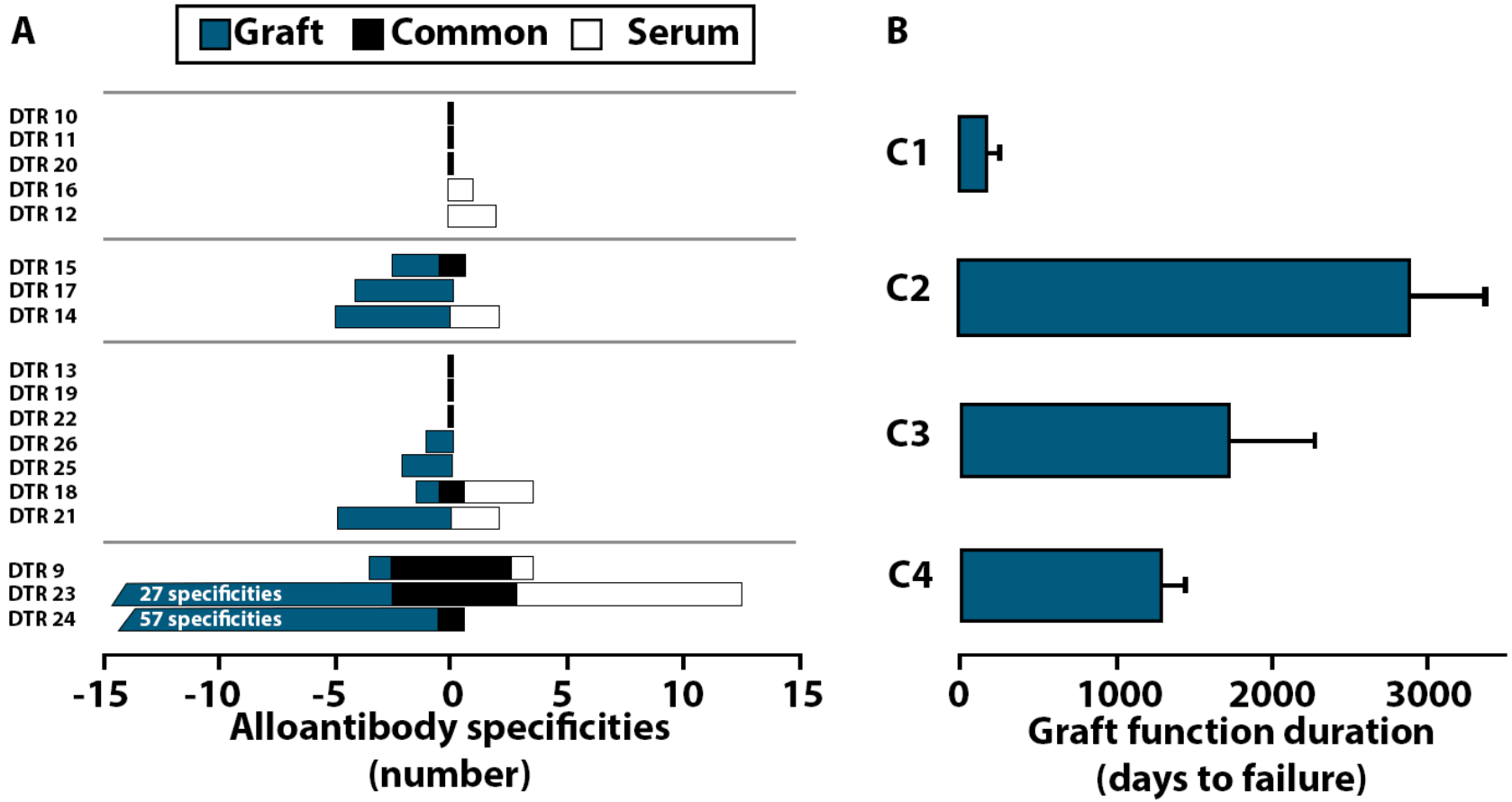
Gene expression profiling

Banff Human Organ Transplant (B-HOT) Panel



Mengel M, et al. *Am J Transplant.* 2020;20(9):2305-2317.

Intragraft Humoral Response versus Systemic Response



Thaunat O, et al. *J Immunol.* 2010;185(1):717-728.

TG in the Absence of HLA-DSA

Risk factors, histopathological features and graft outcome of TG in the absence of HLA-DSA.

Hospitals Leuven
2004 to 2013

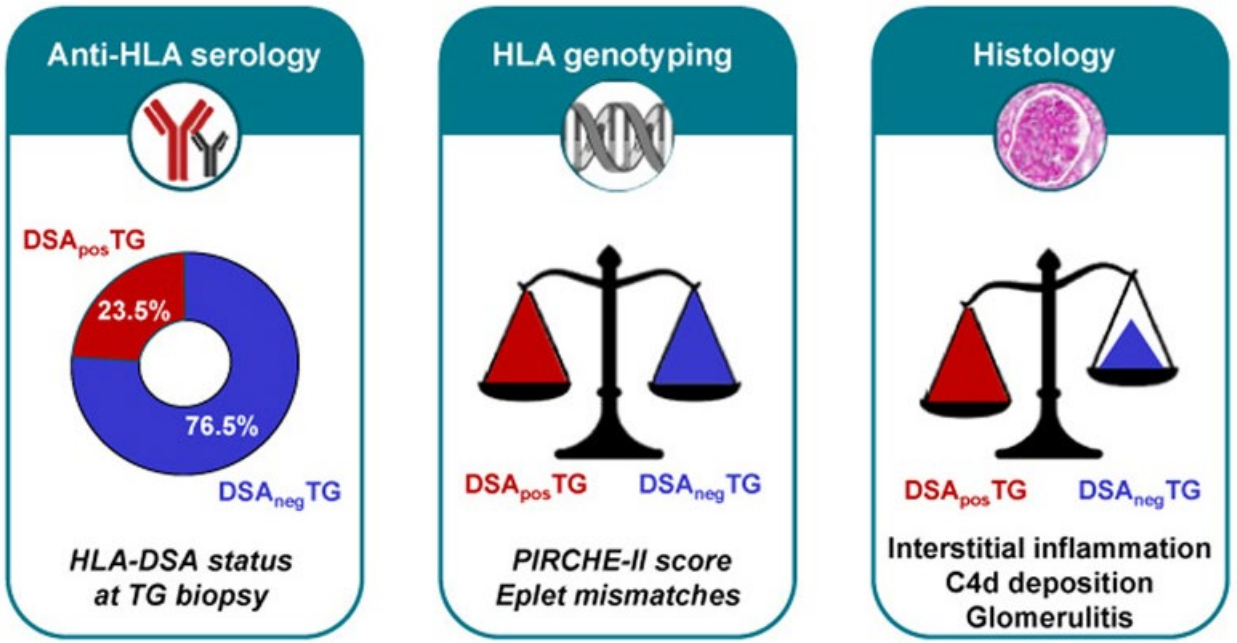
Kidney Transplants
N=954

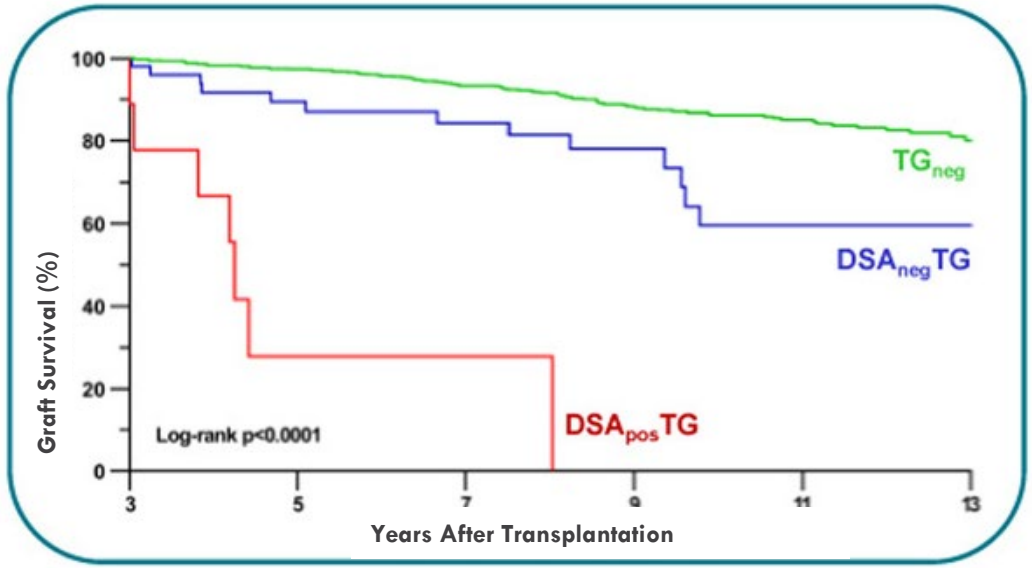
HLA Genotyping
N=893

Allograft Biopsies
N=3744

Anti-HLA Antibodies
2004 to 2019

Patients with TG (N=98)





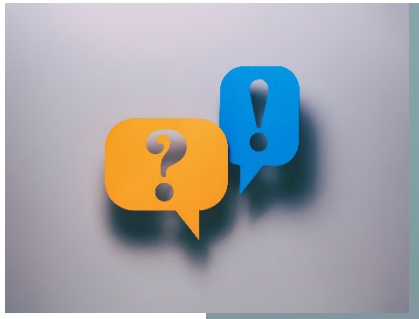
HLA-DSA, donor specific HLA-antibodies; TG, transplant glomerulopathy

Senev A, et al. *Kidney Int.* 2021;100(2):401-414.

CONCLUSION: TG often occurs in the absence of HLA-DSA and represents a different phenotype with better graft survival compared to TG in the presence of HLA-DSA. PIRCHE-II score and eplet mismatches did not associate with TG development.

Predicted Indirectly Recognizable HLA Epitopes

What About the HLA DSA (+) ABMR (-) Phenotype?



Does DSA Have Predictive Value?

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Eskandary et al[1]

- 86 patients with DSA >1000 IgG mean fluorescence intensity (MFI)
- Positive predictive value (PPV) of DSA for the diagnosis of ABMR was **51%** (44/86 samples that were DSA+ were confirmed to have active ABMR by biopsy)

DART Study[2]

- 87 patients from the multicenter study
- PPV of DSA for the diagnosis of ABMR was **48%** (29/61 samples that were DSA+ were confirmed to have active ABMR by biopsy)

1. Eskandary F, et al. *Transplantation.* 2017;101(3):631-641.
2. Jordan SC, et al. *Transplant Direct.* 2018;4(9):e379.

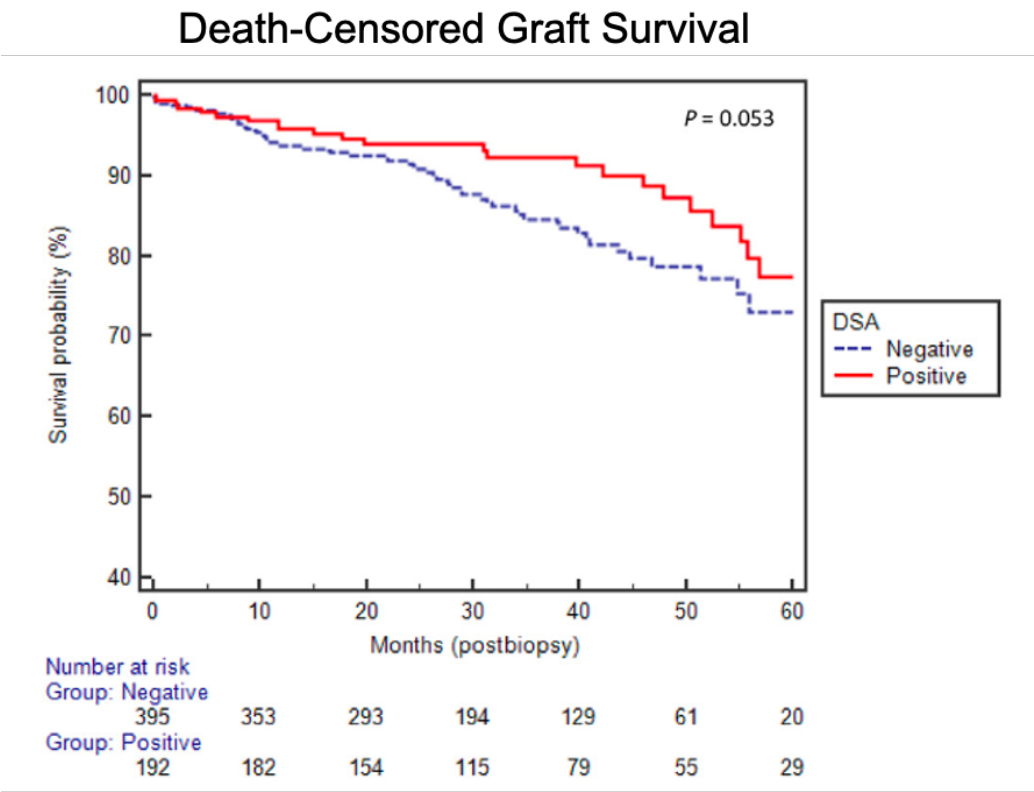
DSA Alone are Not Associated with Increased Risk of Graft Failure

Purpose: Examine long-term outcomes for kidney transplant recipients with DSAs in absence of rejection on biopsy

- 587 total kidney biopsies
  - 192 DSA+
  - 395 DSA-

- The definition of *de novo* DSA was new DSA with MFI >300

Conclusion: In the absence of rejection, DSAs are not associated with an increased risk of graft failure



Parajuli S, et al. *Kidney Int Rep.* 2019;4(8):1057-1065.

Bottom Line: Not All DSA are Bad!

Chronic Active ABMR Pathophysiology: Summary and Future Directions

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Poor Outcomes

Chronic active ABMR is common and is associated with poor outcomes

Optimal Treatment Strategies

Better understanding of cellular and molecular pathways involved in the pathogenesis of chronic active ABMR could lead to optimal treatment strategies

Multiple Phenotypes

Chronic active ABMR has several phenotypes that are associated with different outcomes

Prevention and Early Detection

Prevention (adherence, optimal IS), early diagnosis (novel biomarkers), and treatment could reduce the incidence of graft failure from chronic active ABMR

Patient Video

Panel Discussion

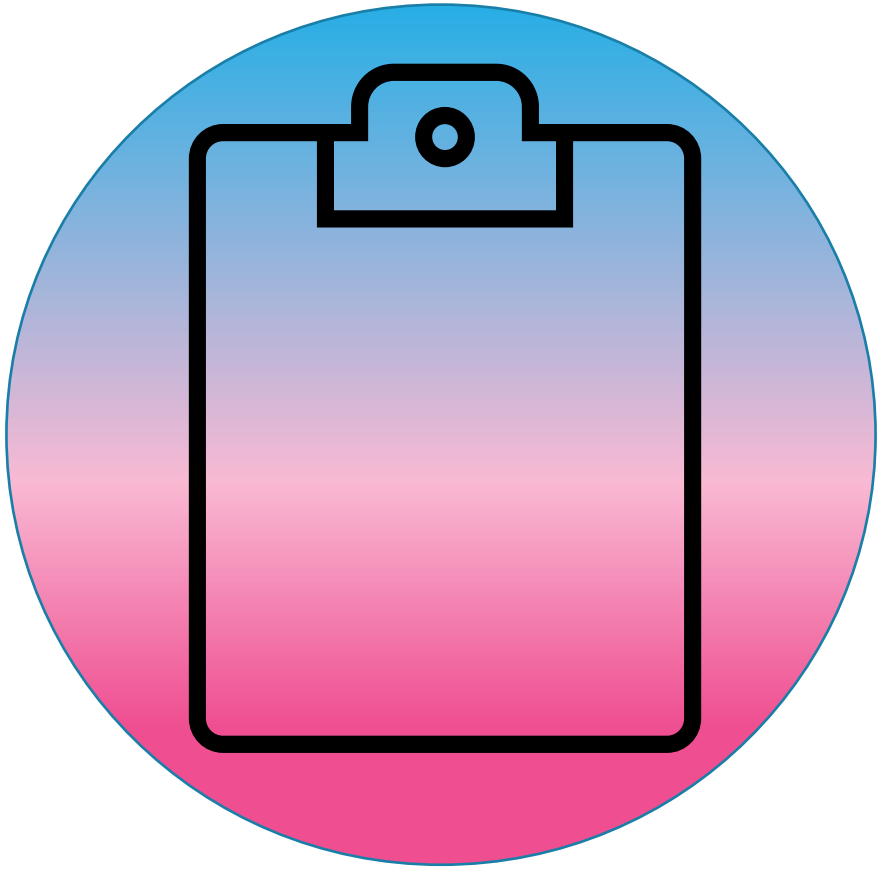
How does your understanding of the different ABMR phenotypes influence your therapeutic approach to your patients?

