Acute and Chronic AMR: A continuum or distinct diseases?

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FDA Workshop
Antibody Mediated Rejection in Kidney Transplantation

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Silver Spring MD

Relevant Financial Disclosures

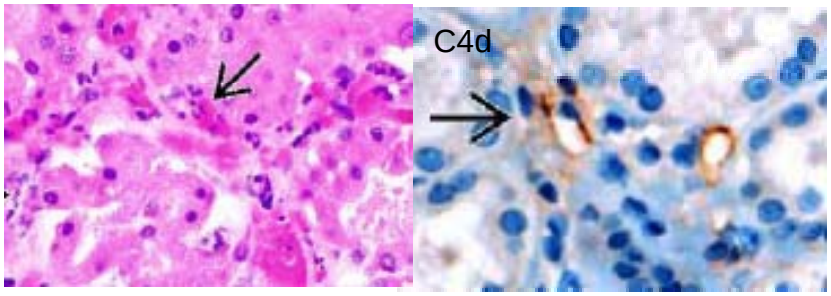
Consultant for Alexion, Shire

(Leader of Central Pathology review)

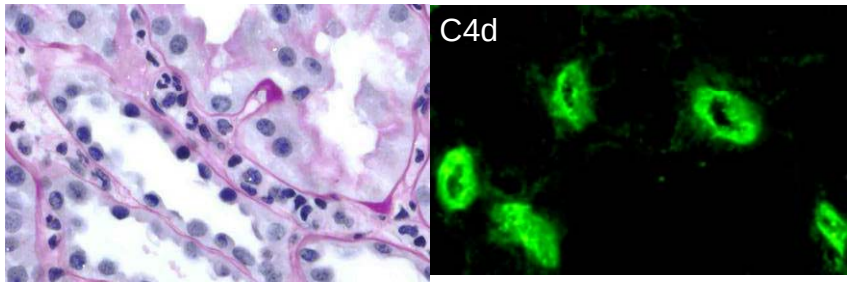
My presentation does not include promotion of off-label use of drugs

