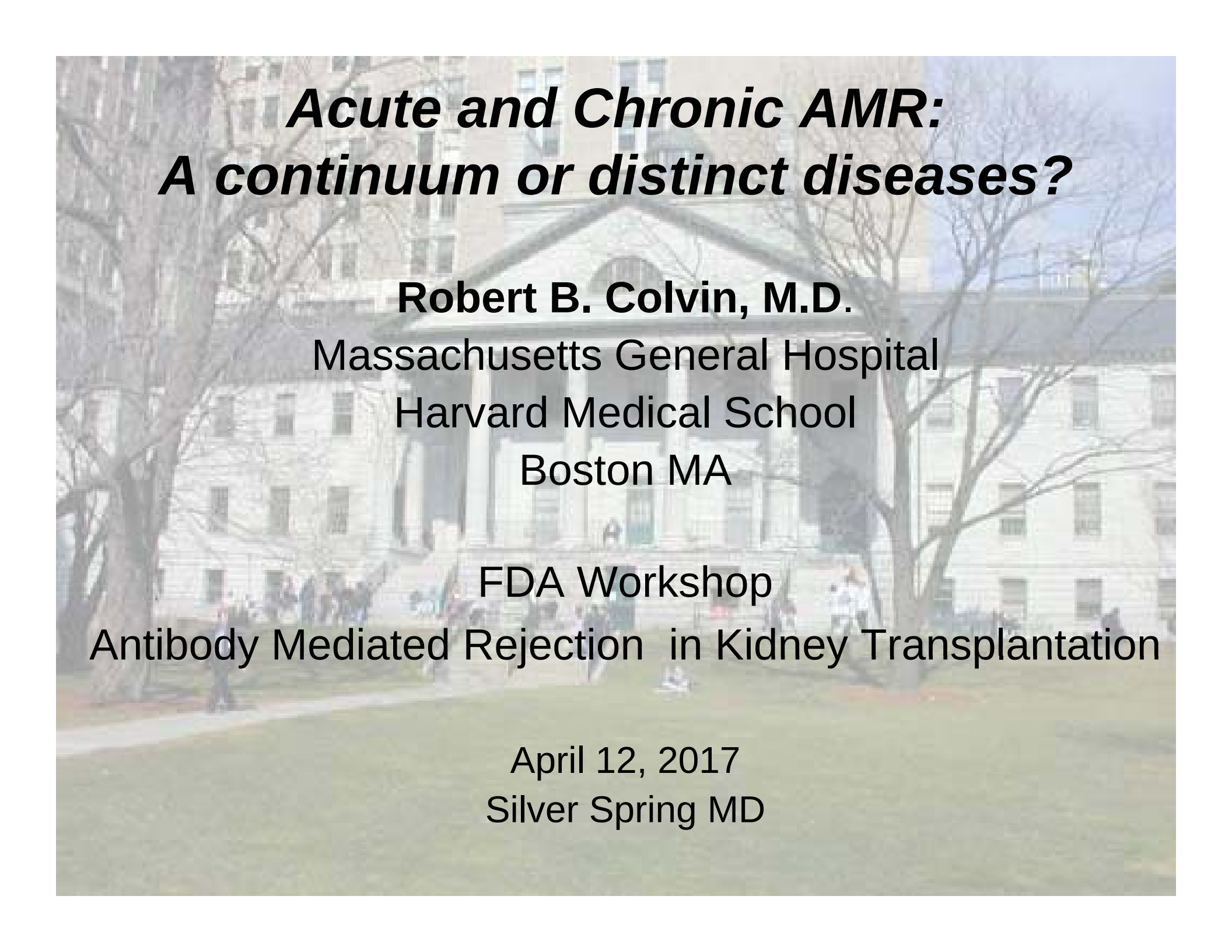




Acute and Chronic AMR: A continuum or distinct diseases?

Robert B. Colvin, M.D.

Massachusetts General Hospital

Harvard Medical School

Boston MA

FDA Workshop

Antibody Mediated Rejection in Kidney Transplantation

April 12, 2017

Silver Spring MD

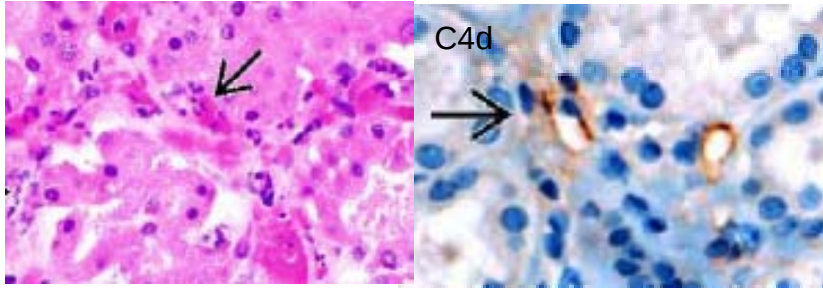
Relevant Financial Disclosures

Consultant for Alexion, Shire
(Leader of Central Pathology review)