Applying Histological Findings to Expedite Chronic Active ABMR Diagnosis

Benjamin Adam, MD, FRCPC
Laboratory Site Chief and *Anatomical Pathology Divisional Director*
University of Alberta Hospital
Associate Professor, Department of Laboratory Medicine and Pathology
Program Director, Renal and Transplantation Pathology Fellowship
University of Alberta
Medical Lead, North Sector Clinical Trials and Research
Alberta Precision Laboratories
Walter C. Mackenzie Health Sciences Centre
Edmonton, Alberta, Canada

Patient Case

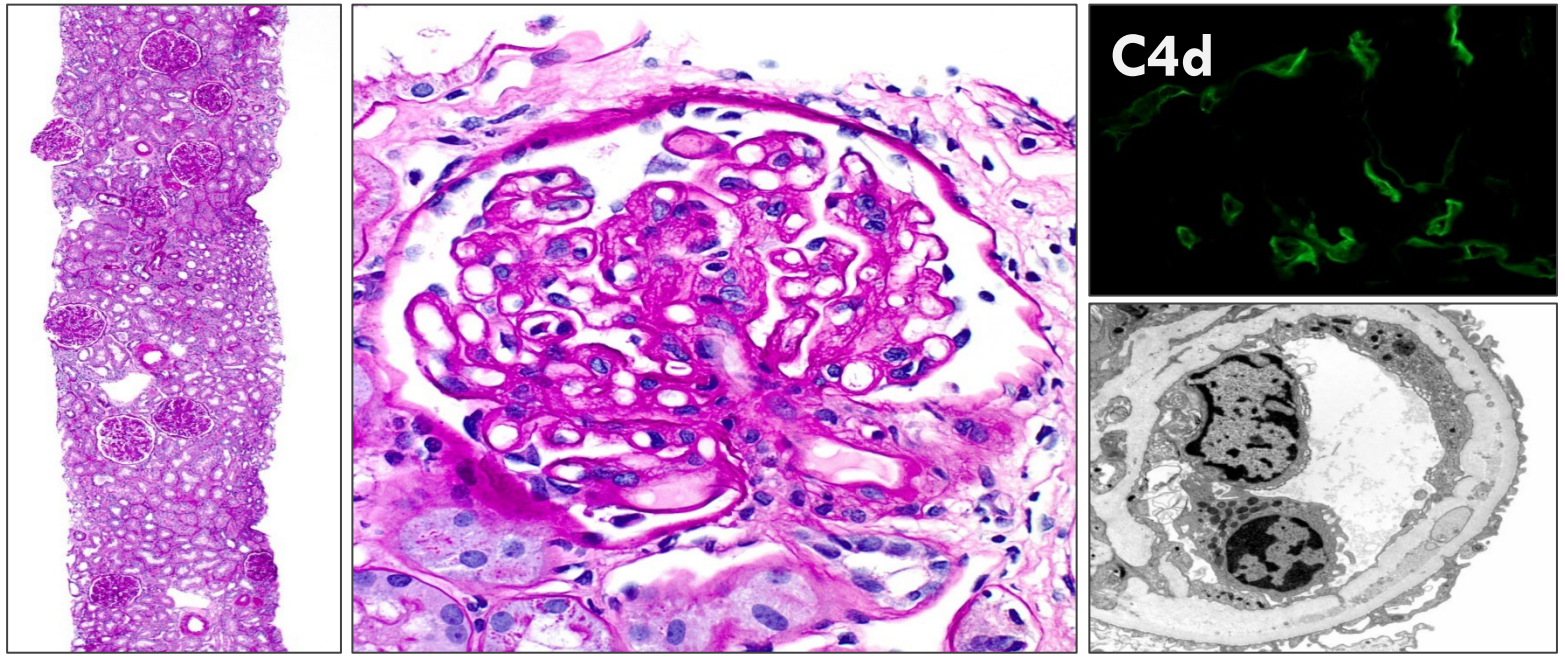
- 64-year-old male
- 10 years post-transplant for polycystic kidney disease
- History of DSA (Class II: DQ2)
- Increasing creatinine to 414 µmol/L (4.7 mg/dL)
- Urine: 3+ protein, 2+ hemoglobin



Patient Case (continued)

Kidney allograft, biopsy (10 years post-transplantation):

- Chronic active antibody mediated rejection
- Banff scores: g1 ptc1 i1 ti2 i-IFTA2 t0 t-IFTA1 v0 cg3 mm2 ci2 ct2 cv2 ah2 C4d2



Banff 2019 Classification Antibody Mediated Rejection

2019 Banff Criteria for Chronic Active ABMR (All 3 criteria must be met for diagnosis)

Morphologic Evidence of Chronic Tissue Injury

Including 1 or more of the following:

- Transplant glomerulopathy
- Severe peritubular capillary basement membrane multilayering
- Arterial intimal fibrosis of new onset, excluding other causes

Evidence of Antibody Interaction with Vascular Endothelium

Including 1 or more of the following:

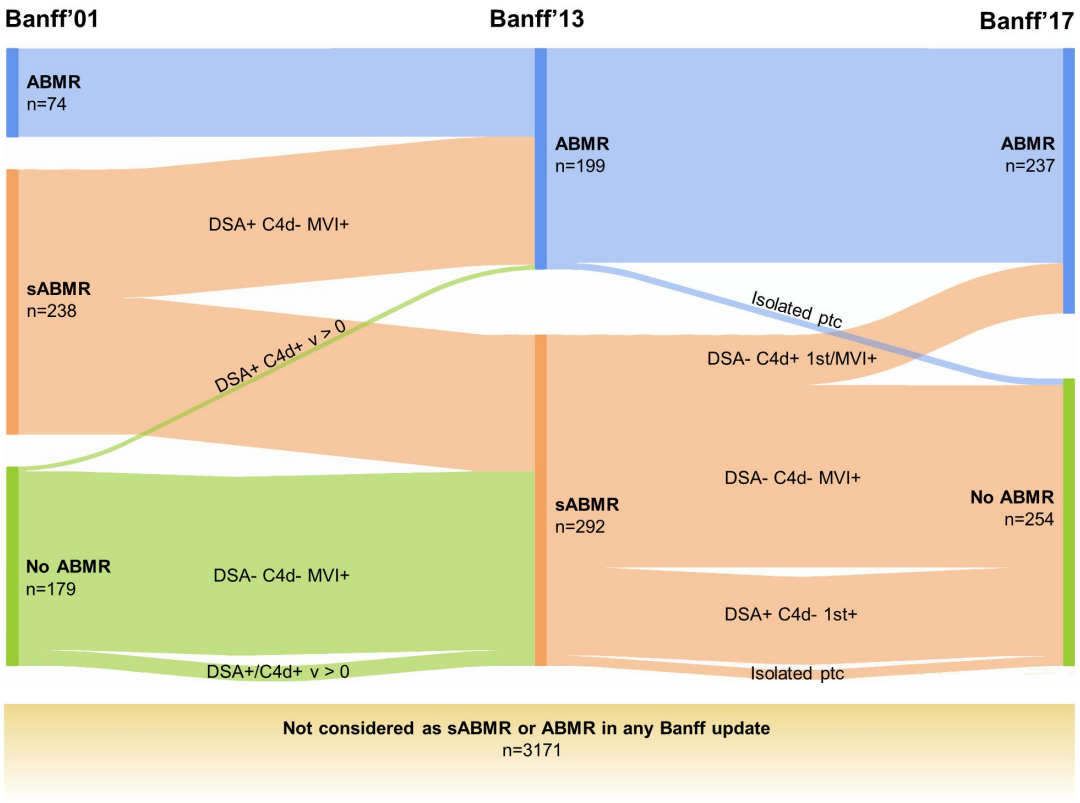
- Linear C4d staining in peritubular capillaries or medullary vasa recta
- At least moderate microvascular inflammation
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR

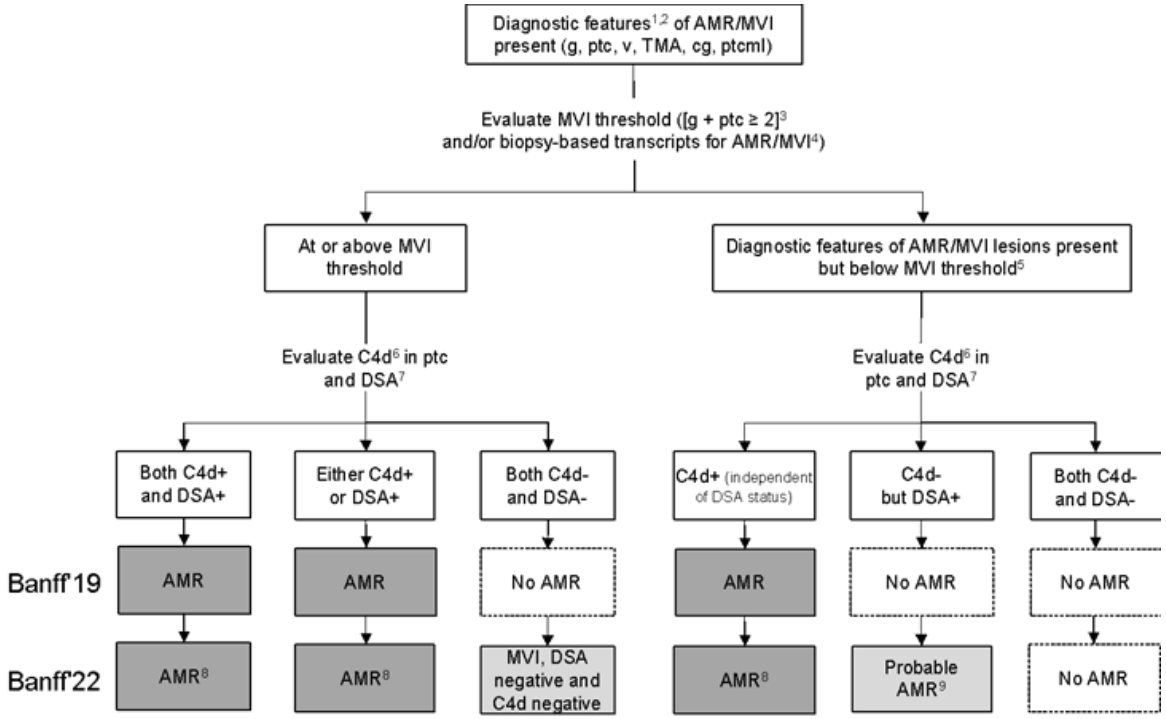
Serologic Evidence of Circulating Donor-specific Antibodies

- DSA to HLA or other antigens
- C4d staining or expression of validated transcripts/classifiers may substitute for DSA
- Thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

Loupy A, et al. *Am J Transplant.* 2020;20(9):2318-2331.

Proposed Changes for Banff 2022: Reintroduction of "Suspicious" Categories



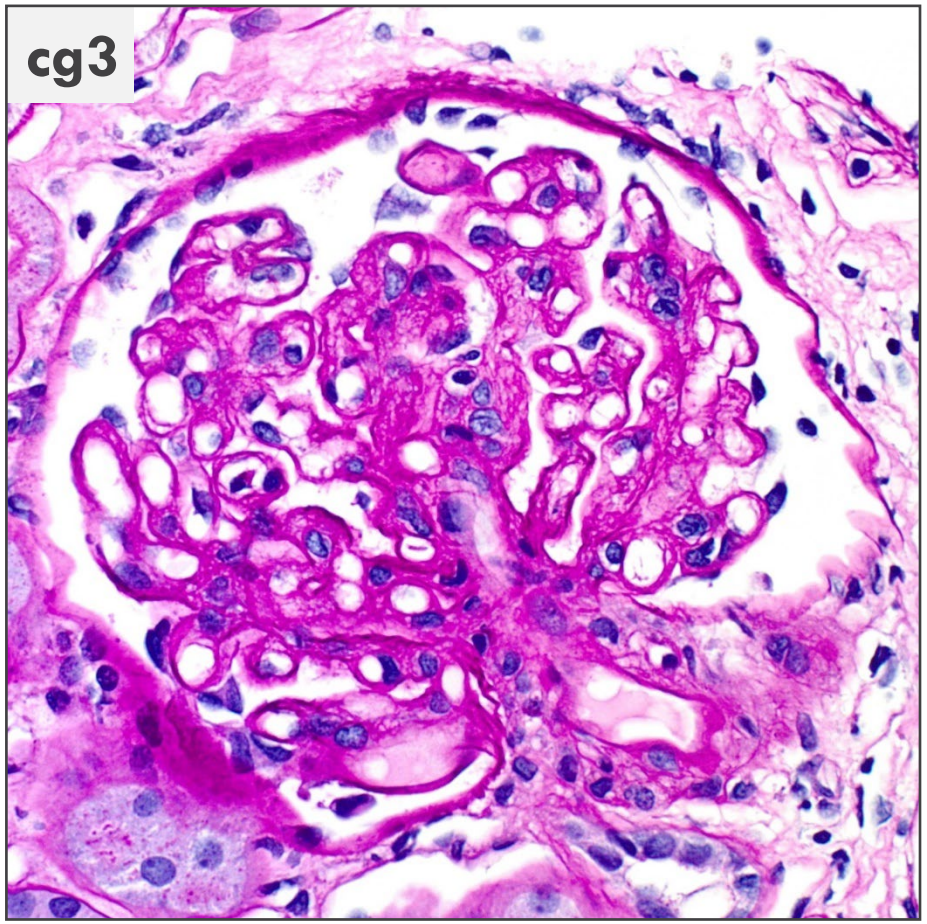


Unpublished

Callemeyn J, et al. *Am J Transplant*. 2021;21(7):2413-2423.

"Chronic": Transplant Glomerulopathy (cg-lesion)

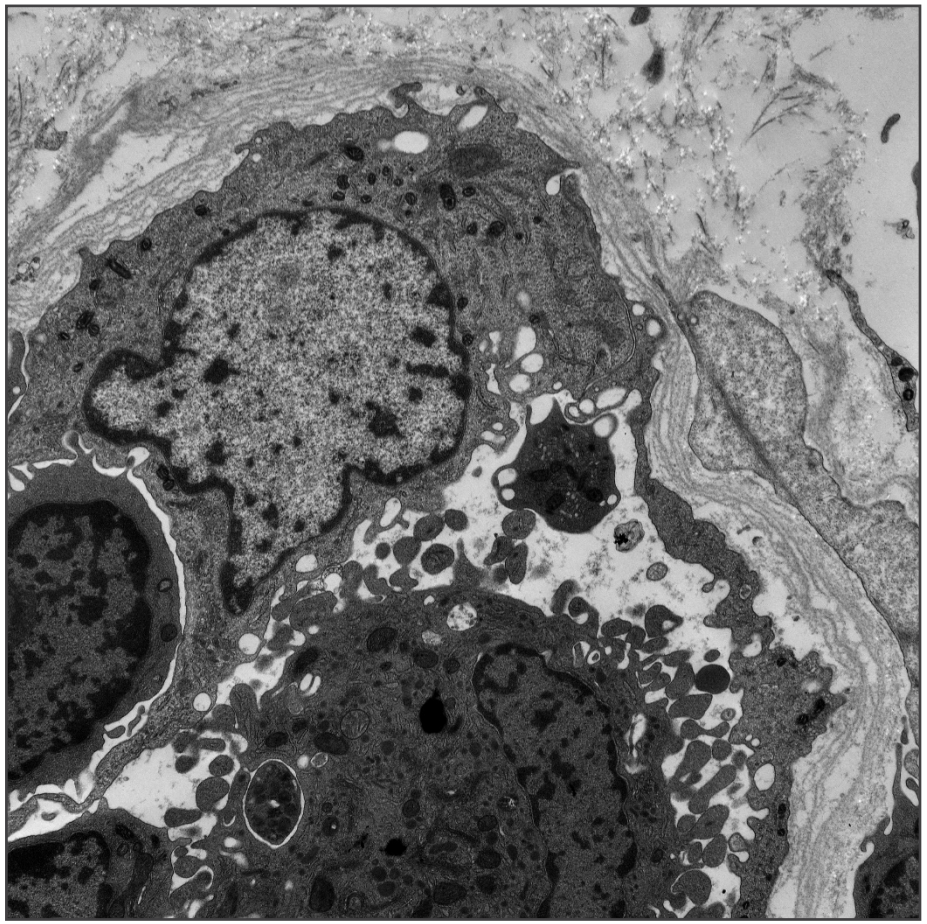
- GBM double contours in ≥1 capillary loop, graded in most severely involved glomerulus (Banff 2013)
  - cg0: No GBM double contours by LM or EM
  - cg1a: No GBM double contours by LM but present in ≥3 glomerular capillaries by EM with associated endothelial swelling and/or subendothelial widening
  - cg1b: GBM double contours by LM (involving <25% of peripheral capillary loops)
  - cg2: 26% to 50% of peripheral capillary loops
  - cg3: >50% of peripheral capillary loops