Multiple Effects of Antibody

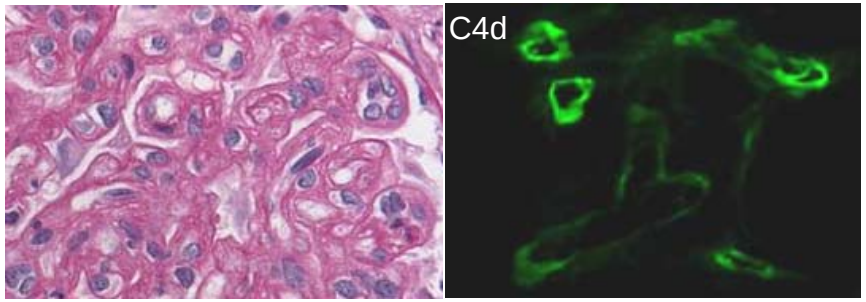
Hyperacute AMR



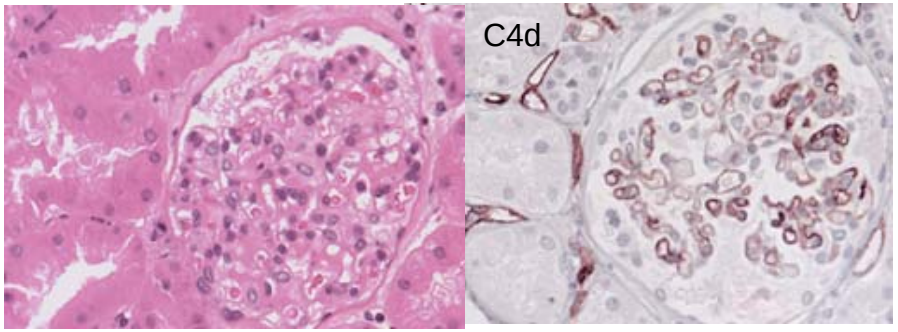
Acute AMR



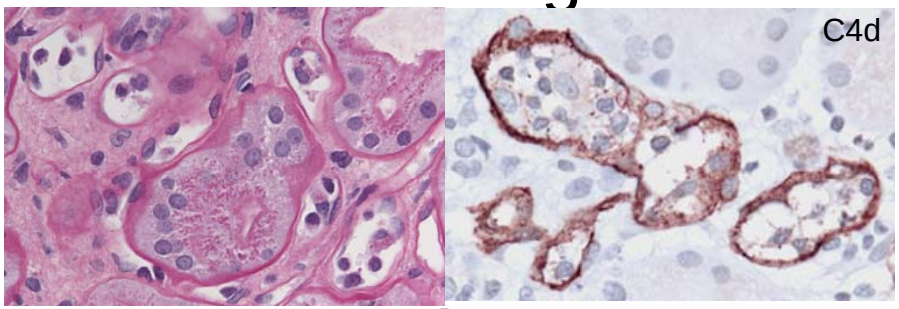
Chronic AMR



Accommodation



"Smoldering" AMR



AMR = antibody mediated rejection

Banff Definitions

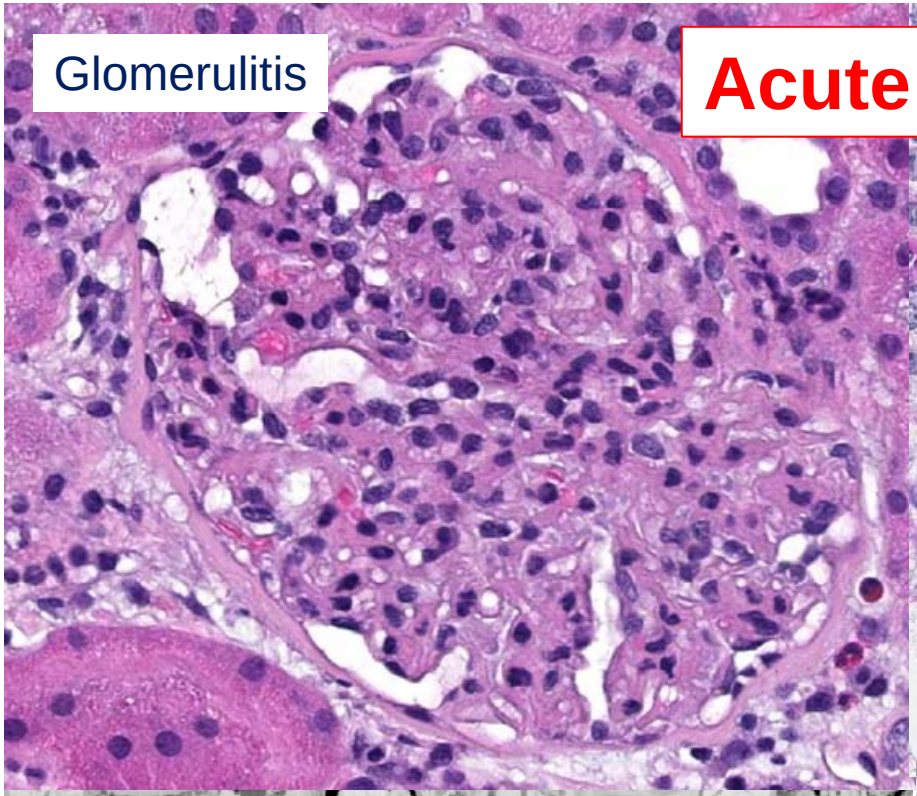
Acute AMR

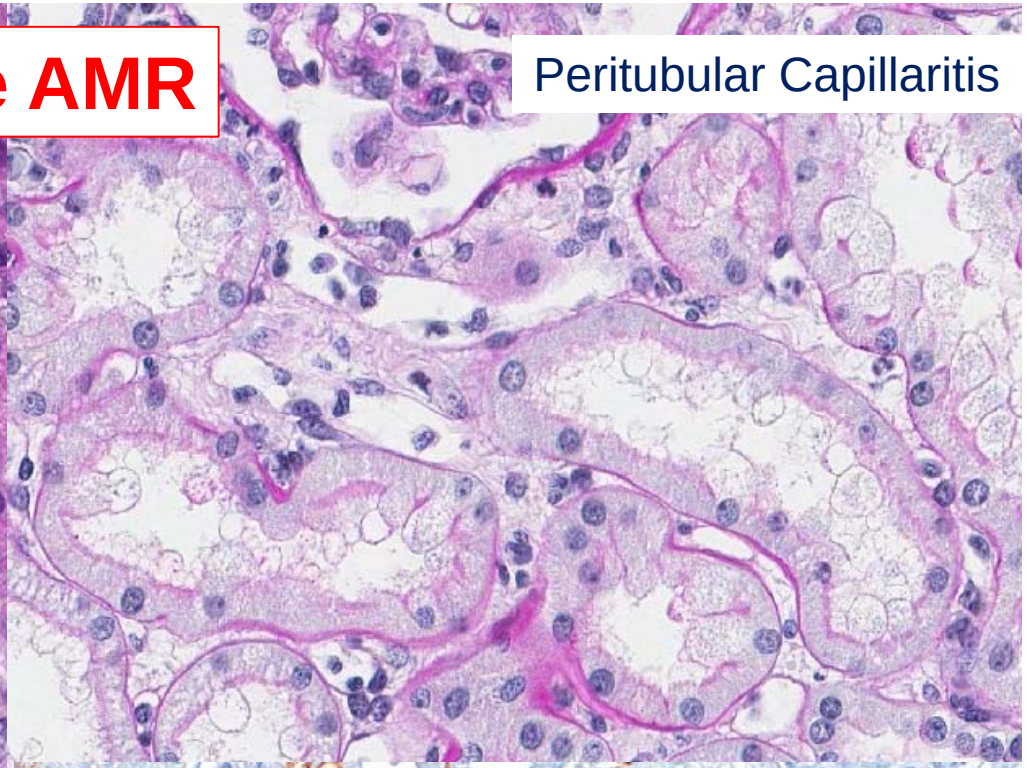
1. **Morphologic evidence of <u>acute</u> tissue injury,** *including at least one of the following:*
   a. Microvascular inflammation (g>0 and/or ptc>0)
   b. Intimal or transmural arteritis (v > 0)
   c. Acute thrombotic microangiopathy
   d. Acute tubular injury

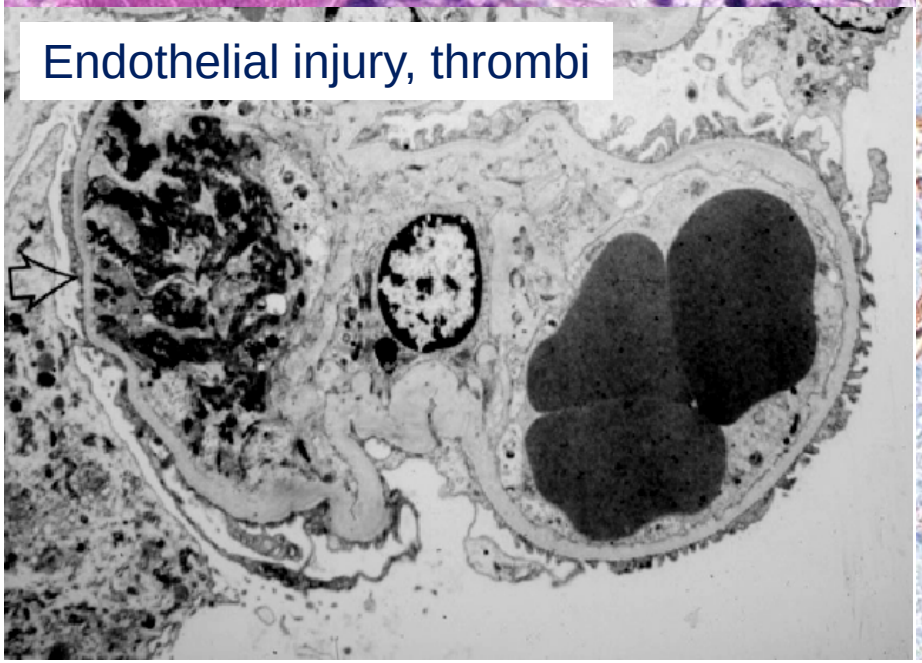
Chronic AMR

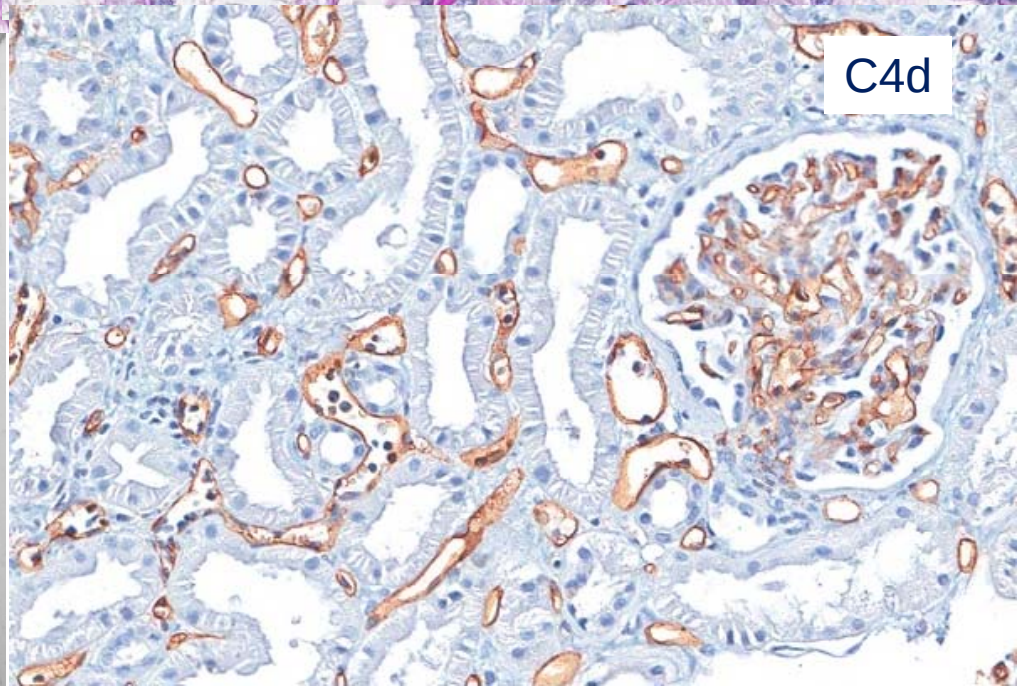
1. **Morphologic evidence of <u>chronic</u> tissue injury,** *including at least one of the following:*
   a. Transplant glomerulopathy (cg >0 LM or EM)
   b. Severe peritubular capillary basement membrane multilayering (EM)
   c. Arterial intimal fibrosis of new onset