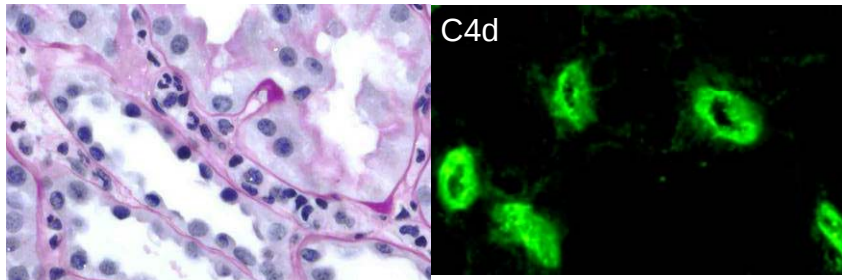
My presentation does not include
promotion of off-label use of drugs

Multiple Effects of Antibody

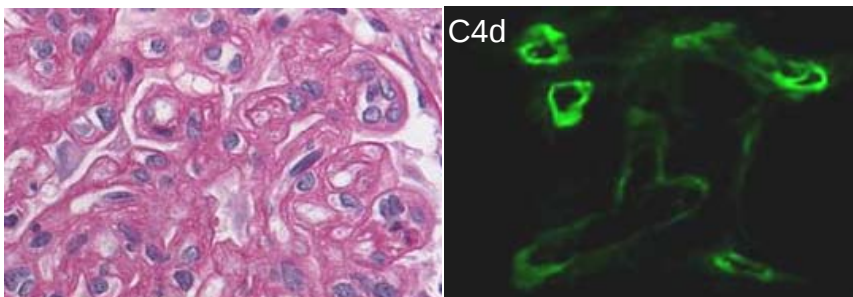
Hyperacute AMR



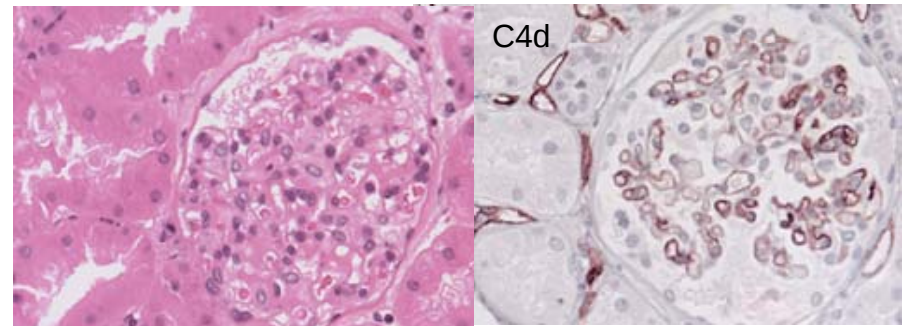
Acute AMR



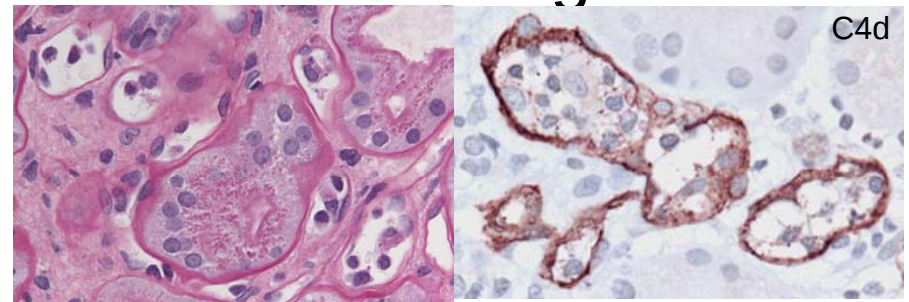
Chronic AMR



Accommodation



“Smoldering” AMR



AMR = antibody mediated rejection

Banff Definitions

Acute AMR

1. Morphologic evidence of **acute 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 **chronic 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
-