GBM. glomerular basement membranes

"Chronic": Peritubular Capillary BM Multi-lamination

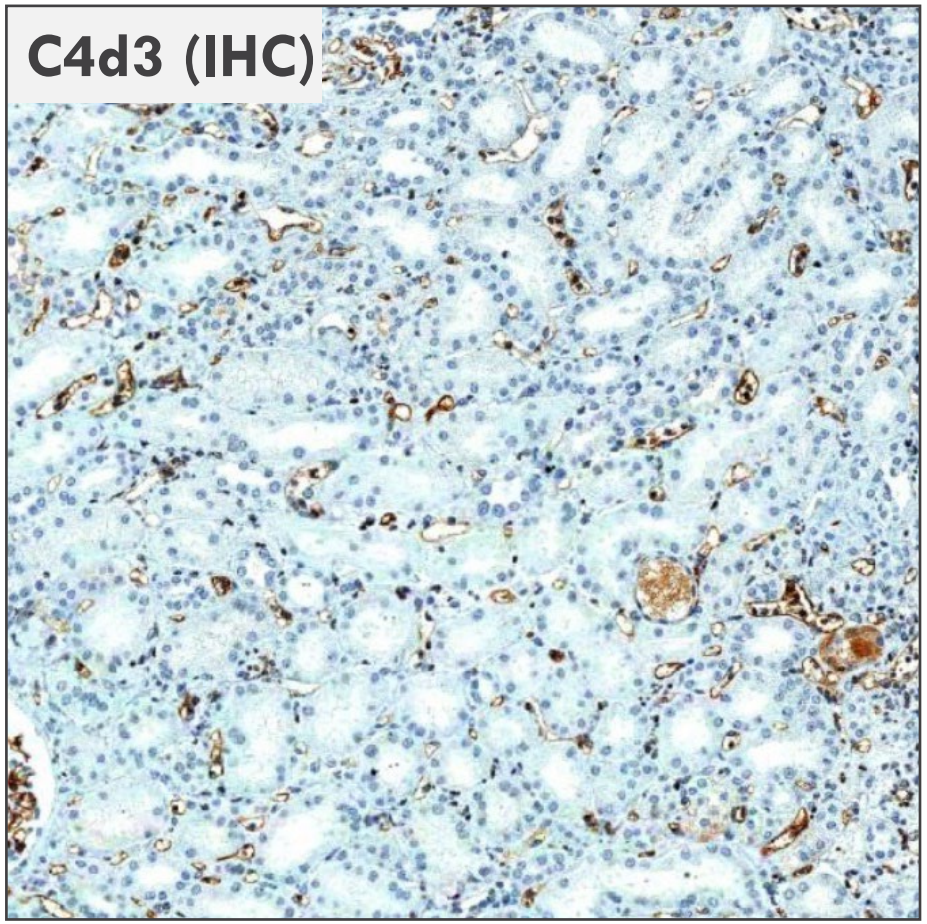
- Circumferential PTC basement membrane multi-lamination (EM)
  - Mild: 2 to 4 layers
  - Moderate: 5 to 6 layers
  - Severe: ≥7 layers
- Diagnostic criteria for "severe" PTCBMML
  - 1 PTC with ≥7 layers plus ≥2 with ≥5 layers
  - Based on 3 most affected of 15 to 20 PTC examined



PTC, peritubular capillary

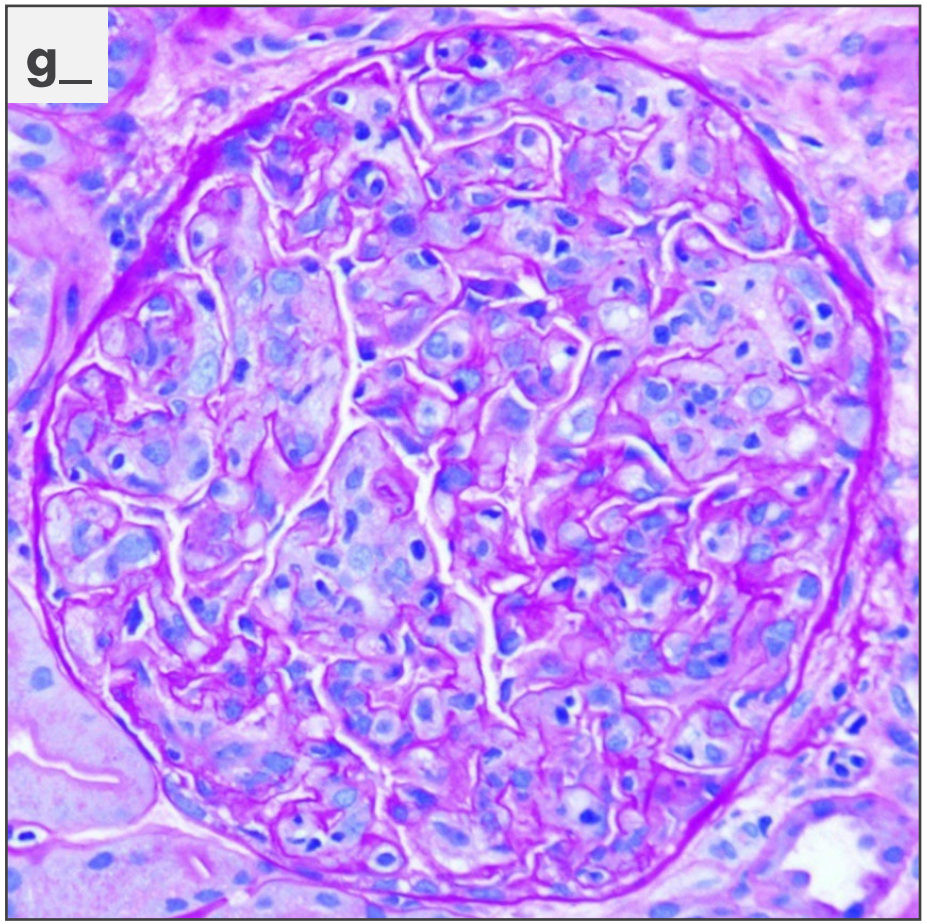
“Active”: C4d Staining (IF or IHC)

- Linear circumferential peritubular capillary staining in cortex/medulla, excluding scarred or necrotic areas (Banff 2003)
  - C4d0: No peritubular capillary staining
  - C4d1: <10% of peritubular capillaries
  - C4d2: 10% to 50% of peritubular capillaries
  - C4d3: >50% of peritubular capillaries
- Positive result:
  - IF: C4d≥2 (strong staining)
  - IHC: C4d≥1 (any staining)



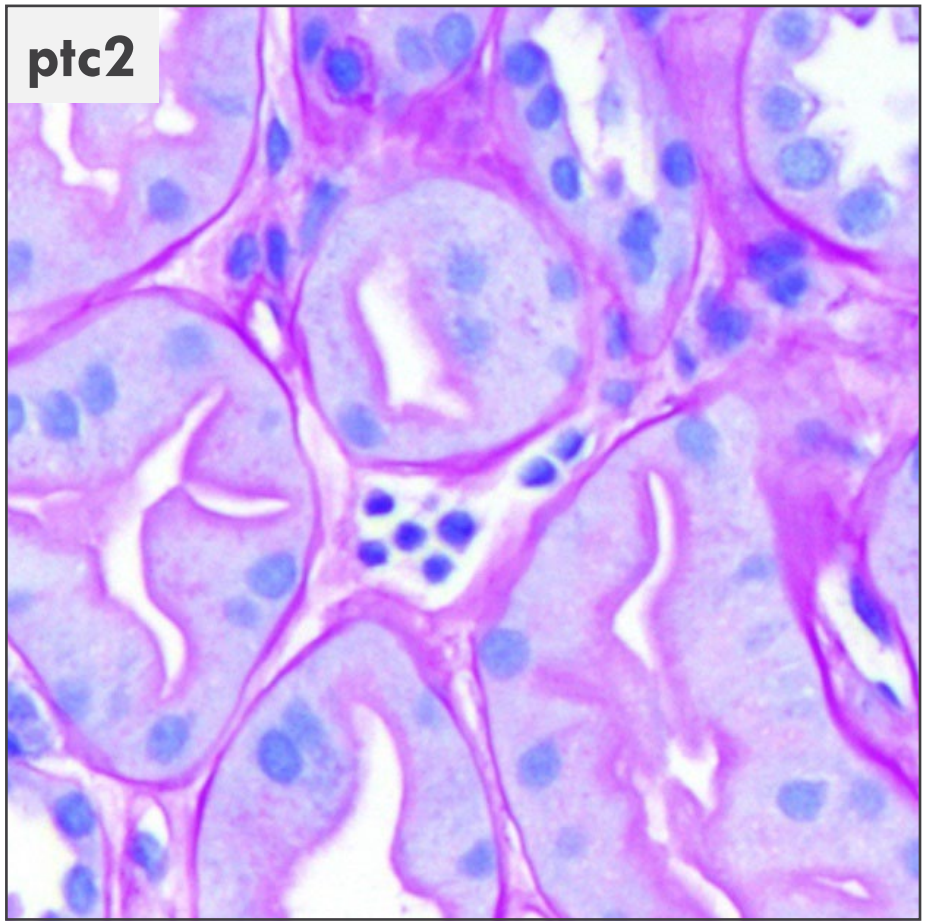
“Active”: Glomerulitis (g-lesion)

- Complete/partial occlusion of at least one glomerular capillary by leukocyte infiltration and endothelial cell enlargement (Banff 2013)
  - g0: No glomerulitis
  - g1: <25% of glomeruli
  - g2: 25% to 75% of glomeruli
  - g3: >75% of glomeruli (mostly global involvement)



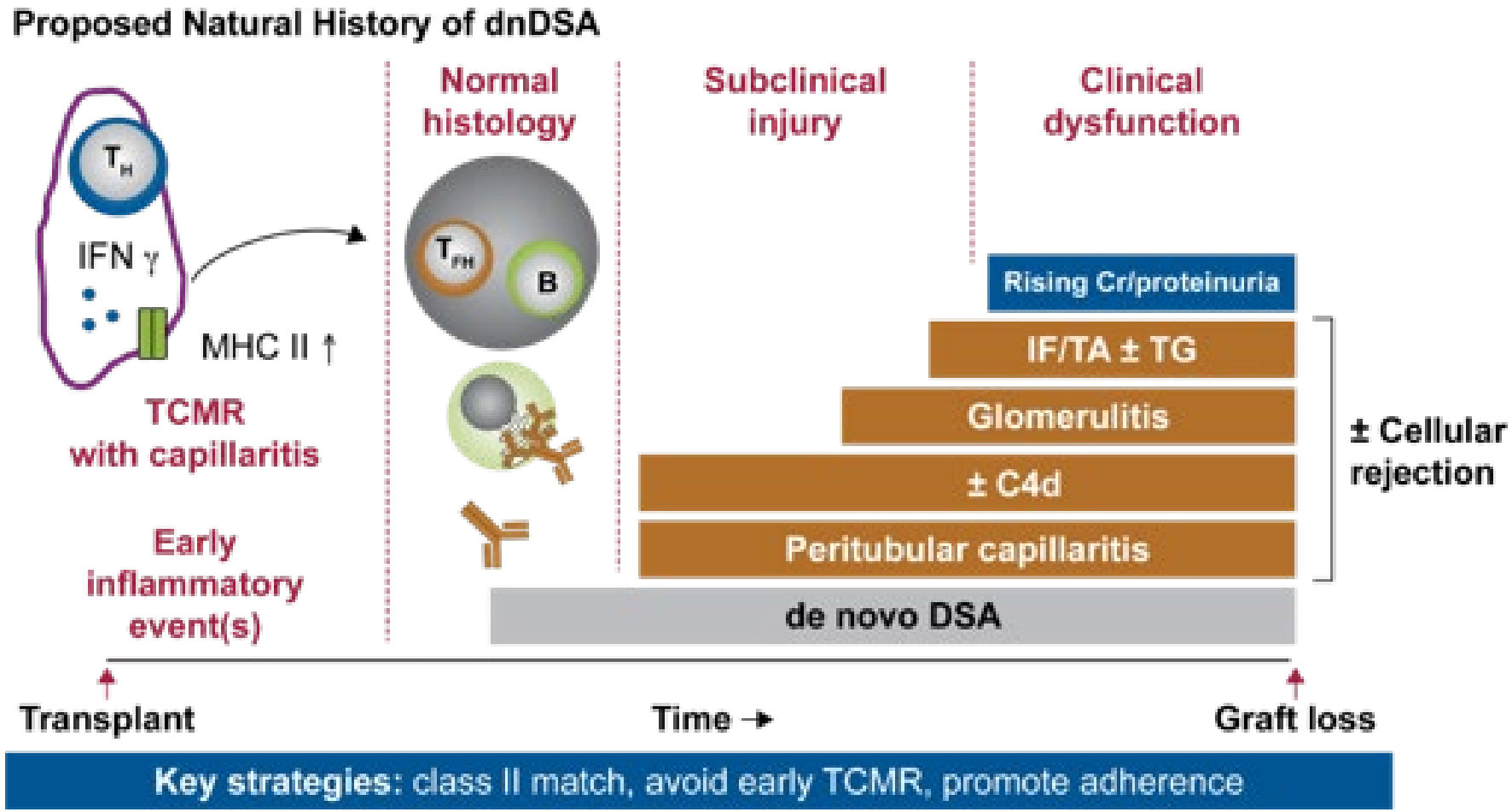
"Active": Peritubular Capillaritis (ptc-lesion)

- ≥10% of cortical peritubular capillaries with intraluminal inflammatory cells (Banff 2007)
  - ptc0: No significant peritubular capillaritis
  - ptc1: 3 to 4 luminal inflammatory cells
  - ptc2: 5 to 10 luminal inflammatory cells
  - ptc3: >10 luminal inflammatory cells



Note 1: Inflammation in <10%, regardless of intensity, is ptc0.
Note 2: Not scored in medulla, areas of pyelonephritis, adjacent to infarcts, or around nodular lymphoid aggregates.
Note 3: Should indicate if ptc is diffuse (>50%) or focal (≤50%).

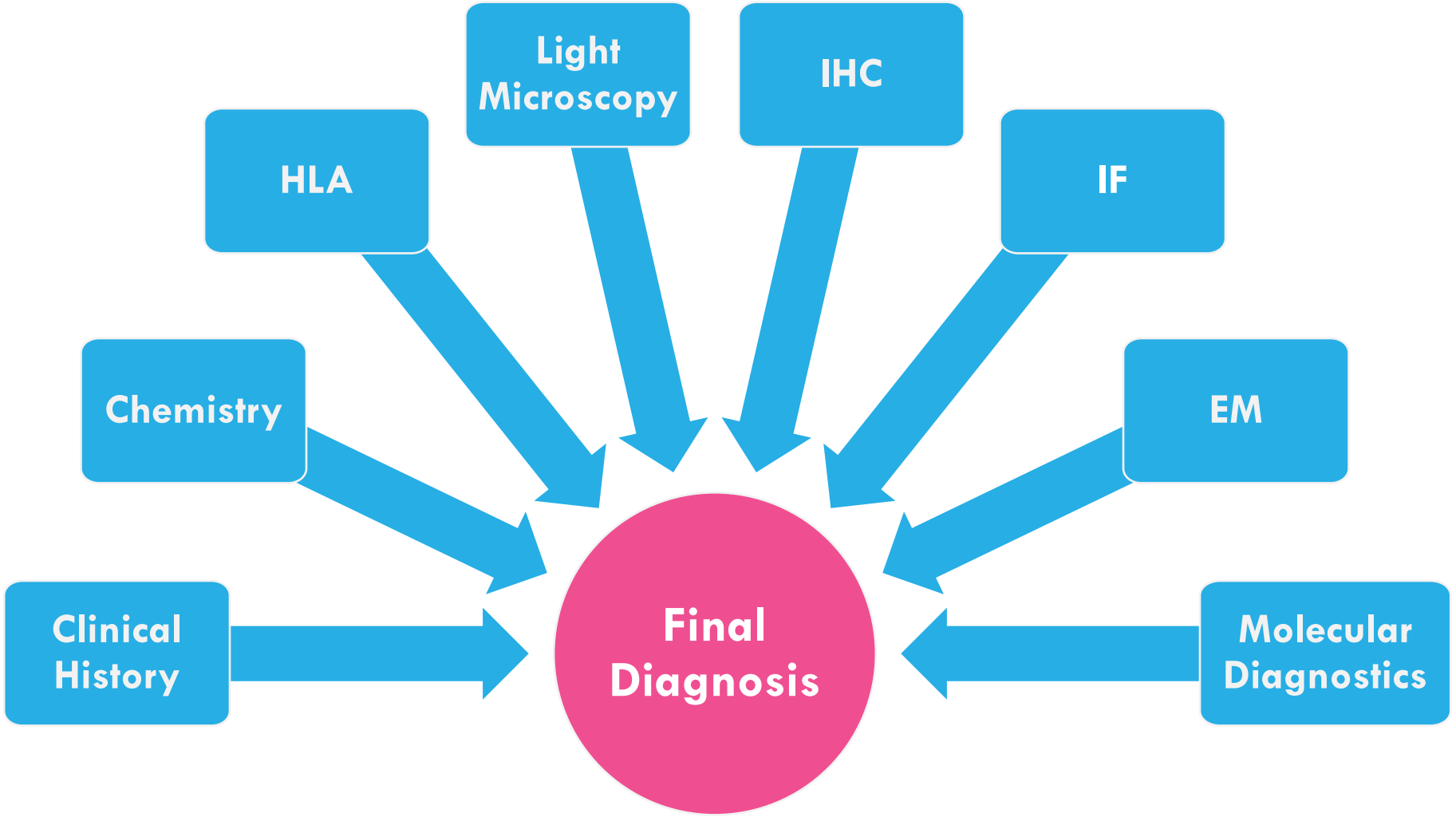
Natural History of ABMR Lesions



TCMR, T cell-mediated rejection

Wiebe C, et al. *Am J Transplant*. 2012;12(5):1157-1167.