Acute AMR

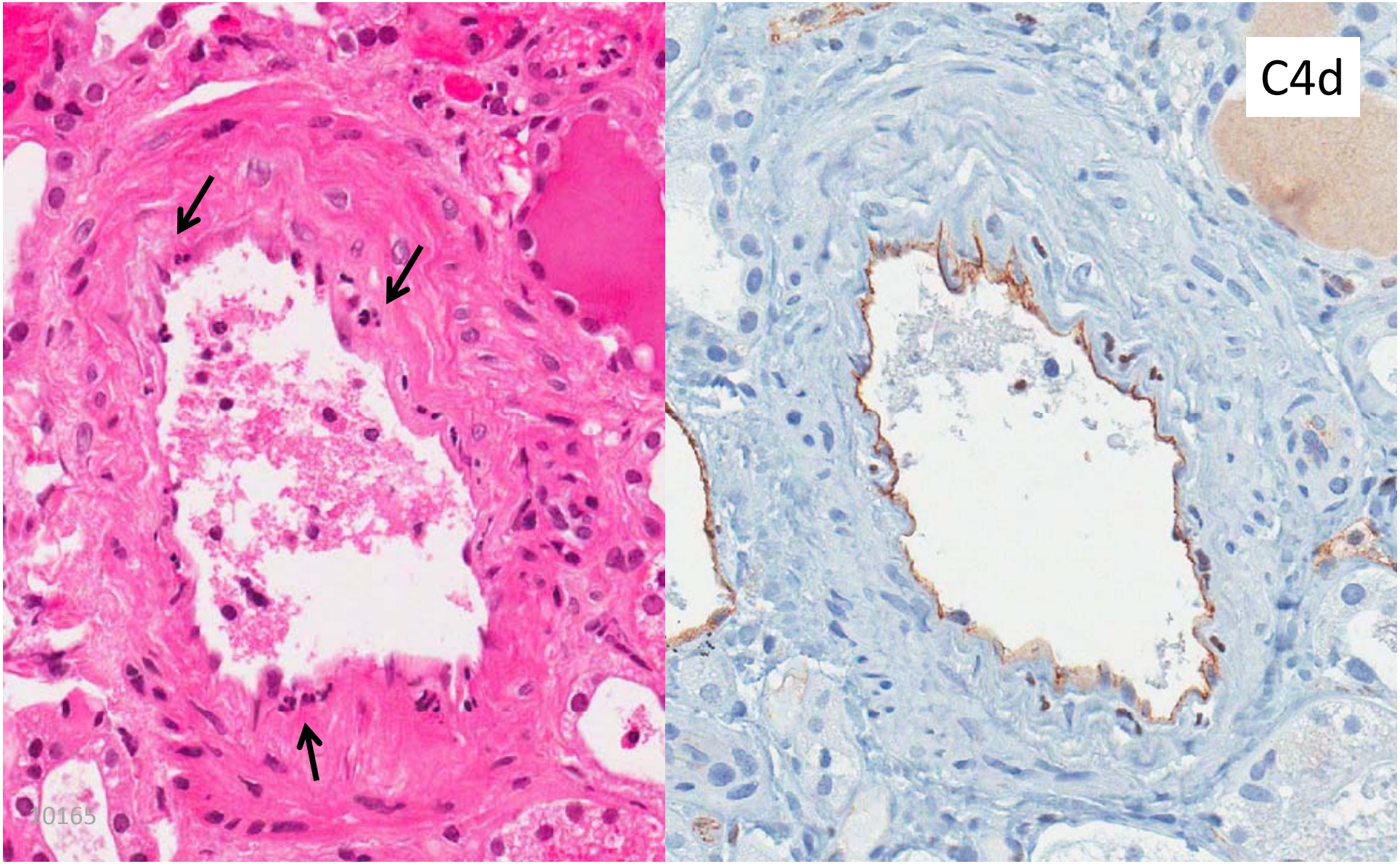

Glomerulitis


Peritubular Capillaritis


Endothelial injury, thrombi

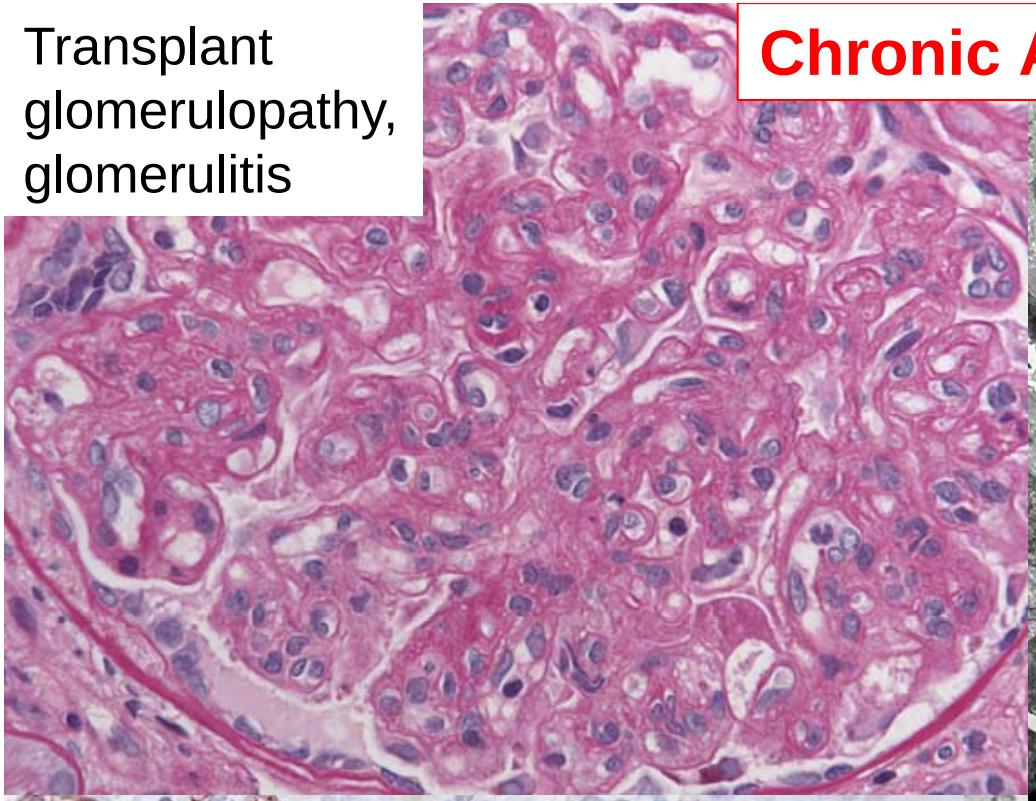

C4d

Endarteritis with neutrophils in acute AMR

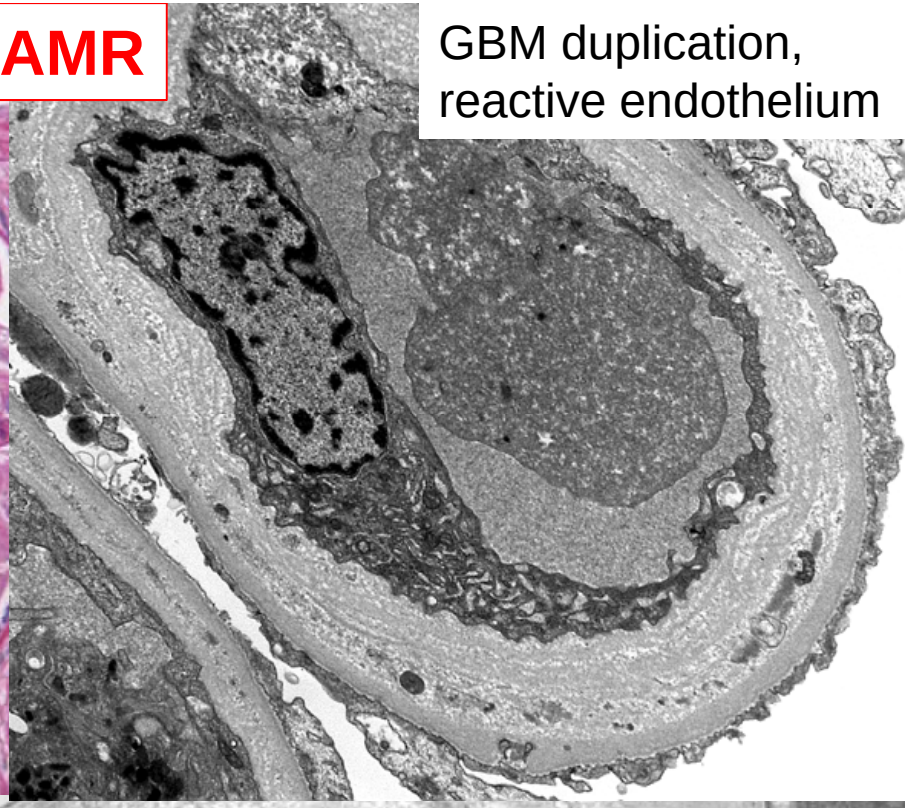


Chronic AMR

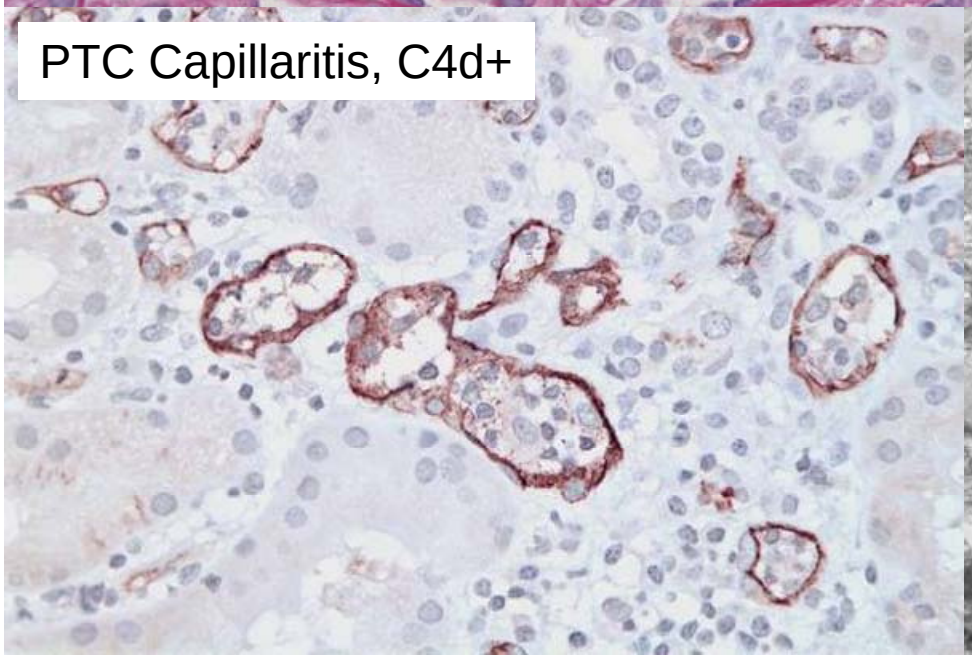
Transplant glomerulopathy, glomerulitis



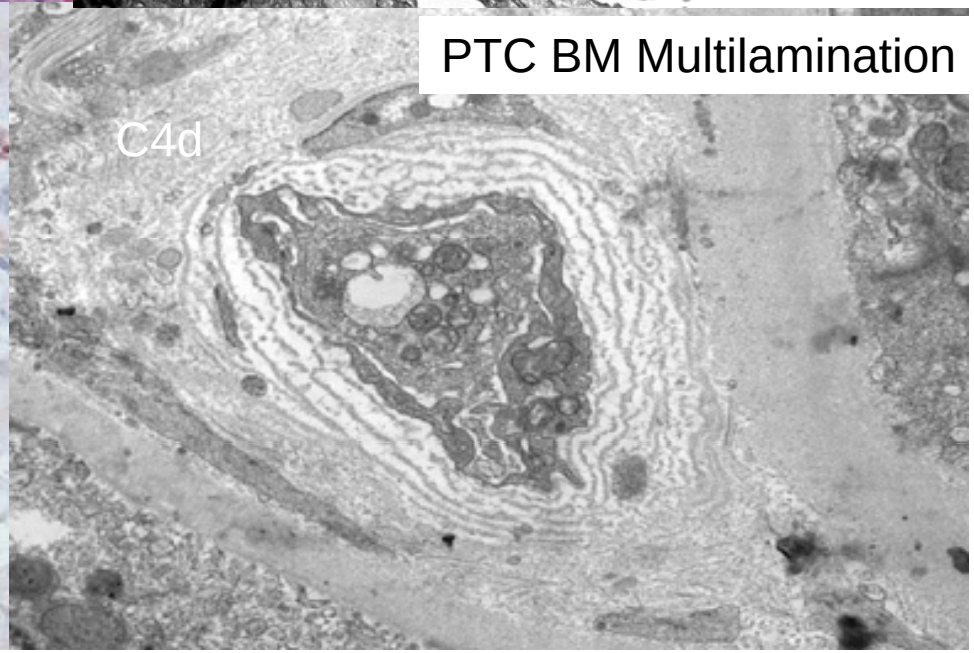
GBM duplication, reactive endothelium

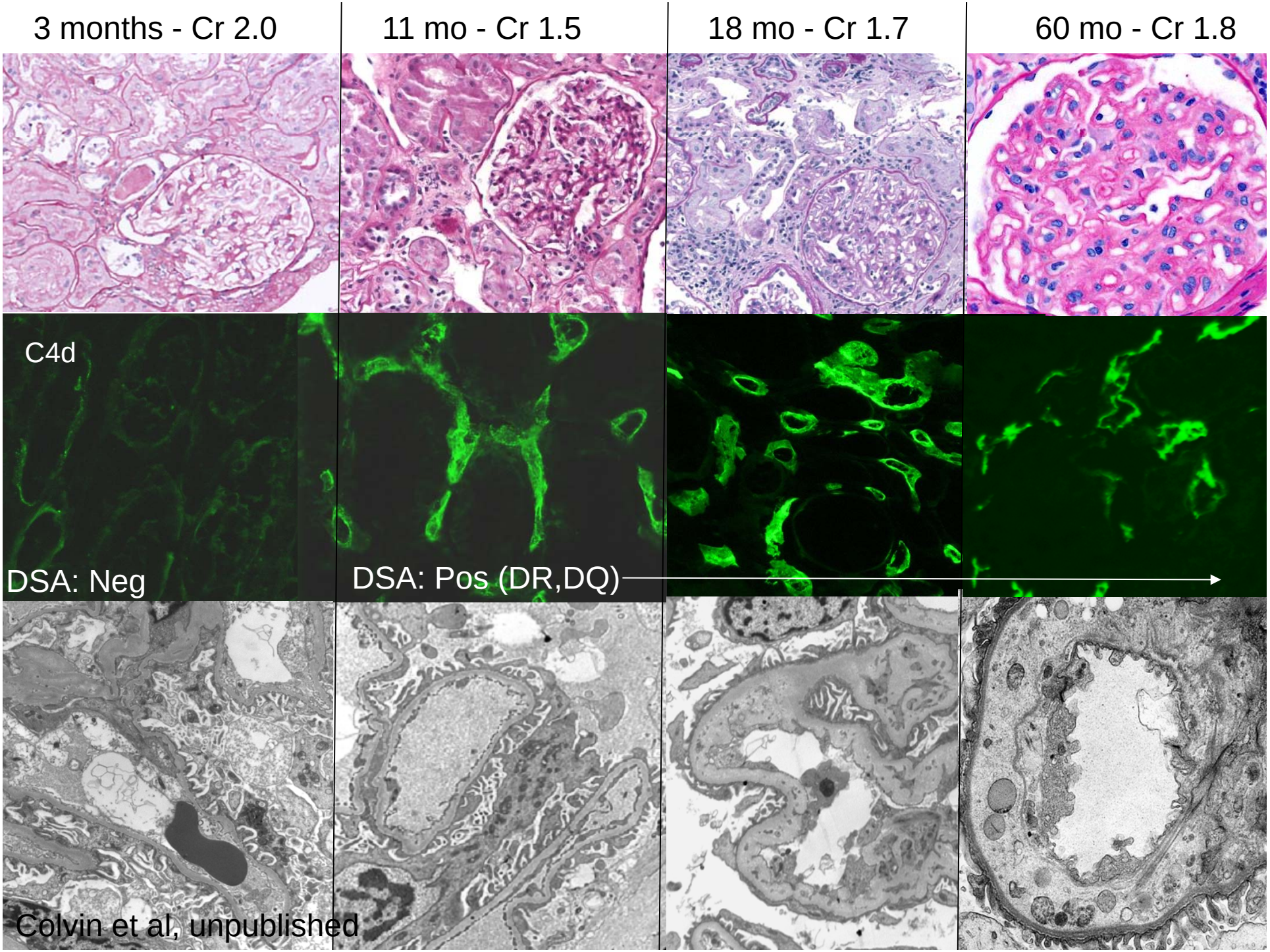


PTC Capillaritis, C4d+

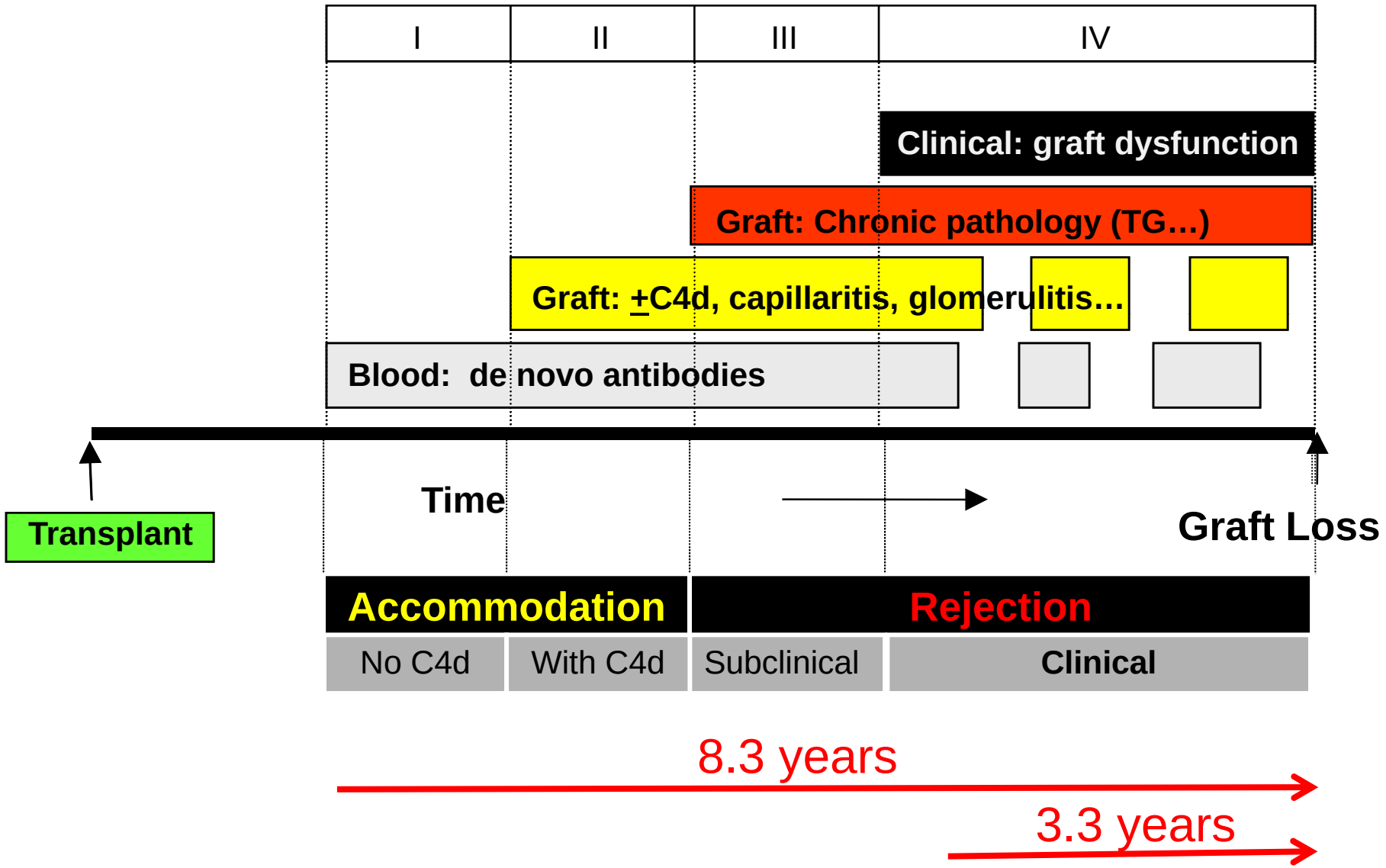