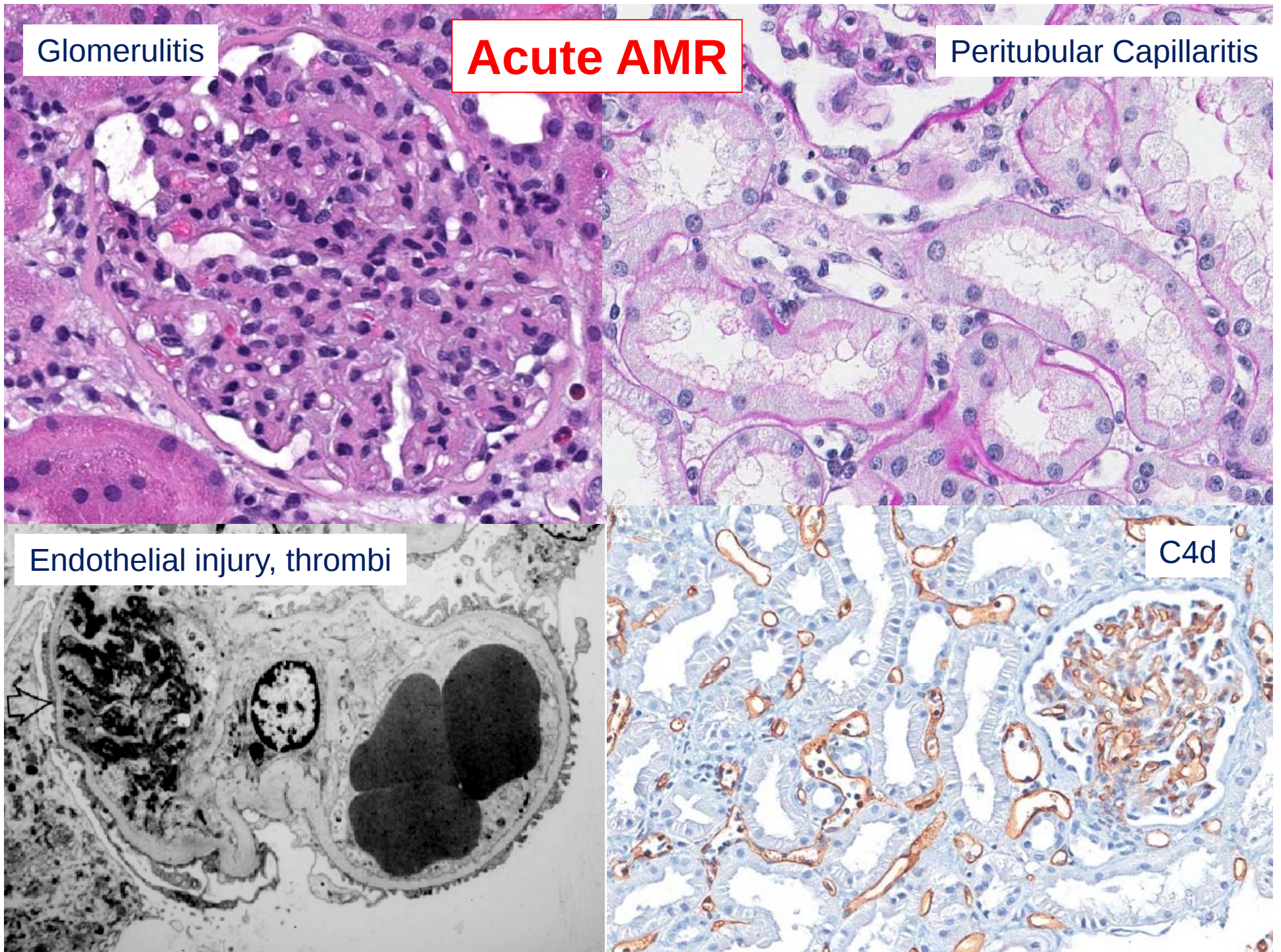
Glomerulitis

Acute AMR

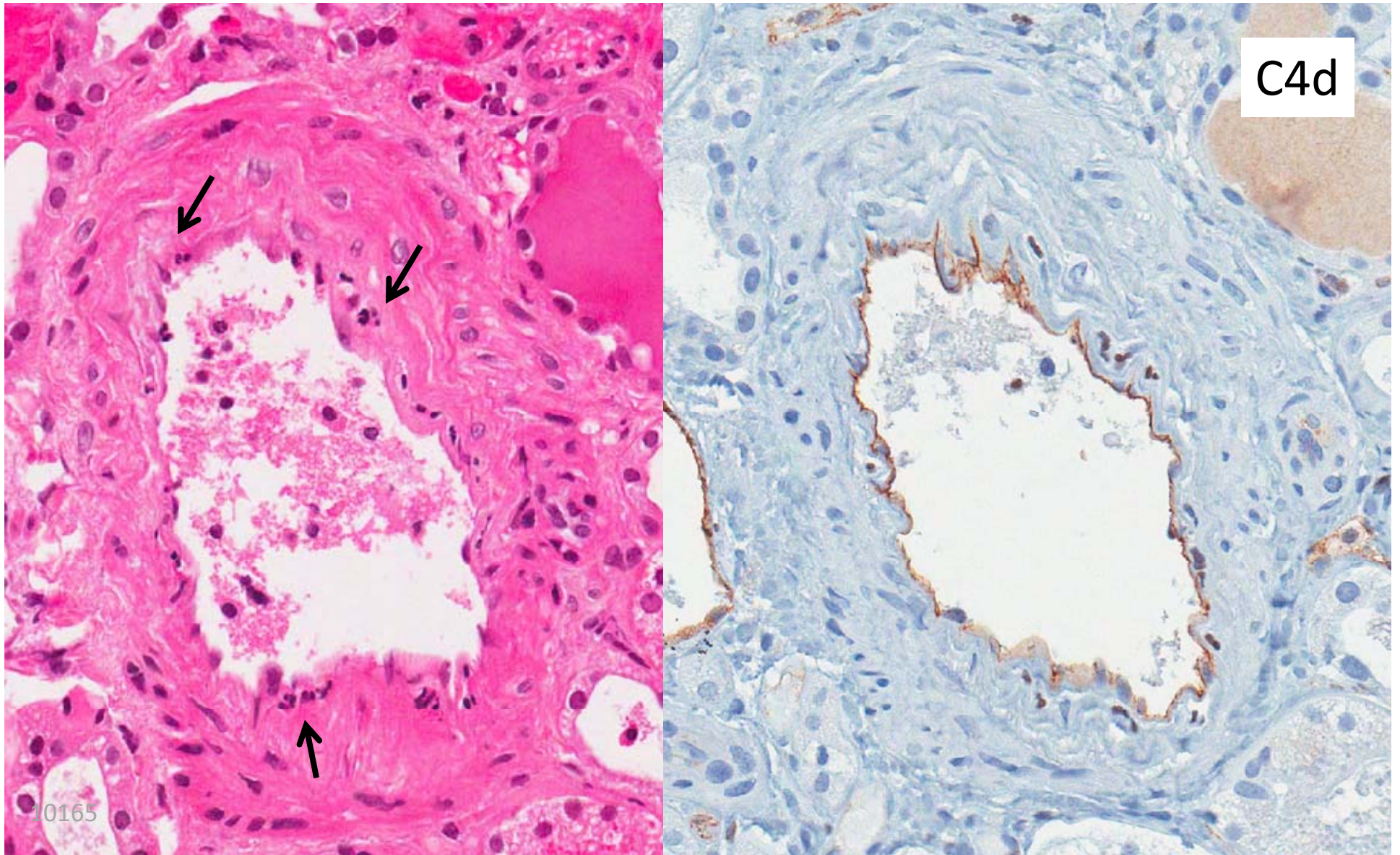
Peritubular Capillaritis

Endothelial injury, thrombi