Diagnostic Tools in Kidney Transplant Pathology



IHC, immunohistochemistry; IF, immunofluorescence; EM, electron microscopy

Banff Human Organ Transplant (B-HOT) Panel

A digital transcription analytics platform

Can use formalin fixed, paraffin embedded (FFPE) samples

Feature	Newer technology based on FFPE tissue	Fresh tissue with cDNA microarrays
Maximum number of transcript targets	**800**	**>47,000**
Off-the-shelf panels available	Yes	Yes
Custom panels available	Yes	Yes
Recommended RNA input quantity	100 ng	50 to 500 ng
Approximate assay turnaround time	24 to 40 hours	25.5 to 37.5 hours
Analysis software provided by manufacturer	Yes	Yes
Ability to use same sample for histology and gene expression	**Yes**	**No**
Immediate access to long-term clinical follow-up data on archival clinical samples	**Yes**	**No**
FDA approved	Yes	Yes
Approximate assay cost per sample	**$275**	**$1000 to $3000**
Integration with local clinical workflow	**Simple**	**Complex**

Mengel M, et al. *Am J Transplant*. 2020;20(9):2305-2317.

Challenges With Gene Expression

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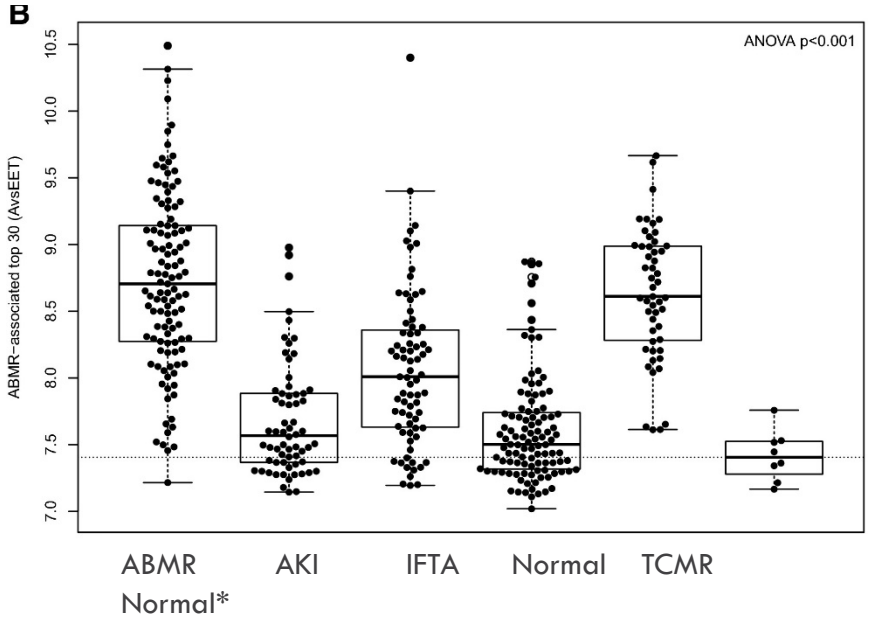
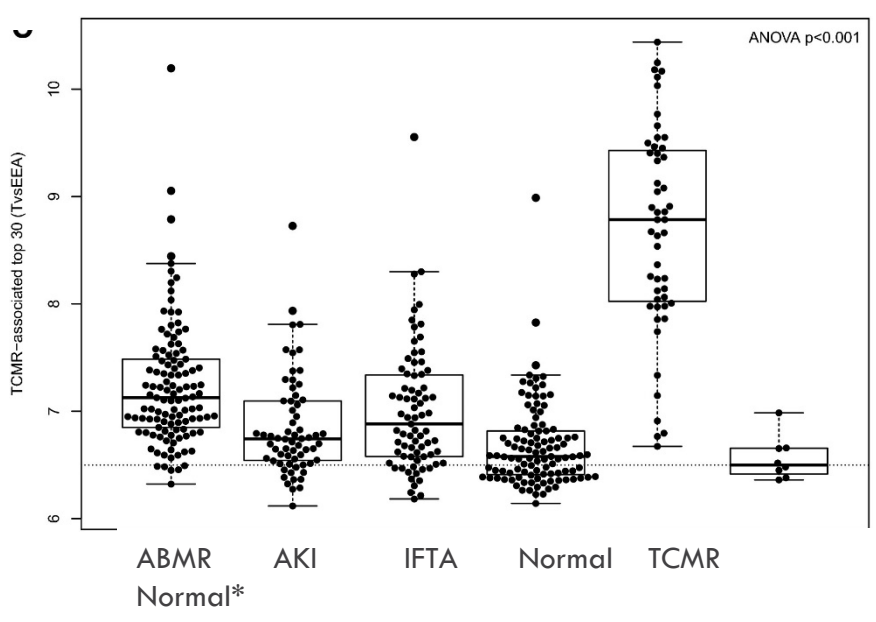
Top ABMR Associated Genes



Top TCMR Associated Genes



Overlap and non-specificity of transcripts

Discrepancy between histology and gene expression

No clear gold standard

Gene expression profiling disagrees with histology ~40% of the time!

Halloran PF, et al. *Am J Transplant*. 2017;17(7):1754-1769.
Madill-Thomsen K, et al. *Am J Transplant*. 2020;20(5):1341-1350.

Path Forward to Using Gene Expression in Practice

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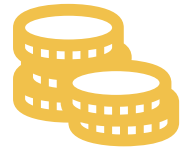
Multicenter standardization



Cost effectiveness

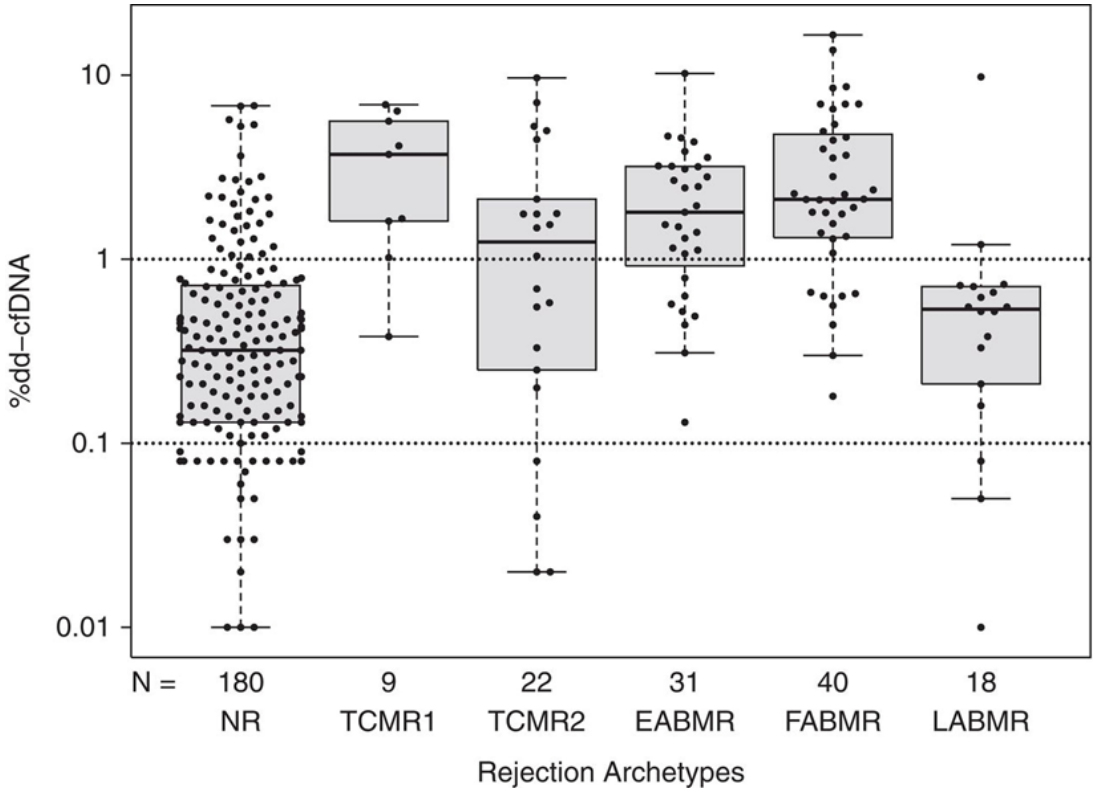
Independent validation

Fast turnaround time

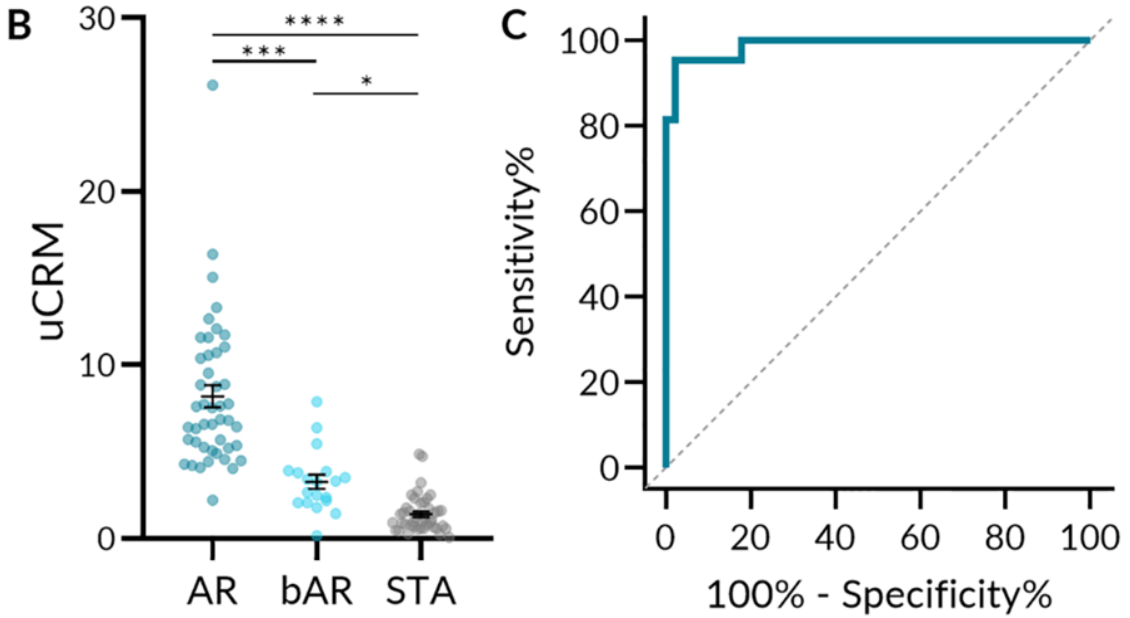
Defined clinical utility

Non-invasive Tools for Diagnosis of ABMR

Donor-derived cell-free DNA (Trifecta Study)



Urine gene expression (qPCR)



Halloran PF, et al. *J Am Soc Nephrol*. 2022;33(2):387-400.

Sigdel TK, et al. *PLoS One*. 2019;14(7):e0220052.

Non-invasive Tools for Diagnosis of ABMR

- Not currently part of the Banff Diagnostic Criteria
- Nonspecific
- $$$ Expensive for routine monitoring
- May have a role when a biopsy cannot be done (patient unable to travel or on anticoagulation)
- More research needs to be done

Comprehensive Banff Automation System: Artificial Intelligence and Multimodality Testing

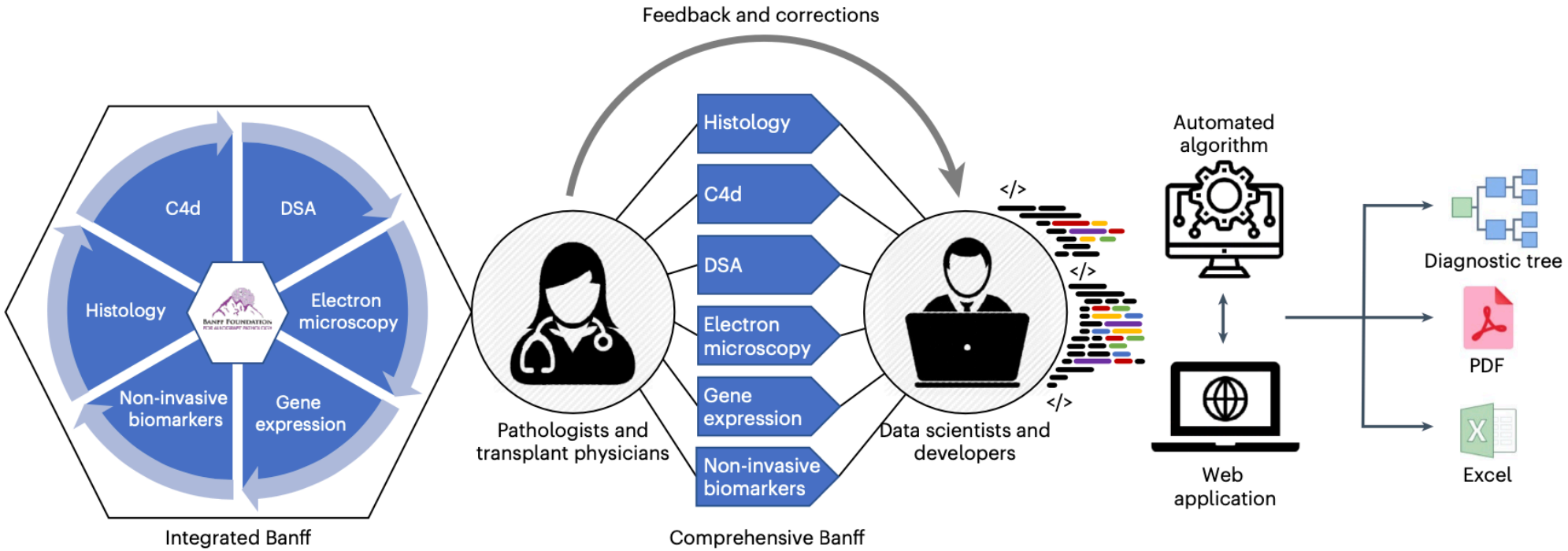
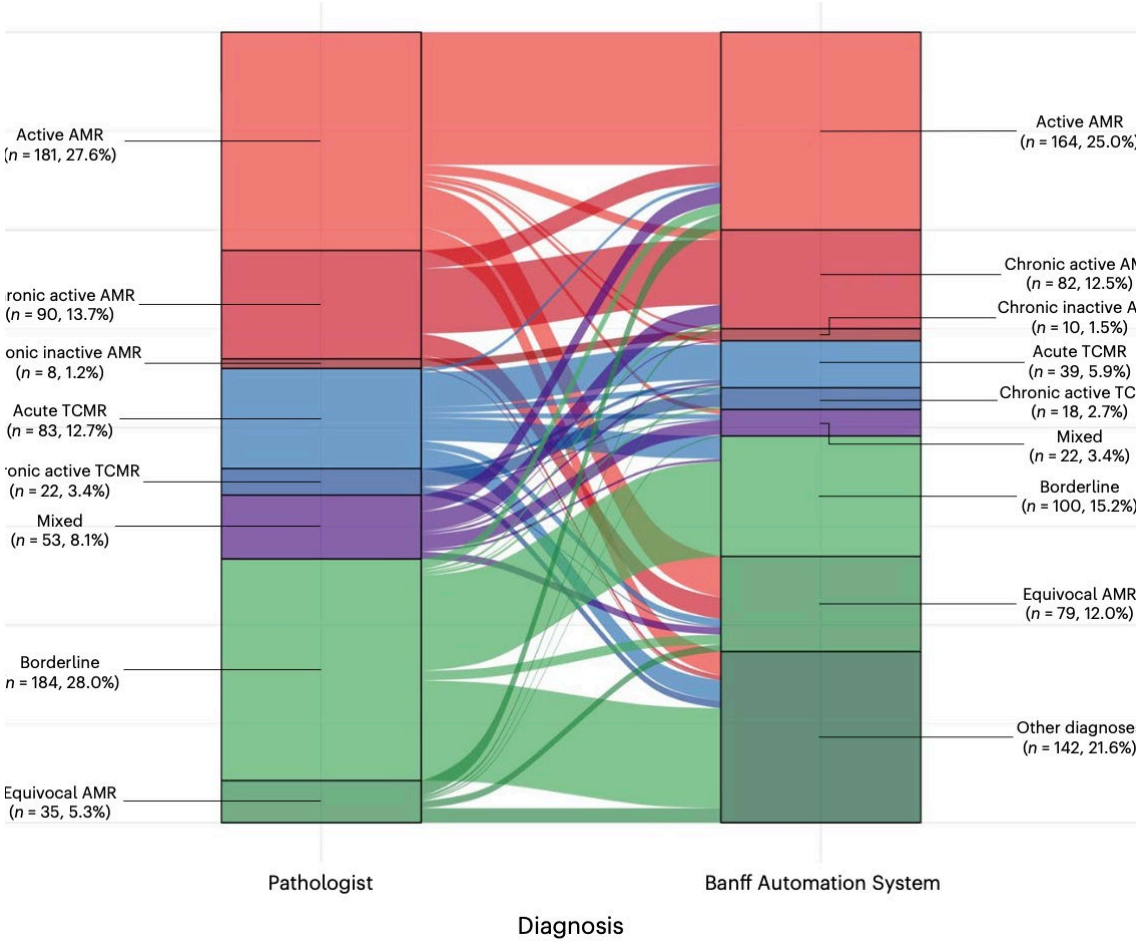
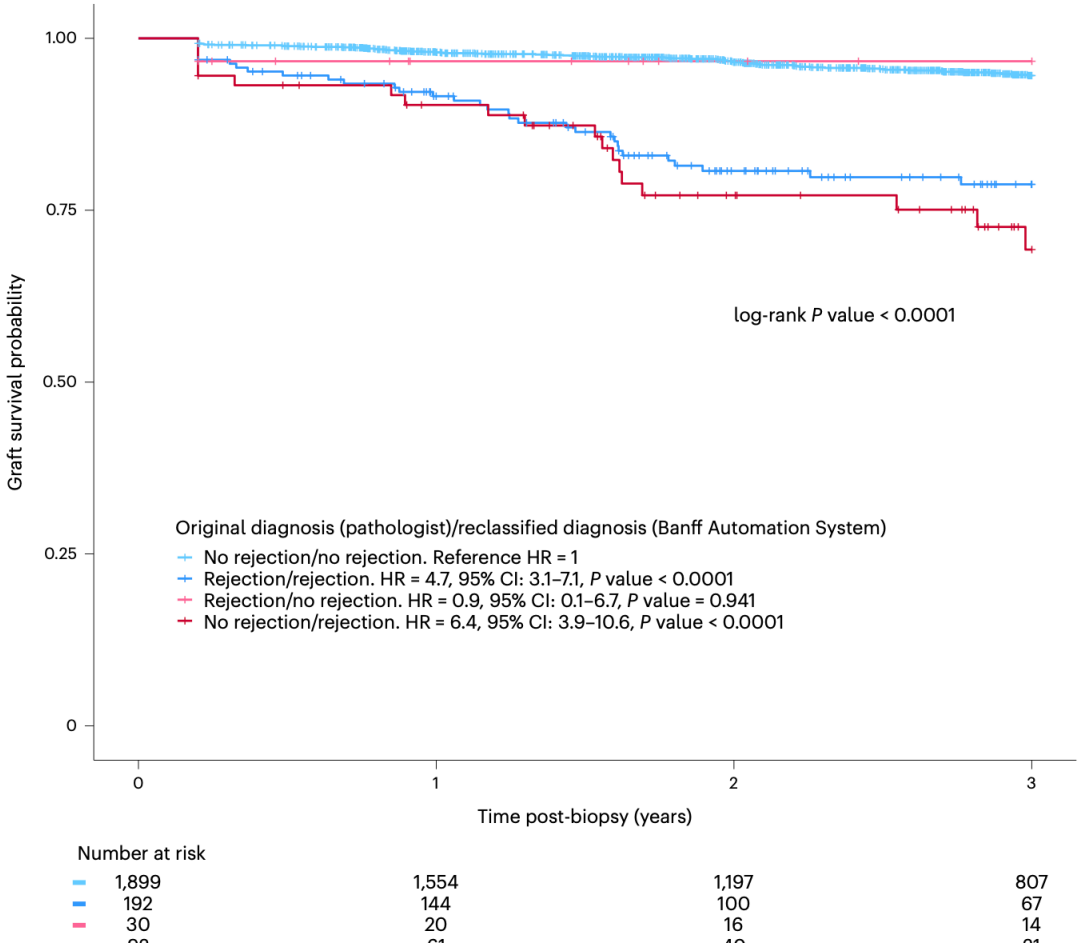