PTC BM Multilamination




3 months - Cr 2.0
11 mo - Cr 1.5
18 mo - Cr 1.7
60 mo - Cr 1.8
C4d
DSA: Neg
DSA: Pos (DR,DQ)
Colvin et al, unpublished

Stages of Chronic Antibody Mediated Rejection



Wiebe et al AJT 2015

Differences

Acute AMR	**Chronic AMR**
Usually presensitized	Usually de novo DSA Association with TCMR
Rapid loss of function (days)	Insidious loss of function (months-years) Most cases not associated with acute AMR
Anti donor HLA class I or II	Anti-class II DSA common
Widespread C4d deposition common	Minimal C4d common
Capillaritis/glomerulitis neutrophils/mononuclears	Capillaritis/glomerulitis macrophages/NK

mRNA Differences

AMR: Presensitized DSA

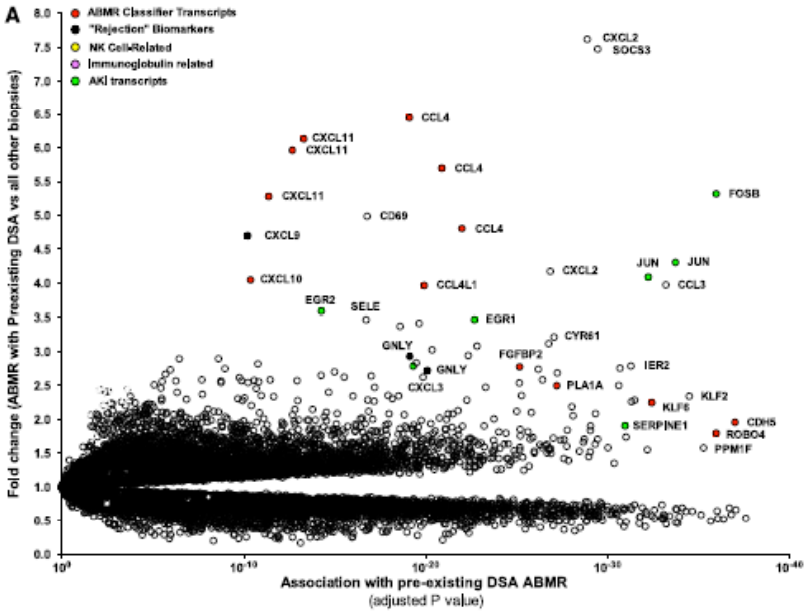
Injury repair response

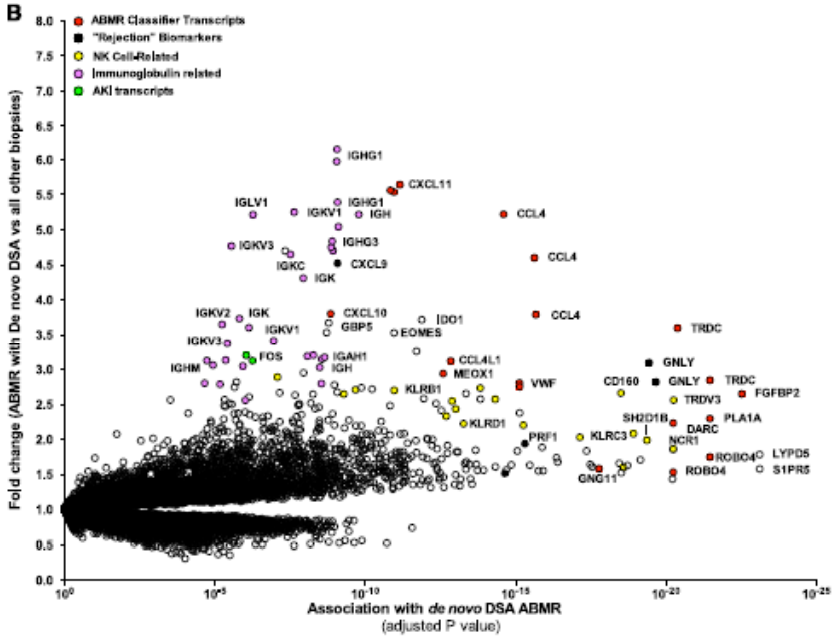
AMR:De Novo DSA

T cell transcripts

NK transcripts

IFNγ related transcripts

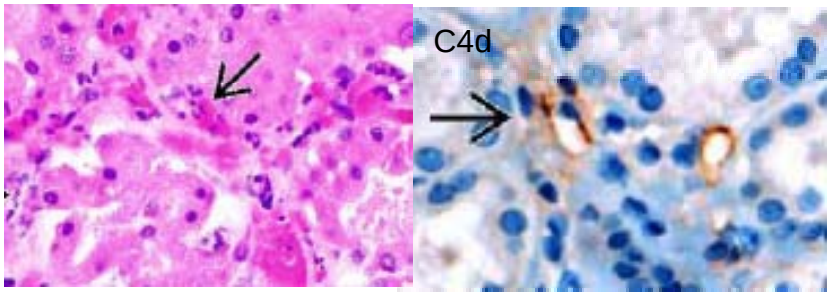




Aubert et al (Paris) JASN 2017

Why Different Effects of Antibody?

Hyperacute AMR



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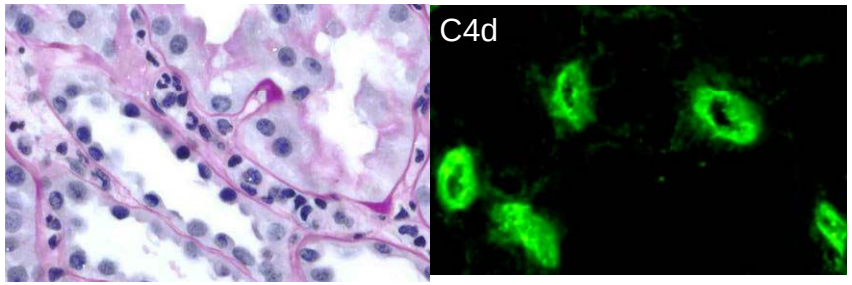
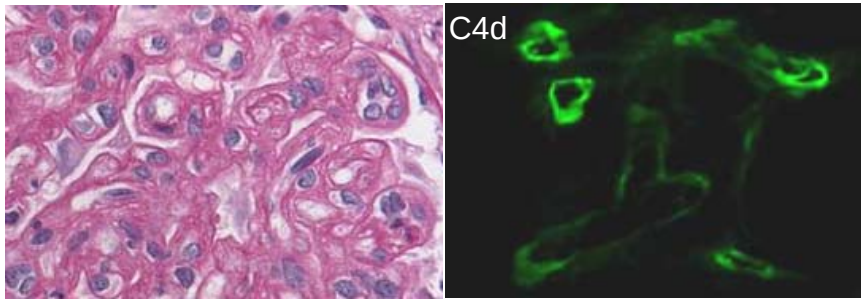