C4d



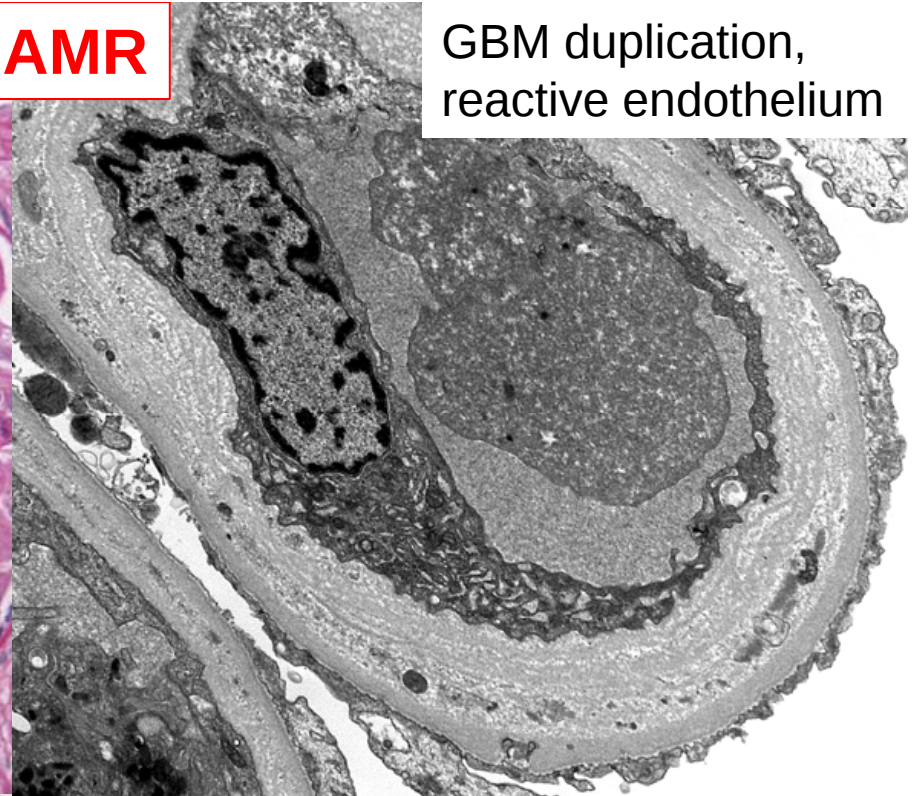
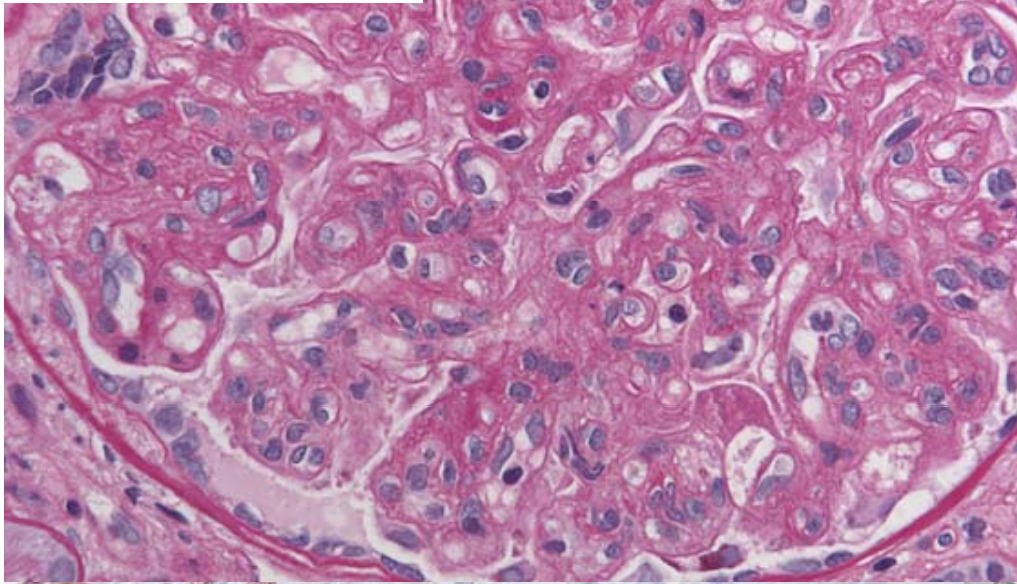
Endarteritis with neutrophils in acute AMR