Fig. 1 | Development of the comprehensive Banff Automation System for kidney allograft precision diagnostics. Schematic diagram illustrating the decoding, encoding and rectifying processes used to construct the Banff Automation System. During the development process, the multidisciplinary consortium (pathologists, transplant physicians, data scientists and developers) worked closely together and improved the application numerous times. The outputs of the application are a decision tree for better visualization of the process that generates the diagnosis and automated reports in either PDF or Excel format. C4d, complement component C4d staining; DSA, donor-specific antibody.

Yoo D, et al, *Nat Med*. May 2023. Online ahead of print.

Clinical Impact of AI and Multimodality Testing





Yoo D, et al, *Nat Med*. May 2023. Online ahead of print.

Ongoing Challenges in ABMR Diagnosis

- Uncertain significance of:
  - Microvascular inflammation (in absence of DSA/C4d)
  - Antibody characteristics (quantity, locus, specificity)
  - Non-HLA DSA
- Clinical implementation of newer ancillary tools:
  - Gene expression
  - Donor-derived cell-free DNA
- Inter-relationship between ABMR and TCMR

Patient Video

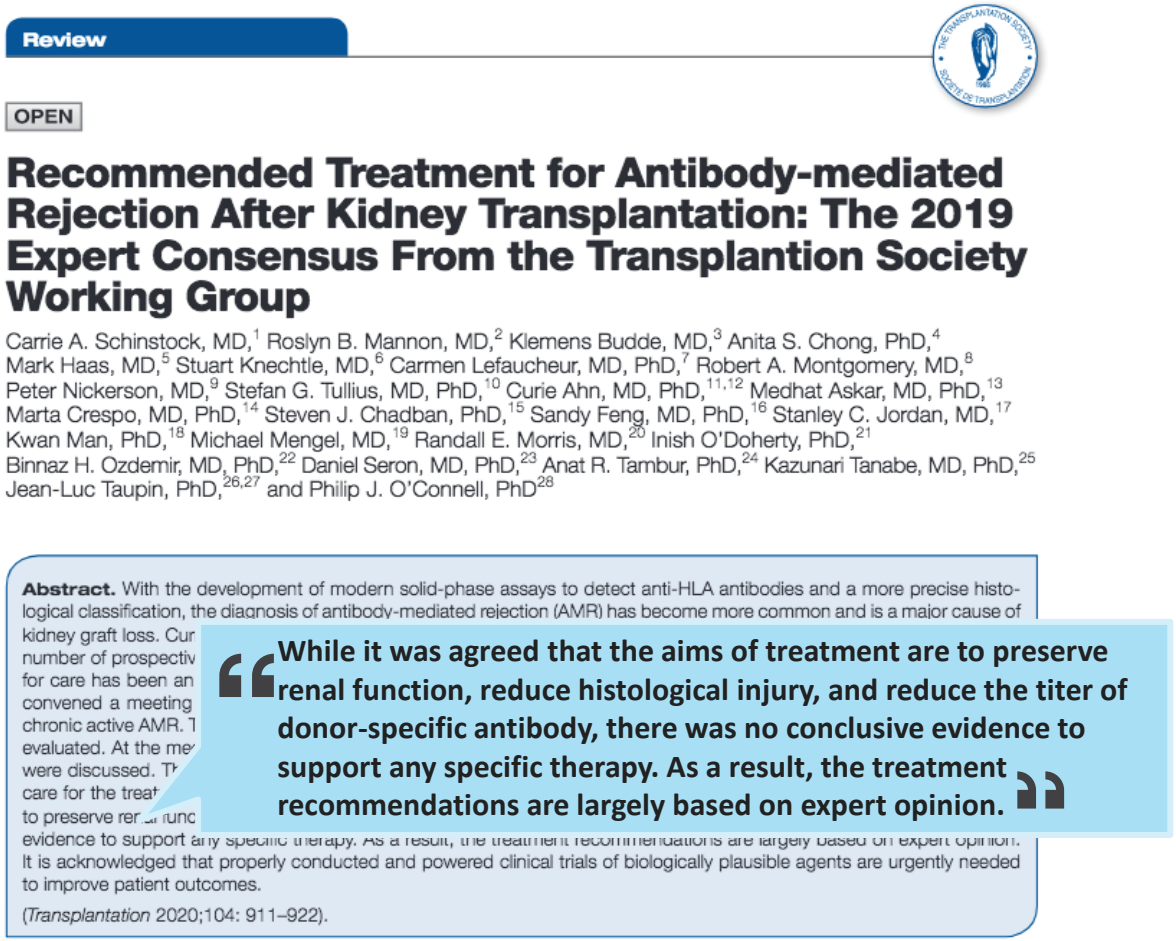
Panel Discussion

What new opportunities do you see on the horizon for newer technologies, such as digital pathology and artificial intelligence, in diagnosis and personalized medicine in ABMR?

Assessing the Clinical Potential of Emerging Therapies for Chronic Active ABMR in Kidney Transplant Recipients

Ashley A. Vo, PharmD, FAST
Professor, Pediatrics
David Geffen School of Medicine at UCLA
Director, Transplant Immunotherapy Program
Comprehensive Transplant Center
Cedars-Sinai Medical Center
Los Angeles, CA, United States

Current Treatments for Chronic Active ABMR



Review

OPEN

Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group

Carrie A. Schinstock, MD,[1] Roslyn B. Mannon, MD,[2] Klemens Budde, MD,[3] Anita S. Chong, PhD,[4] Mark Haas, MD,[5] Stuart Knechtle, MD,[6] Carmen Lefaucheur, MD, PhD,[7] Robert A. Montgomery, MD,[8] Peter Nickerson, MD,[9] Stefan G. Tullius, MD, PhD,[10] Curie Ahn, MD, PhD,[11,12] Medhat Askar, MD, PhD,[13] Marta Crespo, MD, PhD,[14] Steven J. Chadban, PhD,[15] Sandy Feng, MD, PhD,[16] Stanley C. Jordan, MD,[17] Kwan Man, PhD,[18] Michael Mengel, MD,[19] Randall E. Morris, MD,[20] Inish O'Doherty, PhD,[21] Binnaz H. Ozdemir, MD, PhD,[22] Daniel Seron, MD, PhD,[23] Anat R. Tambur, PhD,[24] Kazunari Tanabe, MD, PhD,[25] Jean-Luc Taupin, PhD,[26,27] and Philip J. O'Connell, PhD[28]

Abstract. With the development of modern solid-phase assays to detect anti-HLA antibodies and a more precise histological classification, the diagnosis of antibody-mediated rejection (AMR) has become more common and is a major cause of kidney graft loss. Cur
number of prospectiv
for care has been an
convened a meeting
chronic active AMR. T
evaluated. At the me
were discussed. Th
care for the treat
to preserve ren
evidence to support any specific therapy. As a result, the treatment recommendations are largely based on expert opinion.
It is acknowledged that properly conducted and powered clinical trials of biologically plausible agents are urgently needed to improve patient outcomes.

(*Transplantation* 2020;104: 911–922).

"While it was agreed that the aims of treatment are to preserve renal function, reduce histological injury, and reduce the titer of donor-specific antibody, there was no conclusive evidence to support any specific therapy. As a result, the treatment recommendations are largely based on expert opinion."

IL-6, interleukin-6; Tfh, T follicular helper

Schinstock A, et al. *Transplantation.* 2020;104(5):911-922.

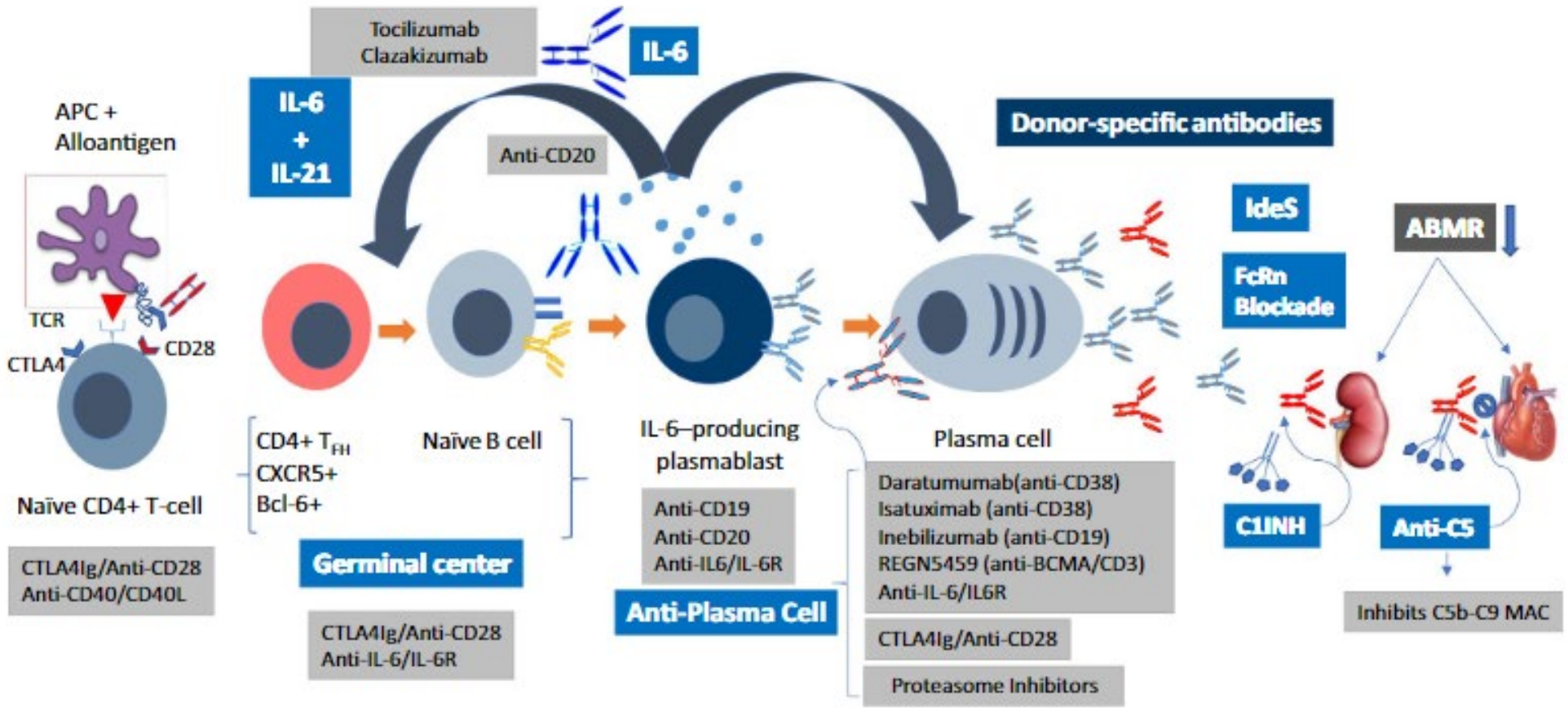
Ideal agent for treatment of cABMR:

- Remove alloantibody
- Prevent ADCC and CDC
- Reduce pathologic markers of injury
- Prevent antibody rebound
- Improve patient and graft outcomes

Aim: Discuss emerging treatments for cABMR based on targeting essential elements of the antibody response to allografts. These include:

- Pathogenic IgG antibodies
- Cytokines (IL-6)
- B-cells & plasma cells

Emerging Therapeutic Approaches to Reducing Alloantibody Injury to Allografts



APC, antigen presenting cell; APRIL, A Proliferation-Inducing Ligand; BAFF, B-cell activating factor; Bcl-6: B-cell lymphoma 6 protein; BCMA, B-cell maturation antigen; CD19: Cluster of Differentiation 19; CXCR5, C-X-C chemokine receptor type 5; C1Q, first component of complement q; TCR, T-cell receptor

Jordan S, et al. *Am J Transplant*. 2020;20(Suppl 4):42-56.