Chronic AMR



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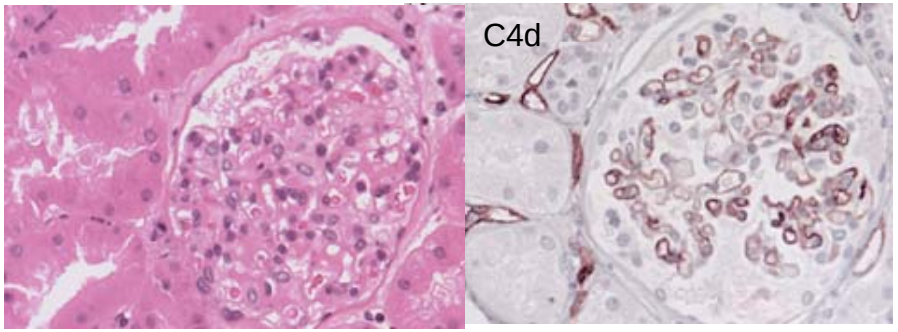

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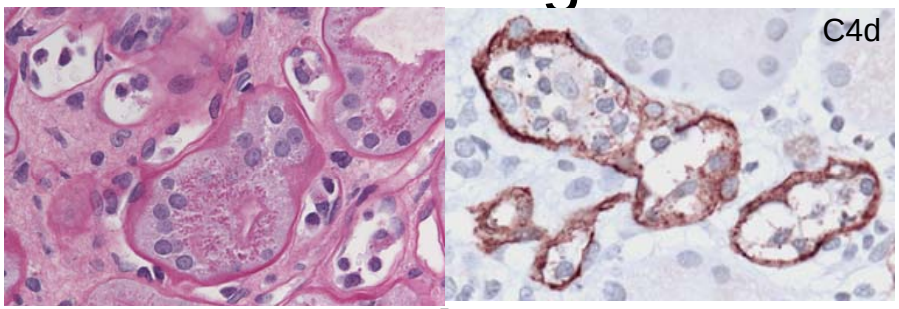
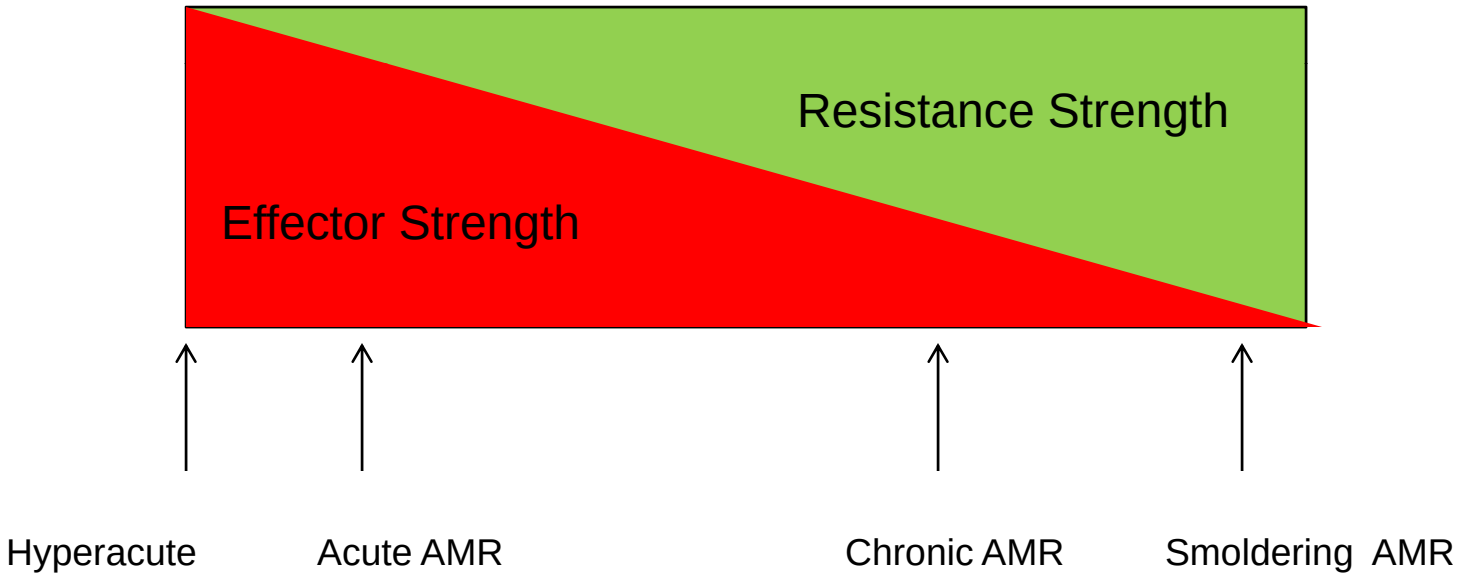


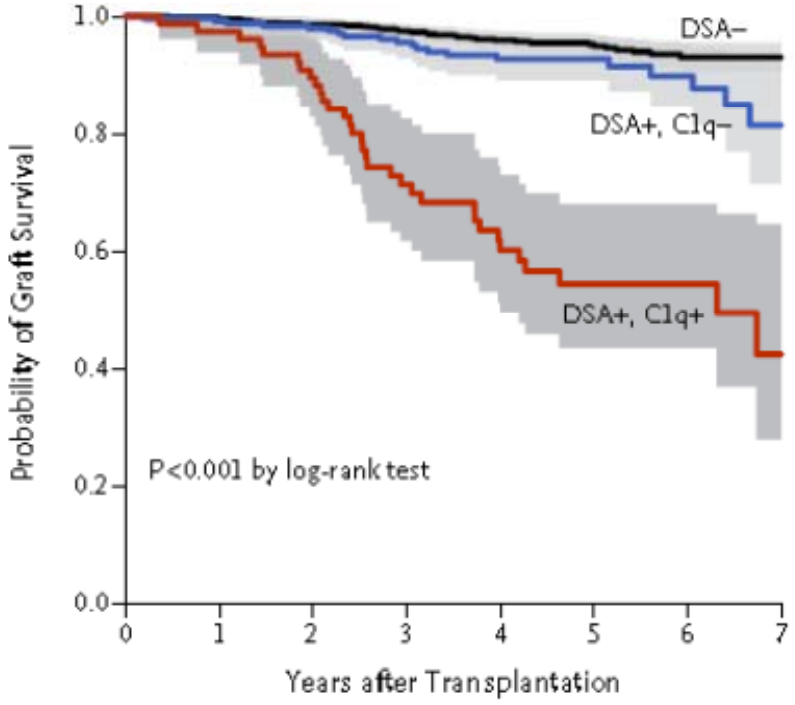
AMR = antibody mediated rejection

Effector/Resistance Theory



Complement Fixation Theory

Graft survival worse with C1q fixing DSA during first year post-transplant (de novo or persistent)



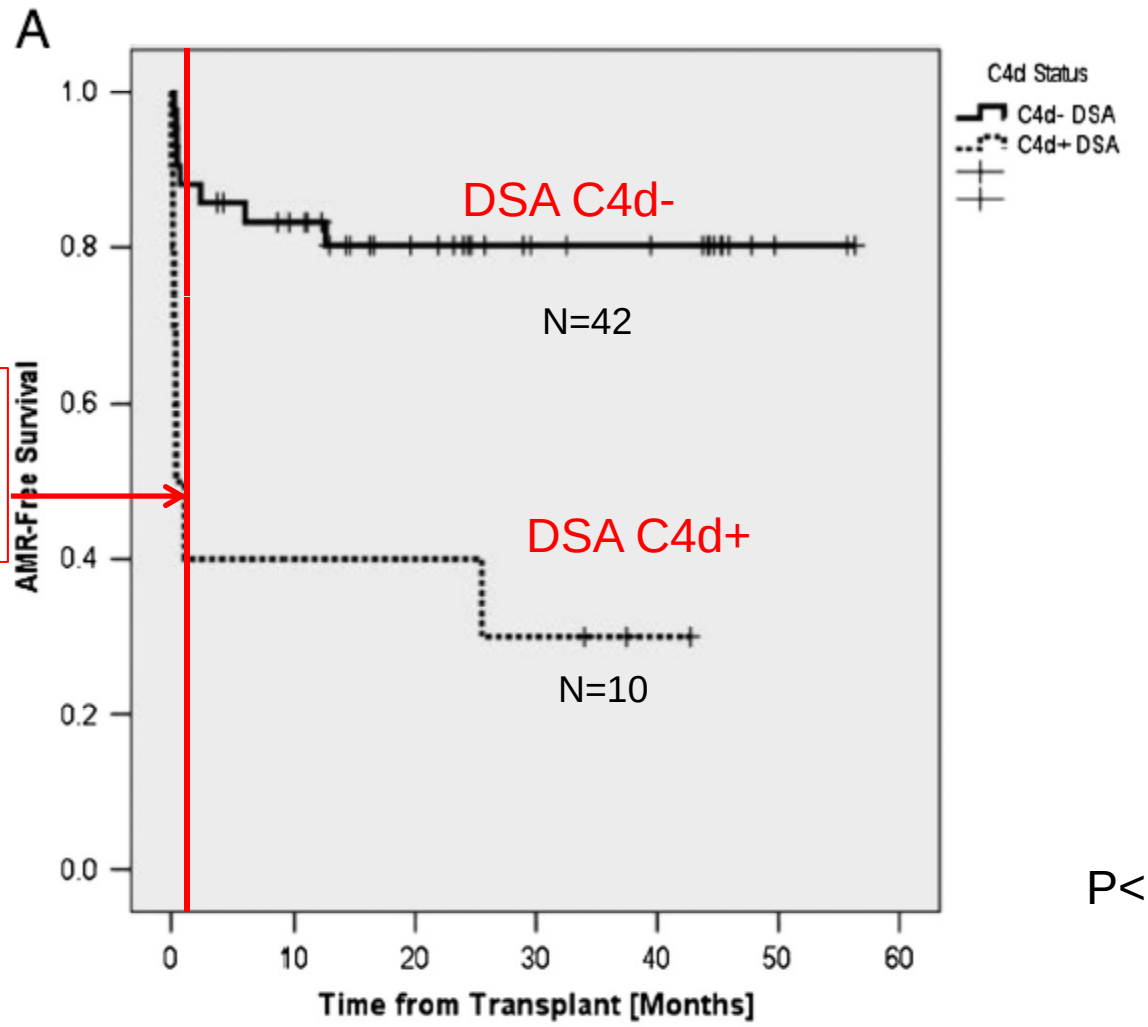
No. at Risk								
DSA–	700	698	667	612	504	338	164	38
DSA+, C1q–	239	237	227	181	139	80	44	14
DSA+, C1q+	77	75	68	48	37	20	12	5