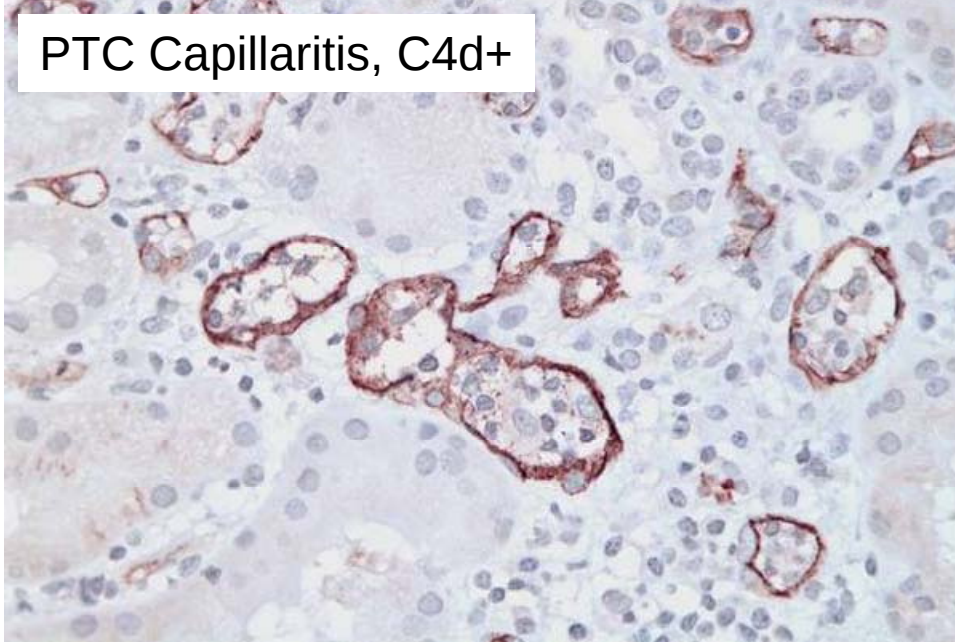
Transplant
glomerulopathy,
glomerulitis

Chronic AMR

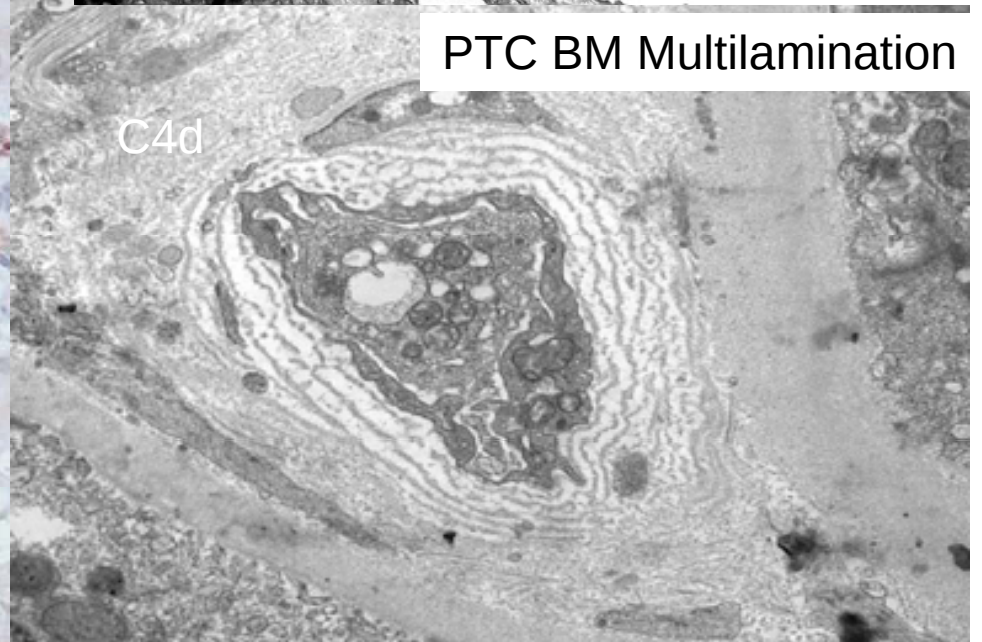
GBM duplication,
reactive endothelium



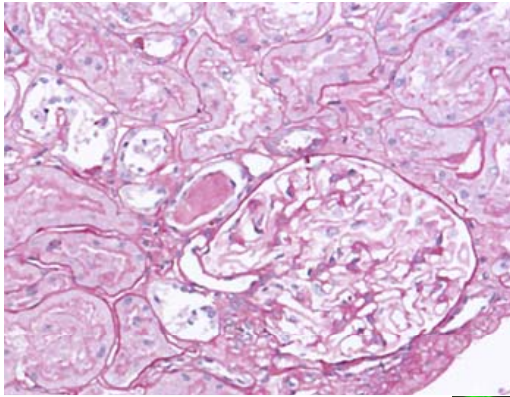
PTC Capillaritis, C4d+



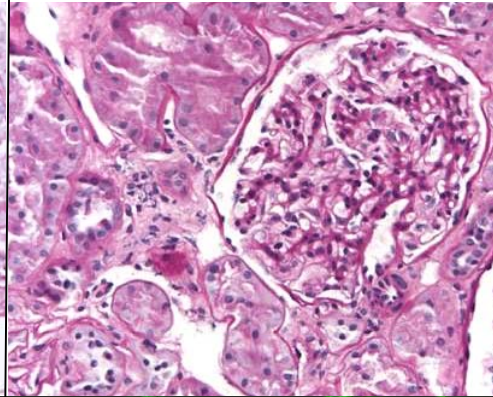
PTC BM Multilamination



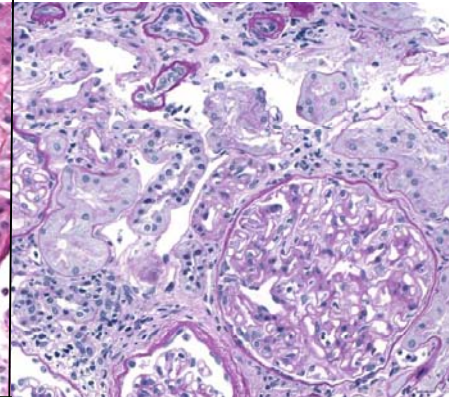