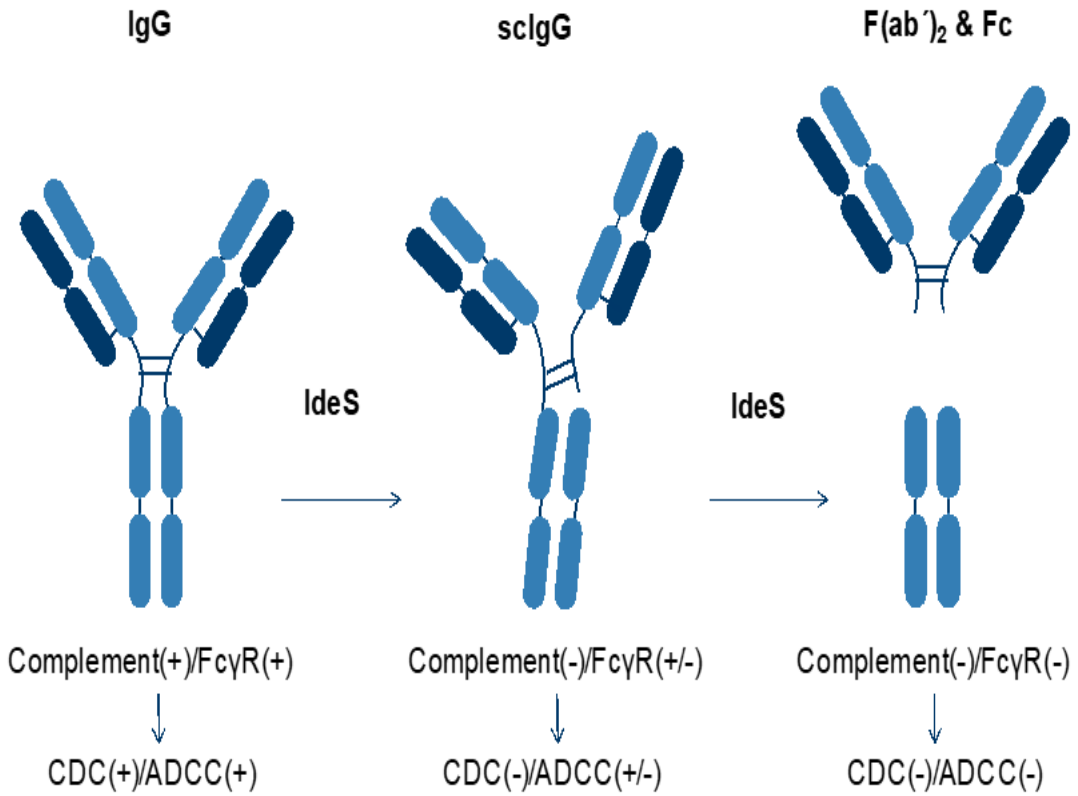
New Beginnings

Antibody-Directed Therapies

Emerging Treatments

IgG Degradation	Anti-IL-6	FcRn Blockers	Anti-CD38/ Anti-BCMA
Imlifidase	Tocilizumab Clazakizumab	Rozanolixizumab	Daratumumab

Imlifidase Mechanism of Action Implications for CDC and ADCC

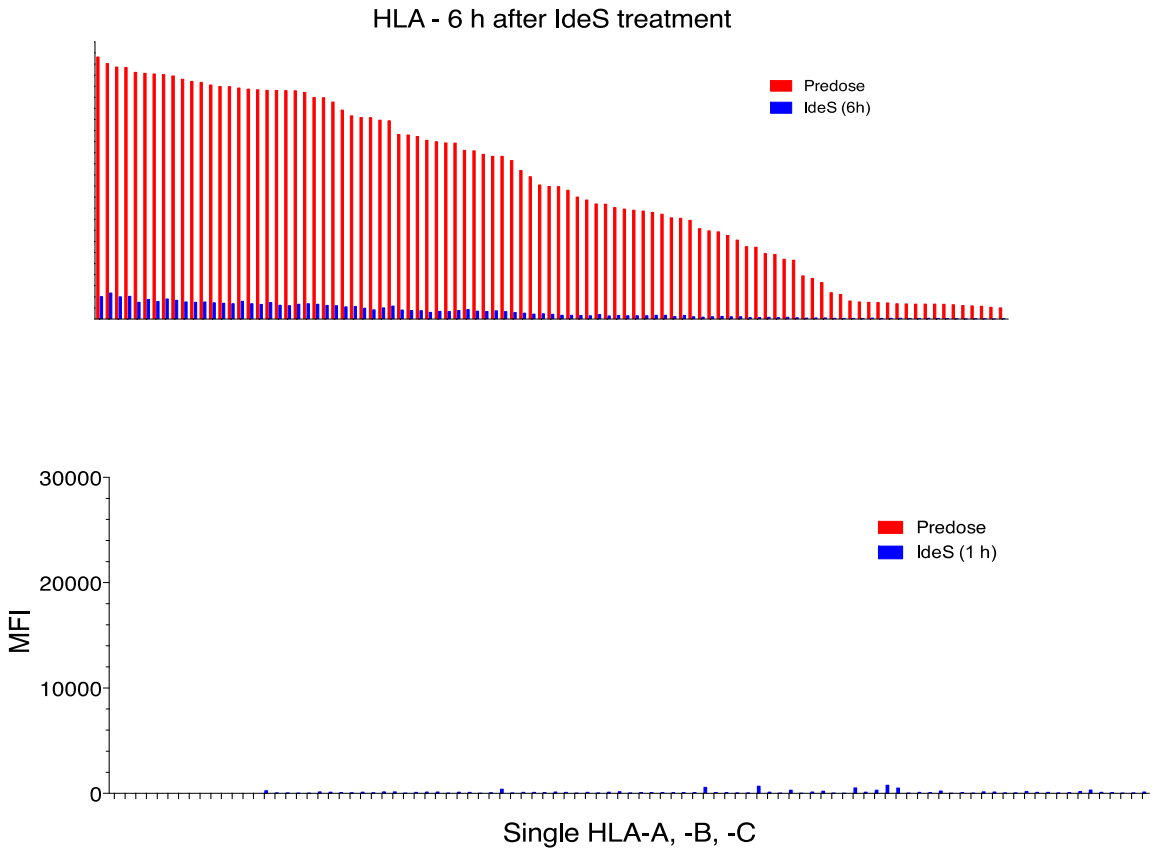


- An IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS)
- Targets pathogenic IgG molecules
- Approved by the European Union for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor
- Not approved by the FDA or in Switzerland

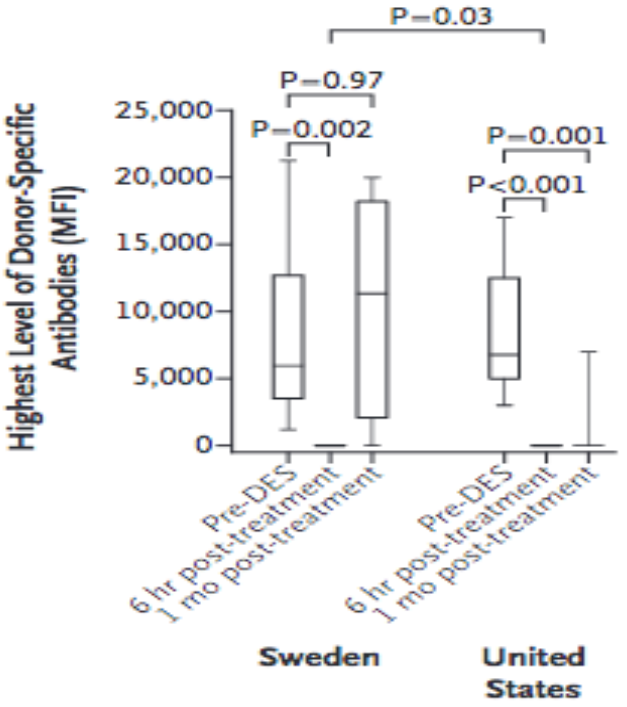
Jordan SC, et al. *N Engl J Med*. 2017;377(5):442-453.

Imlifidase for Desensitization

Imlifidase eliminates pathogenic IgG molecules within hours, preventing ADCC and CDC



Median highest levels of DSAs



Post-transplant IVIg + rituximab
Prevents DSA Rebound!

Jordan SC, et al. *N Engl J Med*. 2017;377(5):442-453.

Emerging Treatments

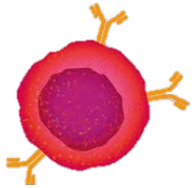
CARE TEAM FORUM®

IgG Degradation	Anti-IL-6	FcRn Blockers	Anti-CD38/ Anti-BCMA
Imlifidase	Tocilizumab Clazakizumab	Rozanolixizumab	Daratumumab

IL-6: Pleiotropic Cytokine Impacting Multiple Organ Systems

CARE TEAM FORUM®

Immune Cells

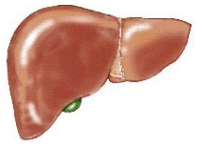


1. **Stimulate B-cells differentiation to antibody producing plasma cells**
2. **Plasma cell and myeloma cell growth factor**
3. Maintains Th1 and Th2 cell activities
4. **Increases Th17 and Tfh cells**
5. **Decreases Tregs**

Lungs

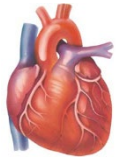
1. Cytokine Release Syndrome
2. Severe pneumonia
3. Pleural effusions /fibrosis
4. Death

Liver



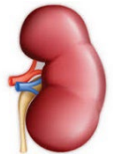
1. Increase CRP
2. Increase Serum Amyloid A
3. Increase Fibrinogen
4. Increase Hepcidin (anemia of chronic disease)
5. Decreases albumin and transferrin

Cardiac



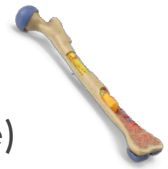
1. Increase VEGF to increase angiogenesis
2. Increase risk for coronary artery disease
3. Increases mortality from cardiovascular disease in ESRD patients

Kidney



1. Increase mesangial cell proliferation
2. Contributes to glomerular crescent formation
3. **Contributes to chronic antibody rejection of kidney allografts**

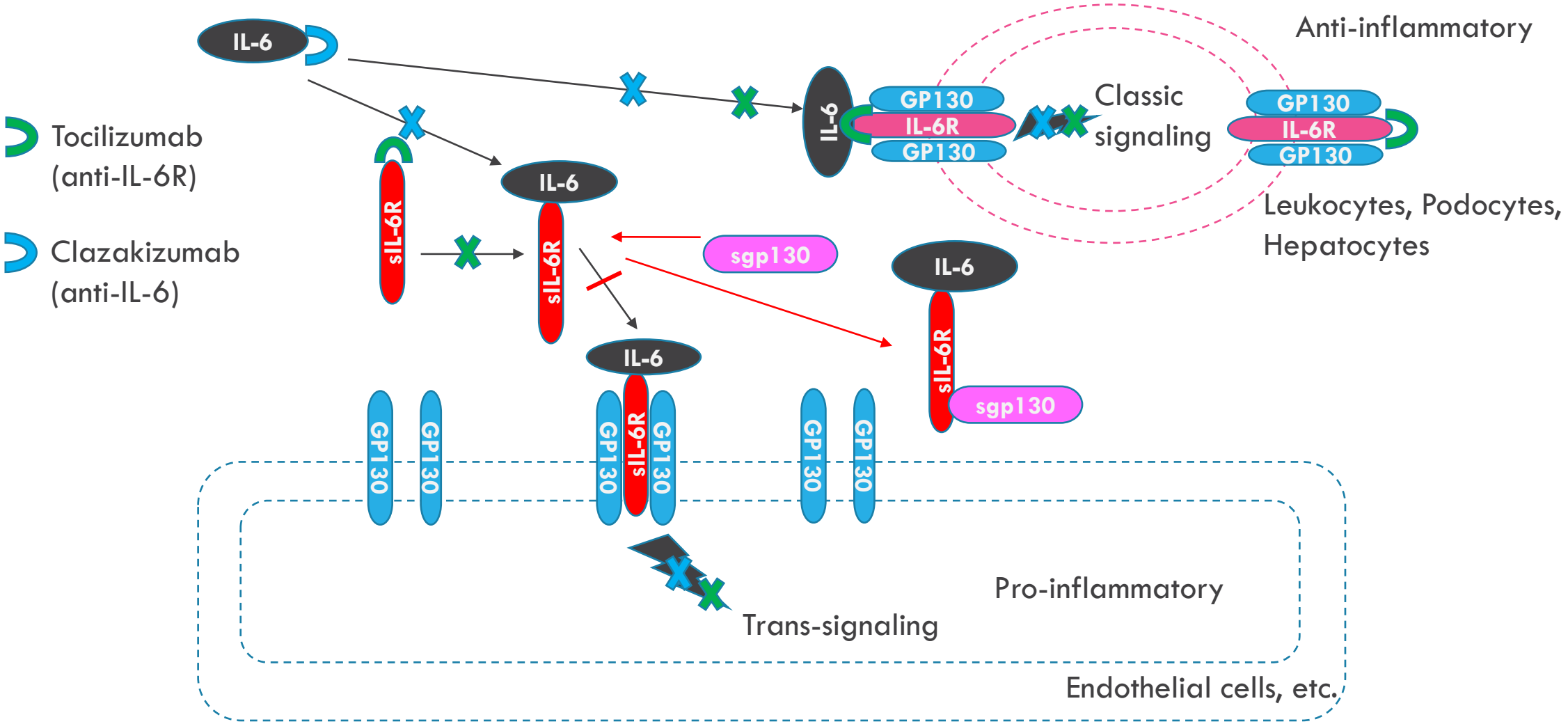
Bone Marrow, Synovial Fibroblast



1. Increase osteoclast differentiation
2. Increase angiogenesis
3. Increase platelet
4. Responsible for joint damage in RA

Jordan SC, et al. *Transplantation*. 2017;101(1):32-44.

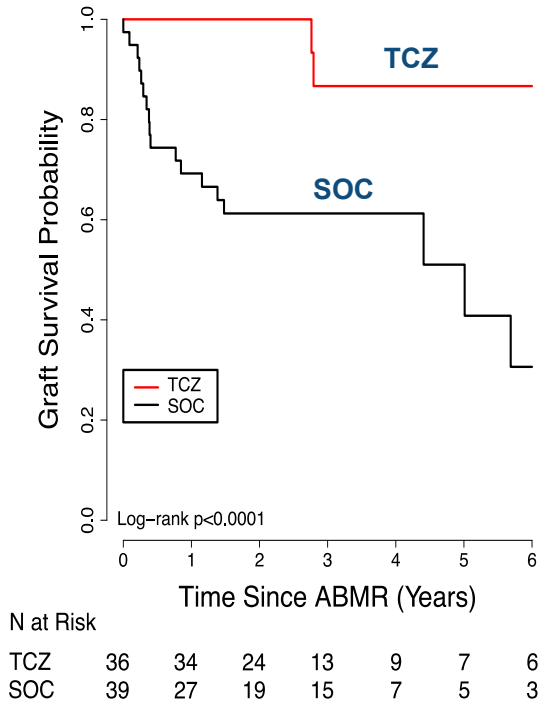
IL-6 Signaling and Its Blockade

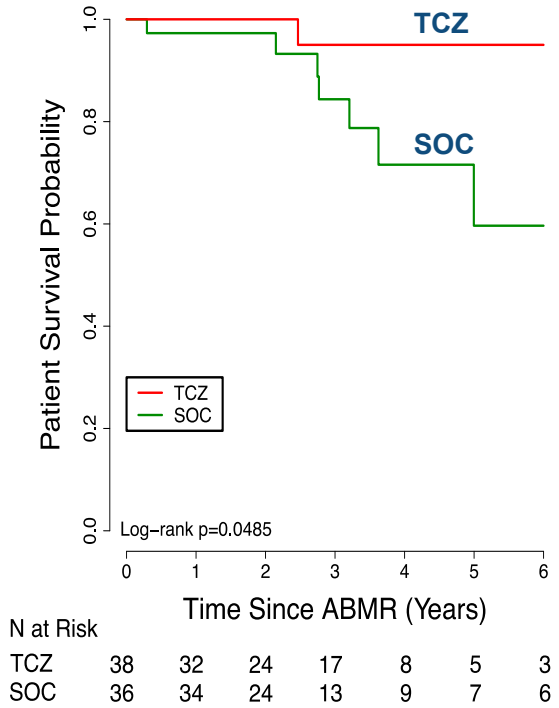


Slide courtesy of: Bong-Ha Shin, PhD

IL-6: Important cABMR Target

Allograft and Patient Survival in Patients Treated with Tocilizumab* for Chronic Active ABMR