DSA tested pretransplant, at time of graft dysfunction in first year or at one year protocol biopsy

Loupy NEJM 2013

Recipients with pre-existing DSA that fix complement (C4d) in vitro have higher risk of early AMR

Difference mainly in immediate outcome <2 months)



P<.001

Lawrence et al (Hammersmith) Transplantation 2013

Meta-analysis of 3485 indication and 868 surveillance biopsies

"Prognostically, the presence of C4d was associated with inferior allograft survival compared with DSA or histopathology alone."

Sapir-Pichhadze et al (Canada) Kidney Int 87: 182, 2015

American Journal of Transplantation 2015; XX: 1–8
Wiley Periodicals Inc.

doi: 10.1111/ajt.13434

Presentation and Outcomes of C4d-Negative Antibody-Mediated Rejection After Kidney Transplantation

B. J. Orandi[1], N. Alachkar[2], E. S. Kraus[2], F. Naqvi[2], B. E. Lonze[1], L. Lees[3], K. J. Van Arendonk[1], C. Wickliffe[1], S. M. Bagnasco[4], A. A. Zachary[2], D. L. Segev[1,*] and R. A. Montgomery[1]

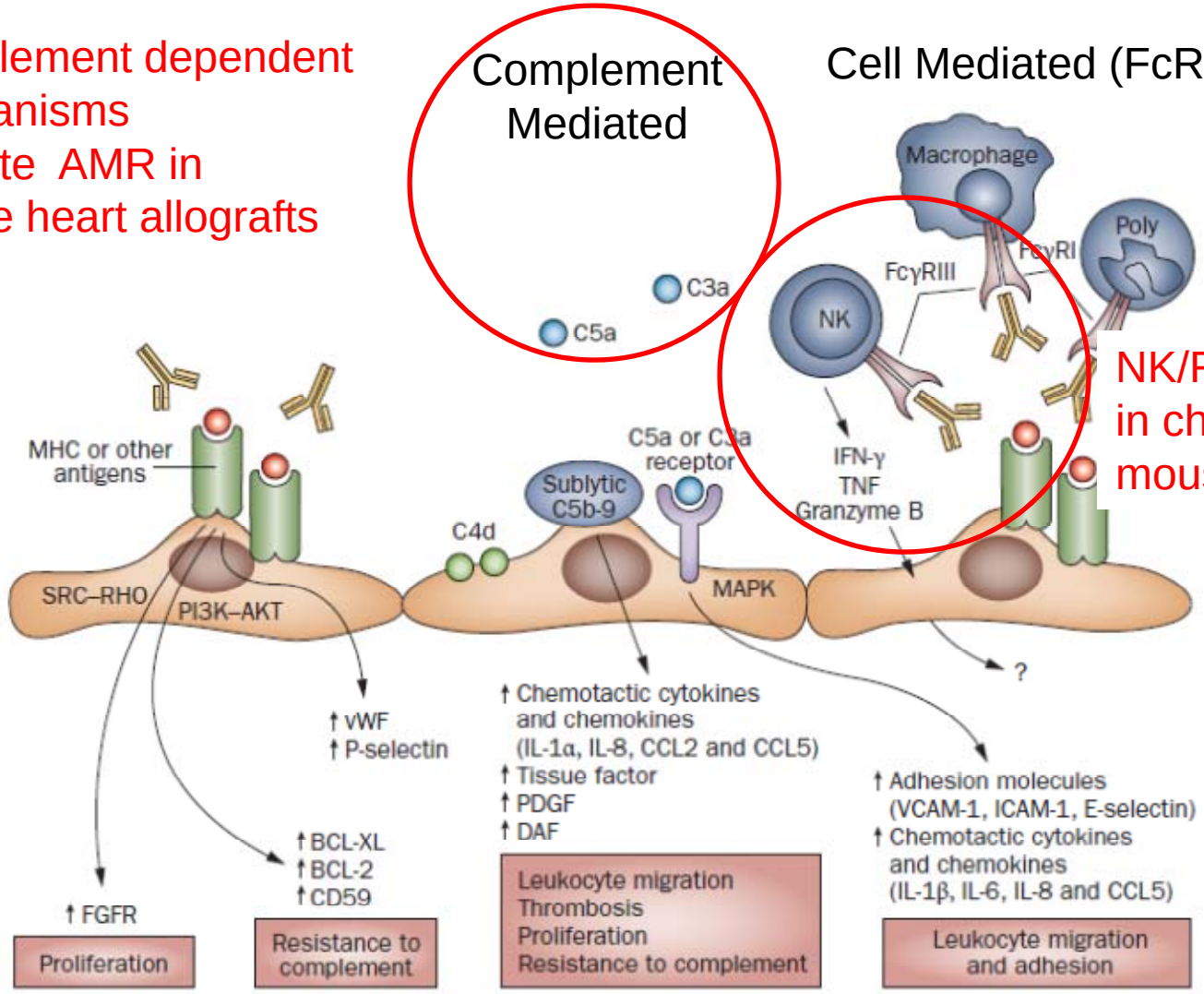
	C4d+	C4d-
N	156	51
Onset	14 d (8-32)	46 d (20-191)*
Graft dysfunction	85%	55%*
Graft loss at 1 yr	13.2%	6.6%
Risk of graft loss (vs no AMR)	3.7	2.56