3 months - Cr 2.0



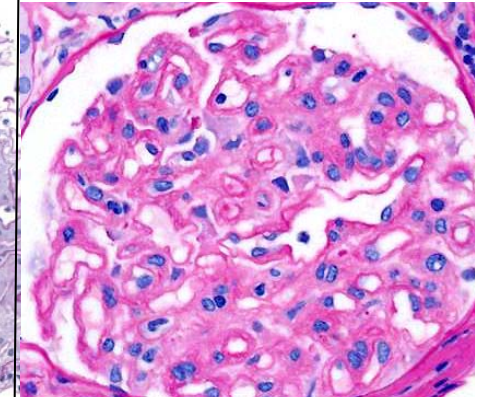
11 mo - Cr 1.5



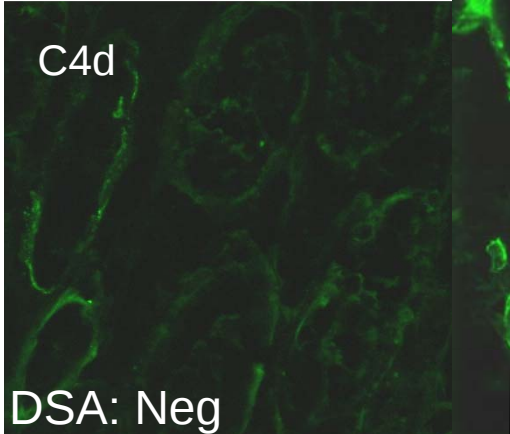
18 mo - Cr 1.7



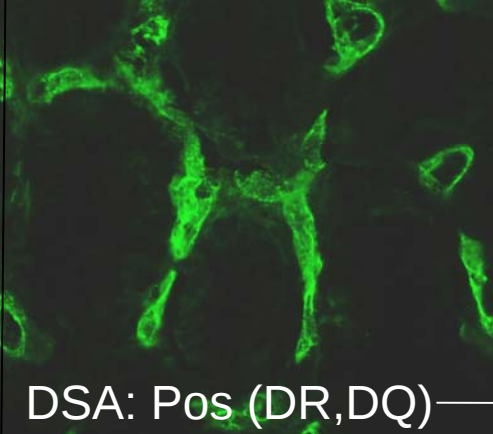
60 mo - Cr 1.8



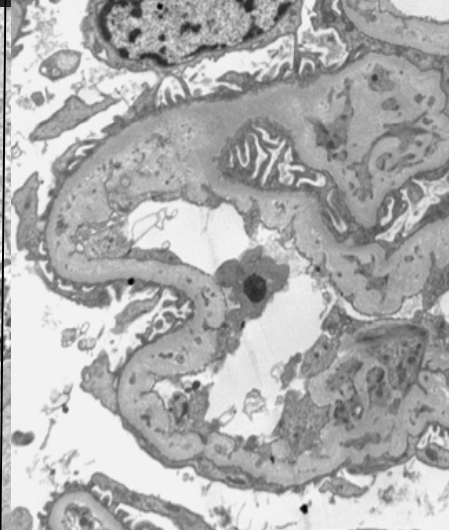
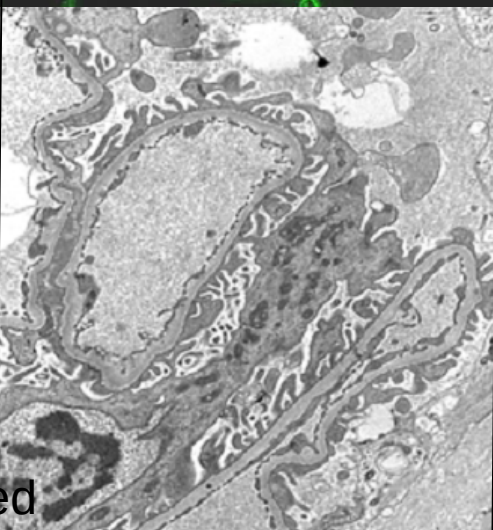
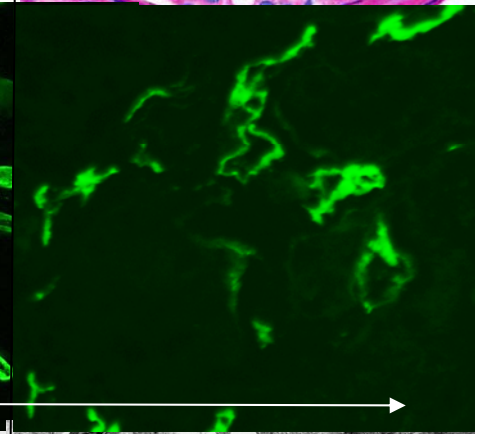
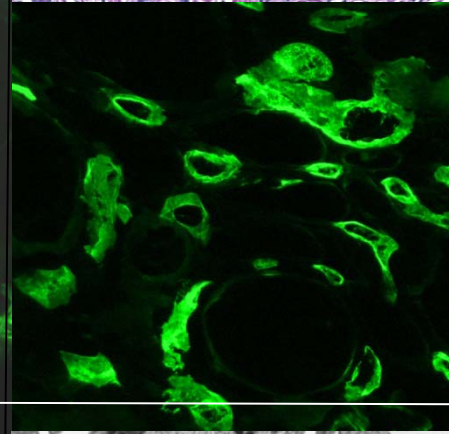
C4d