Anti-IL-6R treatment improved both patient and graft survival

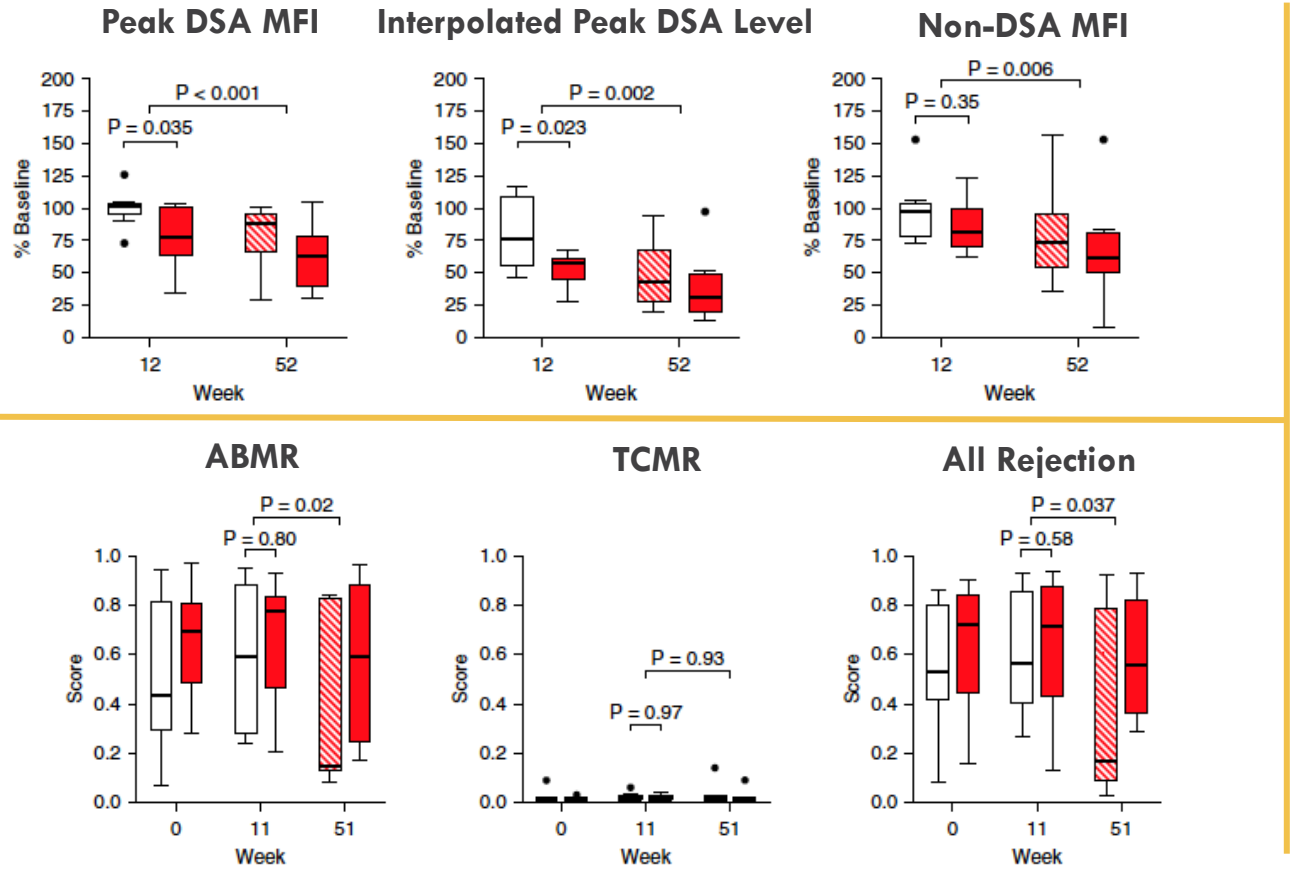
TCZ, tocilizumab; SOC, standard of care

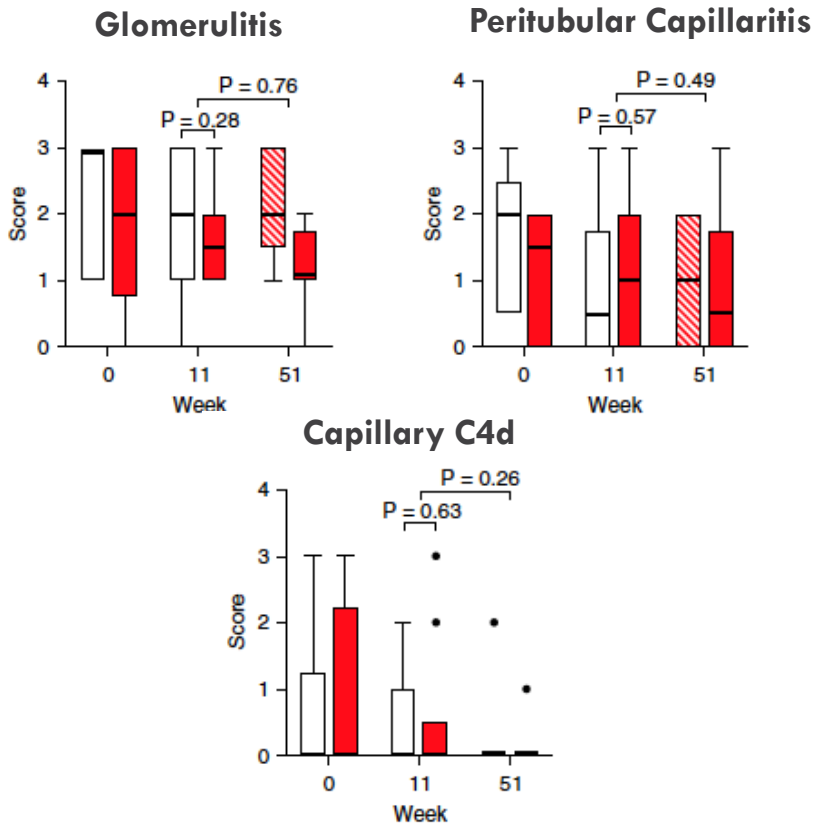
*The use of tocilizumab in kidney transplantation is off-label in Switzerland and Europe.

Choi J, et al. *Am J Transplant.* 2017;17(9):2381-2389.

Clazakizumab in cABMR

Clazakizumab* Decreases DSAs and Banff Pathology Scores and Improves Graft Function and Survival



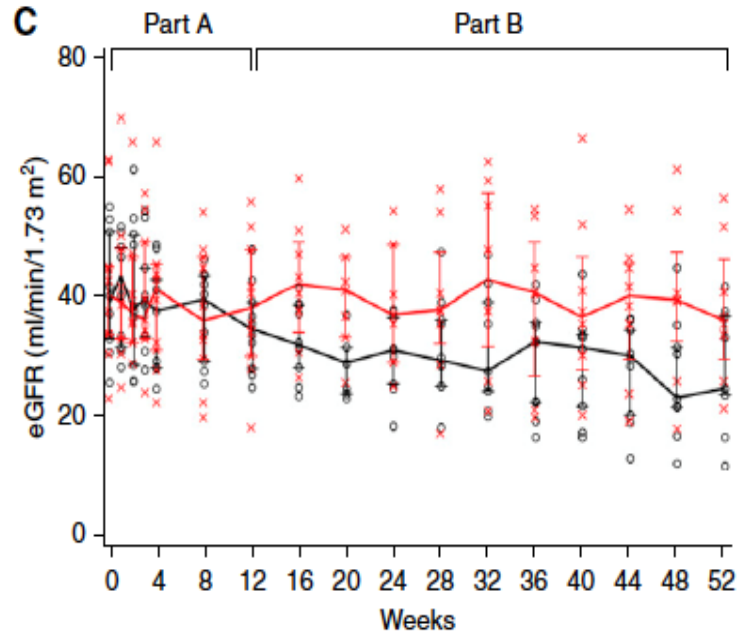


*Clazakizumab is not approved in the United States, Switzerland, nor the European Union.

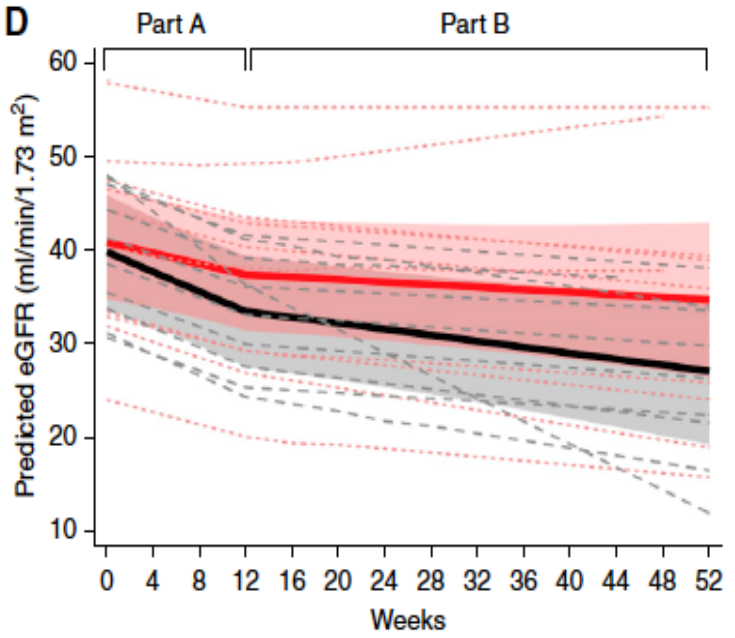
Doberer K, et al. *J Am Soc Nephrol*. 2021;32(3):708-722.

Clazakizumab Stabilizes GFR versus Placebo

Median, Interquartile Range, and Individual Levels of eGFR in Relation to Treatment Allocation in Part A



Individual and Mean eGFR in Relation to Treatment Allocation in Part A



— Clazakizumab*
— Placebo

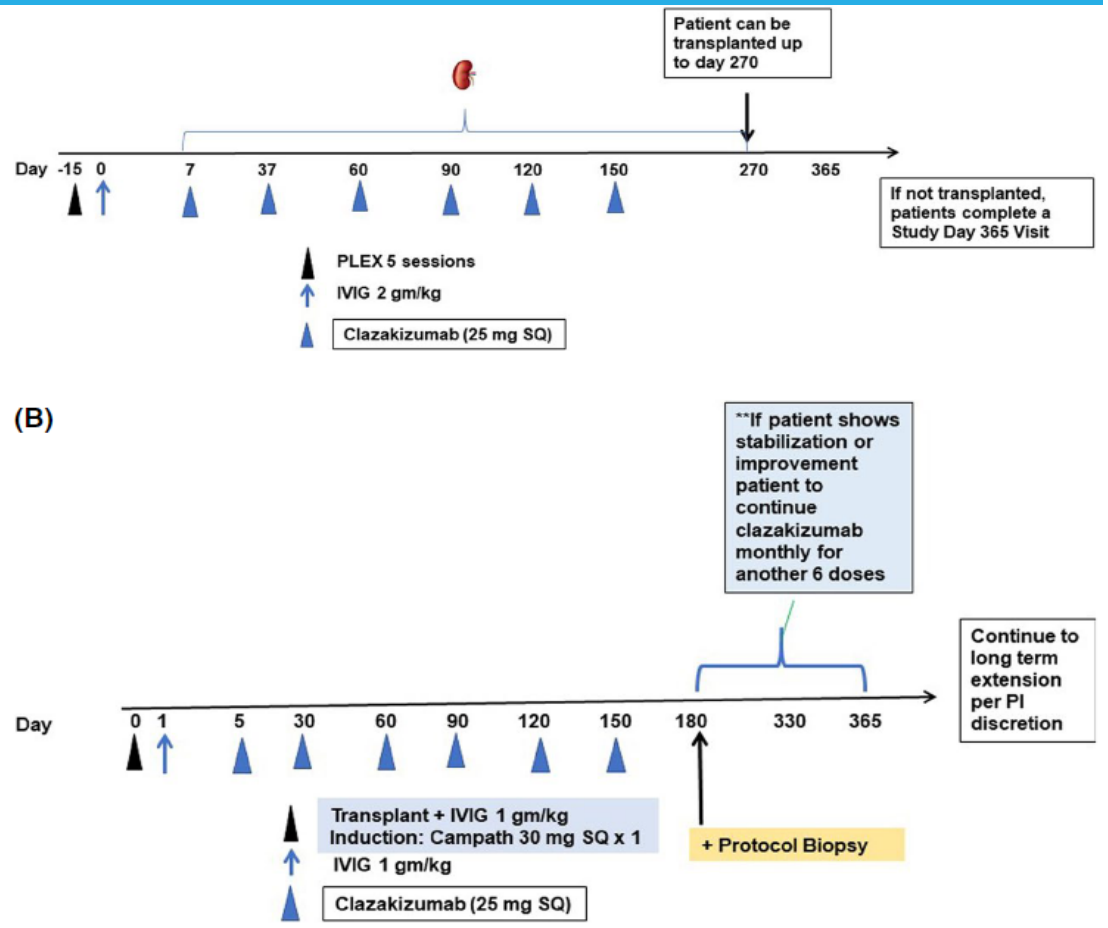
- Clazakizumab*: Red line
- Placebo: Black line
- Individual: Dashed lines
- Mean eGFR: Solid Lines
- 95% CIs: Shaded areas

*Clazakizumab is not approved in the United States, Switzerland, nor the European Union.

Doberer K, et al. *J Am Soc Nephrol*. 2021;32(3):708-722.

Clazakizumab for Desensitization

Await an acceptable crossmatch/DSA reduction → transplant



Regimen

Patients received PLEX + IVIG, then anti-IL-6 25 mg SQ monthly

Evaluation

Changes in MFI for all HLA antibodies and DSAs evaluated at 6 months (study end)

Post-transplant

Anti-IL-6 continued post-transplant

*Clazakizumab is not approved in the United States, Switzerland, nor the European Union.

Vo AA, et al. *Am J Transplant*. 2022;22(4):1133-1144.

Effects of Anti-IL-6 Desensitization

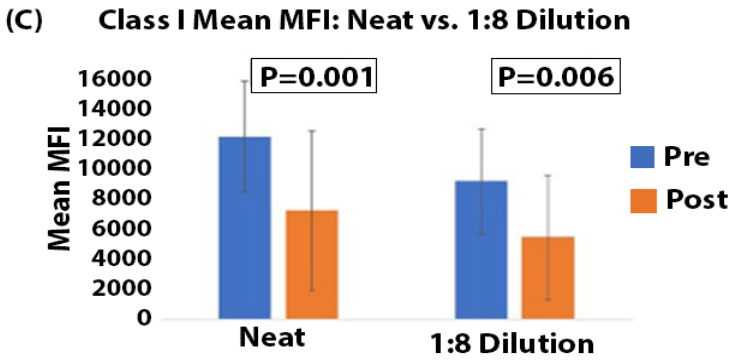
Time from dialysis to transplant: 92 ± 54M

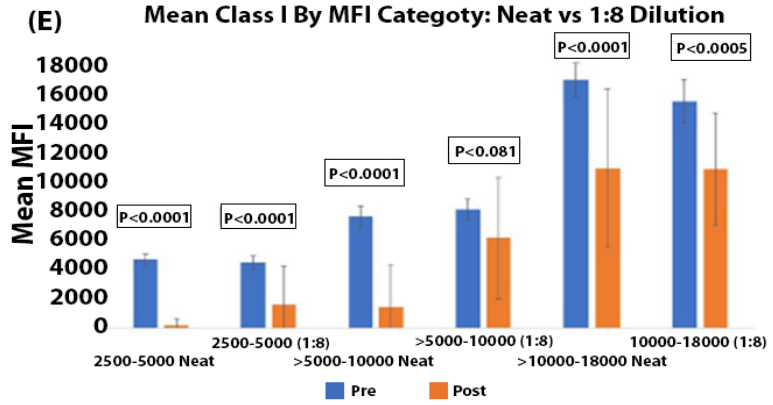
Time from last clazakizumab to transplant: 2.9 ± 4.0M

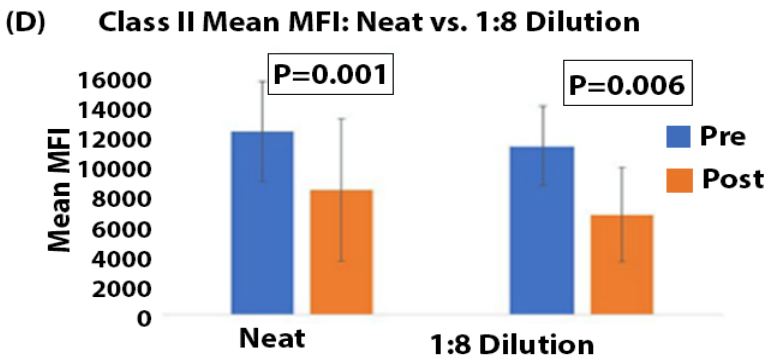
60% of patients had CPRA >99.5% to100%

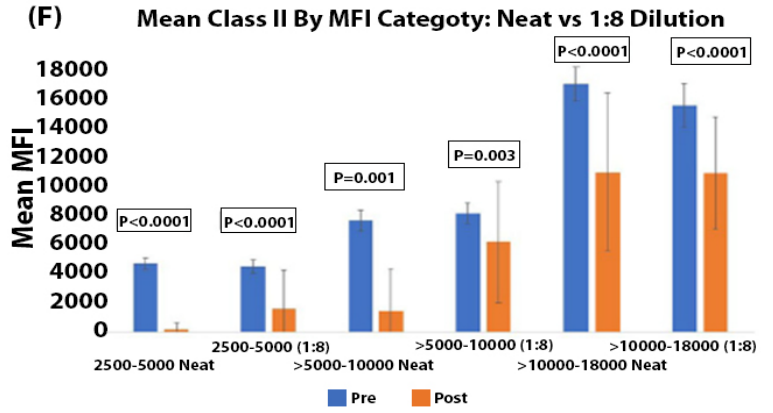
50% of patients had FCMX+/DSA+

75% had DSA+ at time of transplant







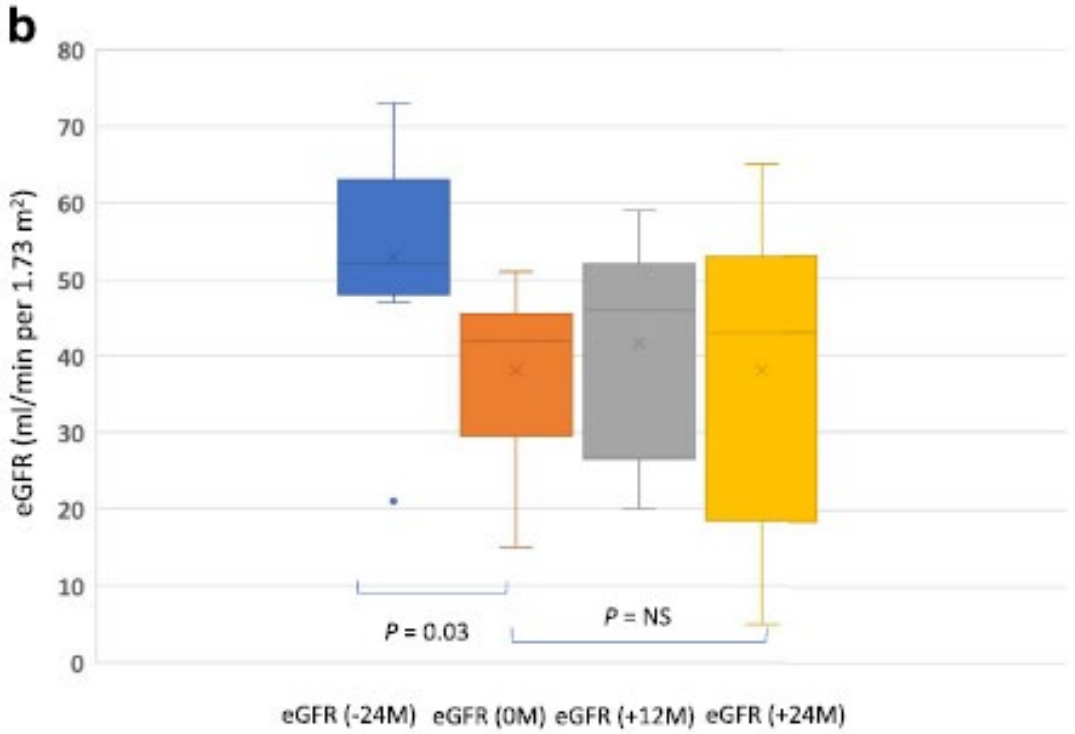


*Clazakizumab is not approved in the United States, Switzerland, nor the European Union.