*p<.001

C4d- = C4d 0-1 on IF, 0 on IHC

Mechanism Theory

Complement dependent mechanisms in acute AMR in mouse heart allografts

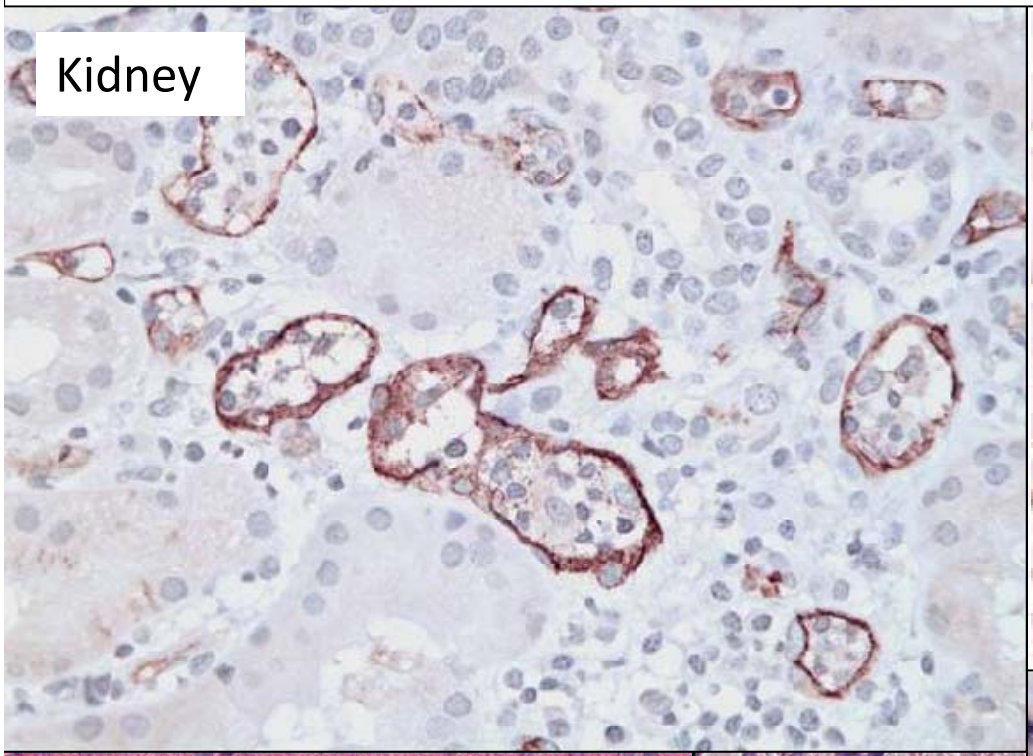


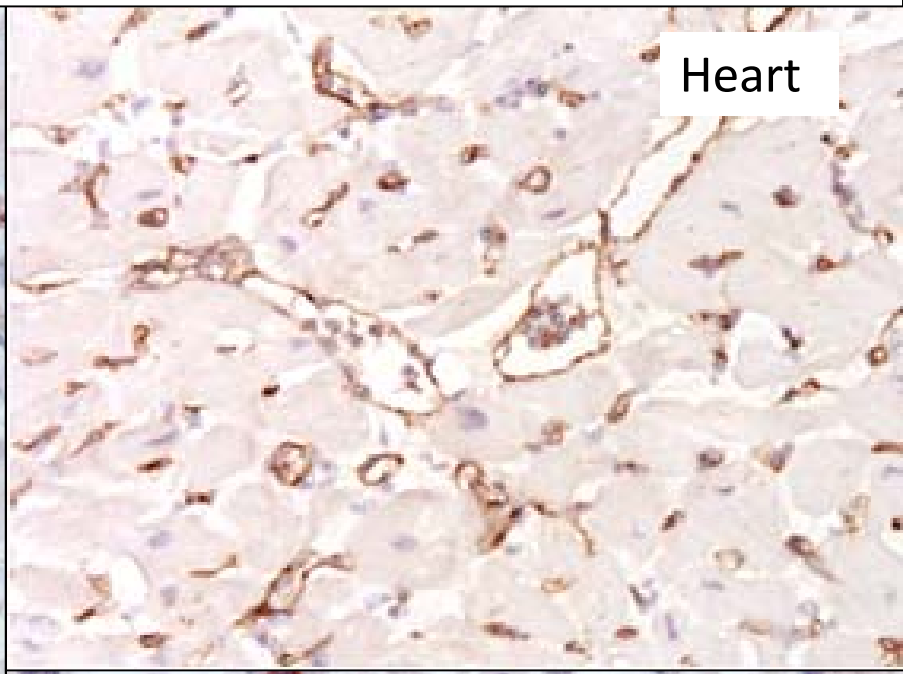
NK/Fc mechanisms in chronic AMR in mouse heart allografts

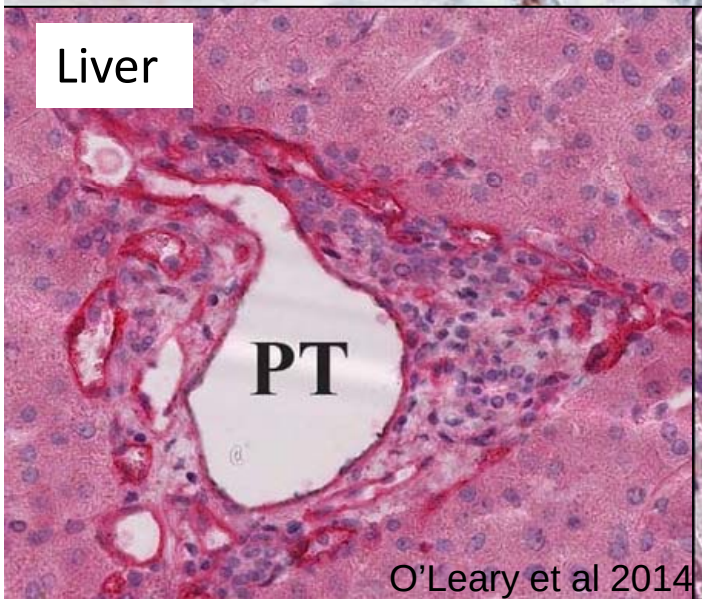
Farkash and Colvin, Nat Rev Nephrol, 2012

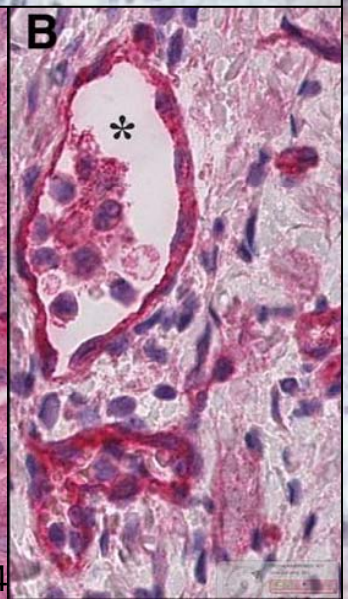
AMR in Other Organs

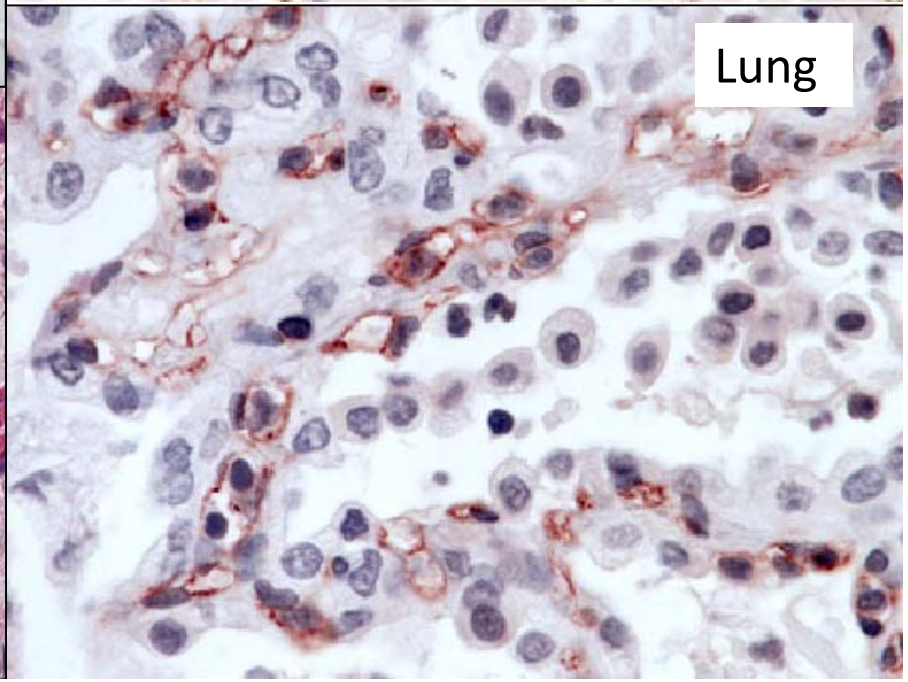
AMR Common Features: Capillaritis, C4d+, Dilation











O'Leary et al 2014

Common Features of AMR

	Kidney	Heart	Liver	Lung
Acute/Early				
Capillaritis	Peritubular, glomerular	Interstitial	Periportal	Alveolar
Capillary dilation	+	+	+	
C4d deposition	+/-	+/-	+/-	+/-
Endothelial activation	+	+	+	
Endarteritis	+ (also TCMR)	Not sampled	+	
Chronic/Late				
Capillary BM duplication	+			
Chronic arteriopathy	+	+	-	
Organ specific	Transplant glomerulopathy		Portal venopathy Portal tract fibrosis Sinusoidal fibrosis	

Summary

Acute AMR (early, type 1)

- usually due to presensitization, class I or class II
- rapid progression to renal failure (days)
- may be complement dependent (to be established)
- C1q fixing DSA and C4d deposition associated with more severe course

Chronic AMR (late, type 2)

- usually due to de novo DSA, related to class II antigens
- slow pace, subclinical
- progresses through stages over several years
- may be complement independent and related to NK/macrophage mediated mechanisms (to be established)

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