DSA: Neg

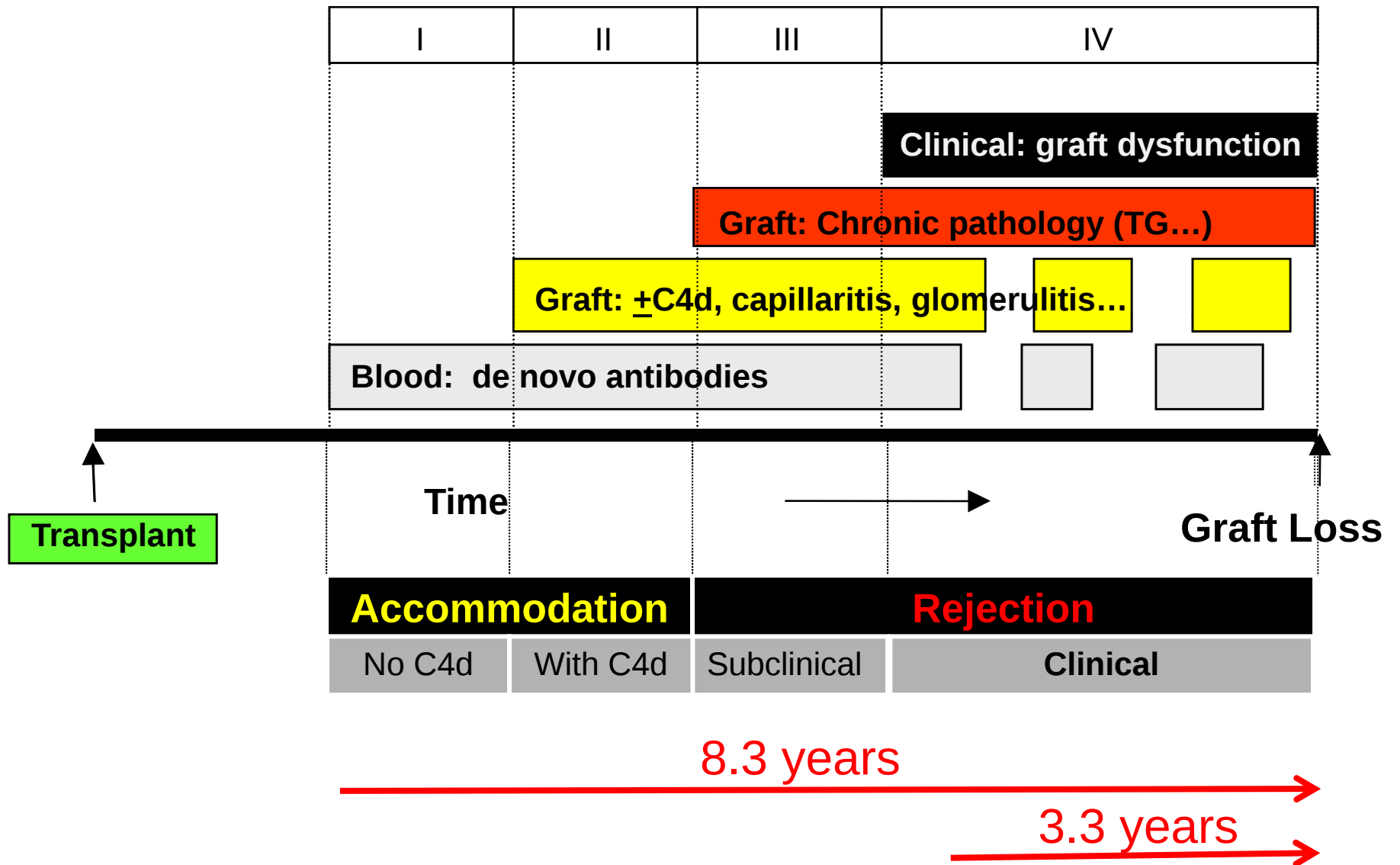


DSA: Pos (DR,DQ)



Colvin et al, unpublished

Stages of Chronic Antibody Mediated Rejection



Differences

Acute AMR

Usually presensitized

Rapid loss of function (days)

Anti donor HLA class I or II

Widespread C4d deposition
common

Capillaritis/glomerulitis
neutrophils/mononuclears

Chronic AMR

Usually de novo DSA