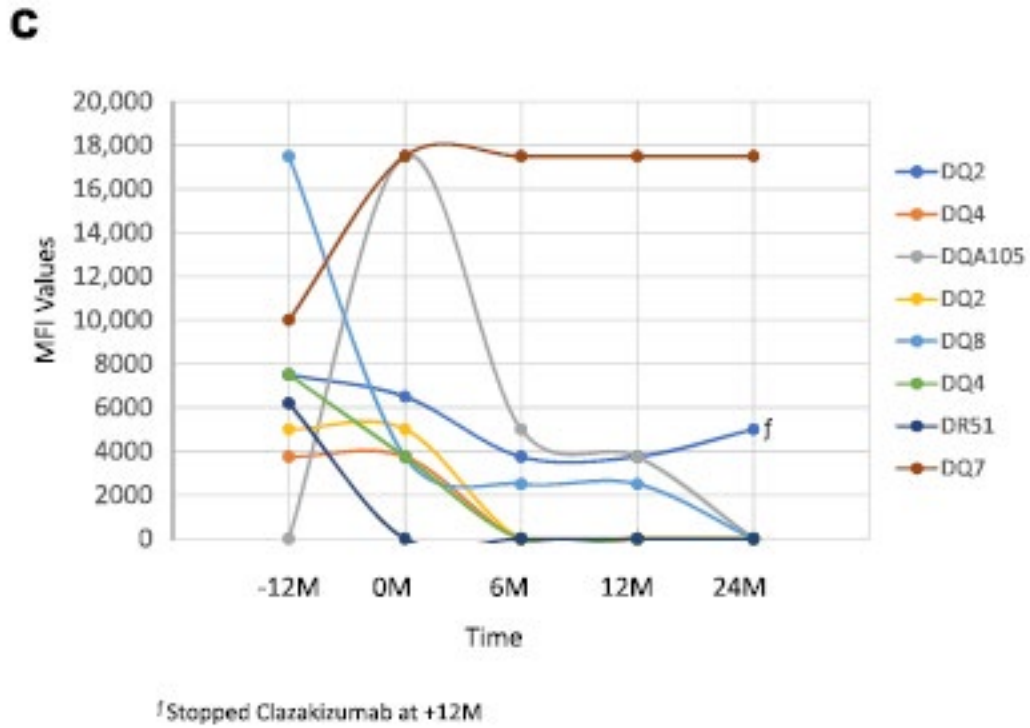
Vo AA, et al. *Am J Transplant.* 2022;22(4):1133-1144.

Clazakizumab in Treatment-Resistant cABMR

eGFR Stabilization Observed Over 24 Months



DSA Levels Over 24 Months



Jordan SC, et al. *Kidney Int Rep*. 2022;7(4):720-731.

IMAGINE Study: Clazakizumab in Treatment-Resistant cABMR

Design

Phase	3
Intervention	Clazakizumab, Placebo
Study Type	Interventional (Clinical Trial)
Estimated Enrollment	350 participants
Allocation	Randomized
Intervention Model	Parallel Assignment
Masking	Quadruple
Actual Study Start Date	October 14, 2019
Estimated Completion Date	February 2030

Primary Outcome

Time to all-cause composite allograft loss*

Status

Recruiting

NCT03744910

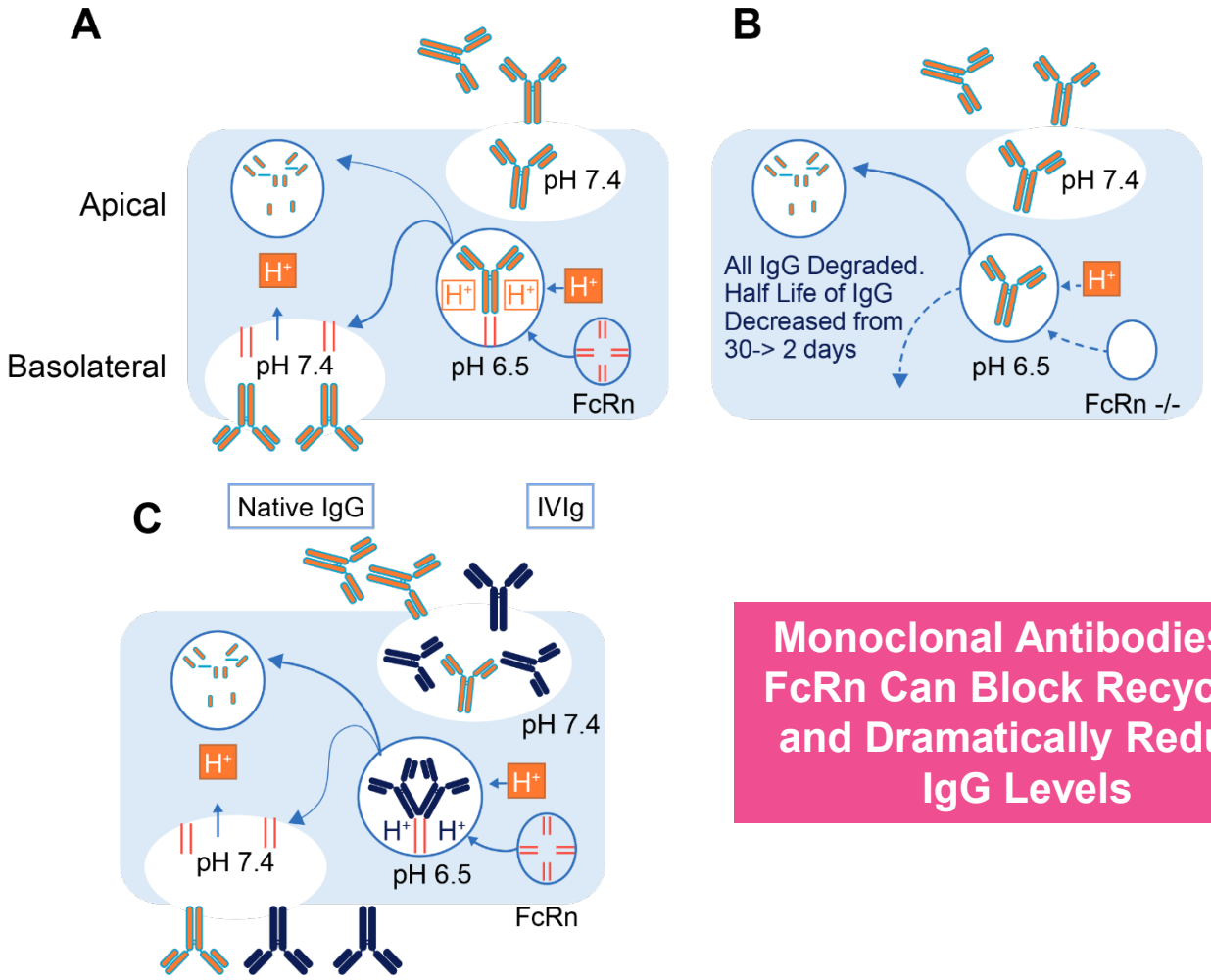
*Defined as eGFR <15 mL/min/1.73 m^2 (total cumulative duration of eGFR <15 mL/min/1.73 m^2 AND/OR dialysis ≥60 days), return to dialysis, allograft nephrectomy, re-transplantation, or death from any cause.

Emerging Treatments

CARE TEAM FORUM®

IgG Degradation	Anti-IL-6	FcRn Blockers	Anti-CD38/ Anti-BCMA
Imlifidase	Tocilizumab Clazakizumab	Rozanolixizumab	Daratumumab

Fc Neonatal Receptor (FcRn): An Emerging Target for Immunotherapeutics



Monoclonal Antibodies to FcRn Can Block Recycling and Dramatically Reduce IgG Levels

A: Biology of FcRn-IgG interactions that lead to decreased lysosomal degradation & extended $t_{1/2}$ of IgG

B: Importance of FcRn in maintaining IgG and albumin levels in plasma

C: Saturation of FcRn with high-dose IVIG accelerates the degradation of ambient IgG/pathogenic molecules

*Rozanolixizumab is not approved in the United States, Switzerland, nor the European Union.

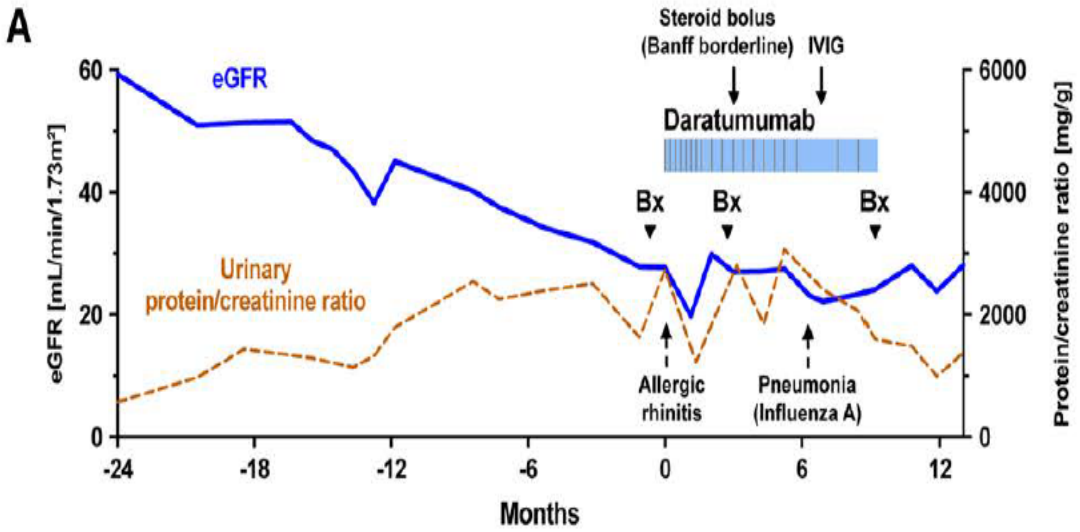
Jordan CS, et al. *Transplantation*. 2020;104(1):17-23.

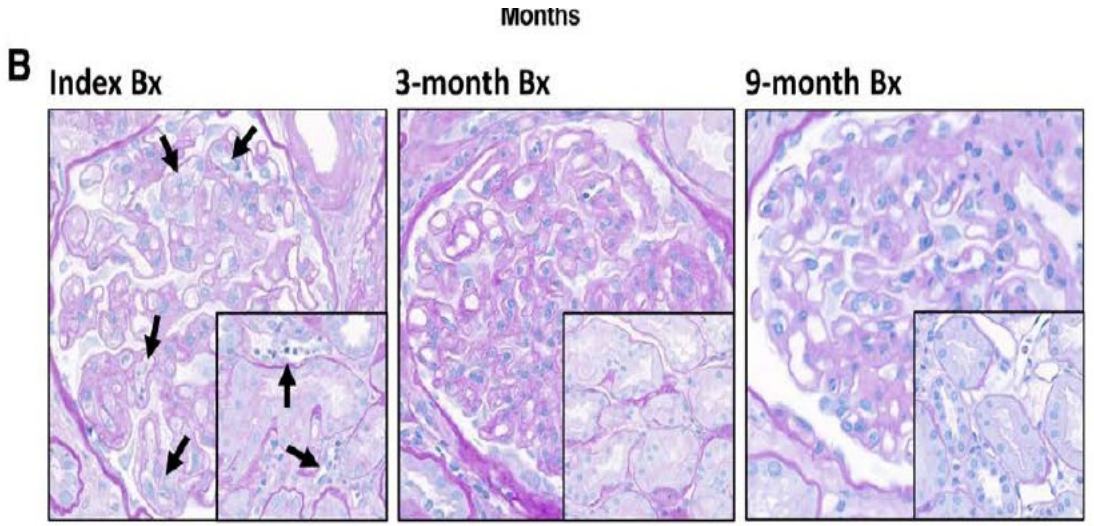
Emerging Treatments

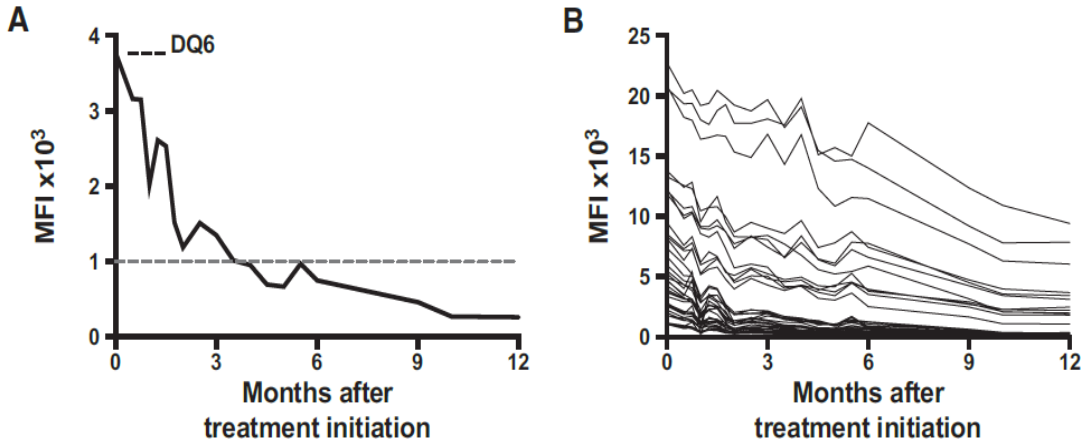
CARE TEAM FORUM®

IgG Degradation	Anti-IL-6	FcRn Blockers	Anti-CD38/ Anti-BCMA
Imlifidase	Tocilizumab Clazakizumab	Rozanolixizumab	Daratumumab

Daratumumab: CD38 Antibody for cABMR







Doberer K, at al. *Transplantation.* 2021;105(2):451-457.

Summary

Most Promising Emerging Treatments for 2023

Imlifidase

- Already approved in Europe, studies in the United States for desensitization (enrolling) and treatment of ABMR (completed)

Anti-IL-6 (Clazakizumab)

- For desensitization in combination with PLEX + IVIG at initiation, results in long-term reductions in HLA antibodies and very effective in reducing rebound DSA post-transplant
- Ongoing trial (IMAGINE Study) for cABMR with plan to complete Interim Analysis #1 in 2023

Anti-CD38/Anti-BCMA

- Studies beginning with these plasma cell-directed monoclonals

FcRN Blockers

- Will be exciting to evaluate as they can reduce deleterious IgG antibodies long-term and re-use is not a problem
- May also reduce immune activation events associated with antigen presentation

Patient Video

Panel Discussion

How do you see these emerging agents being utilized in the current treatment paradigm?