Association with TCMR

Insidious loss of function
(months-years)

Most cases not associated
with acute AMR

Anti-class II DSA common

Minimal C4d common

Capillaritis/glomerulitis
macrophages/NK

mRNA Differences

AMR: Presensitized DSA

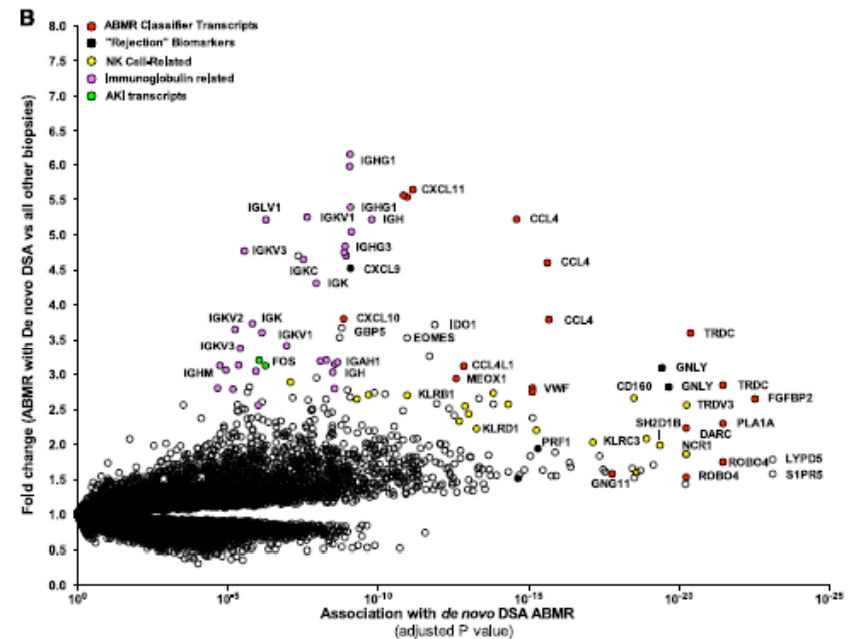
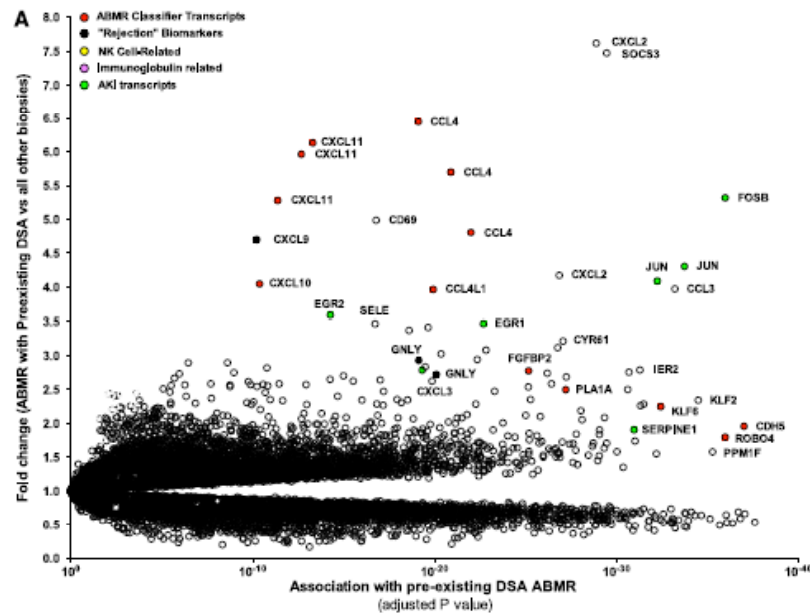
Injury repair response

AMR:De Novo DSA

T cell transcripts

NK transcripts

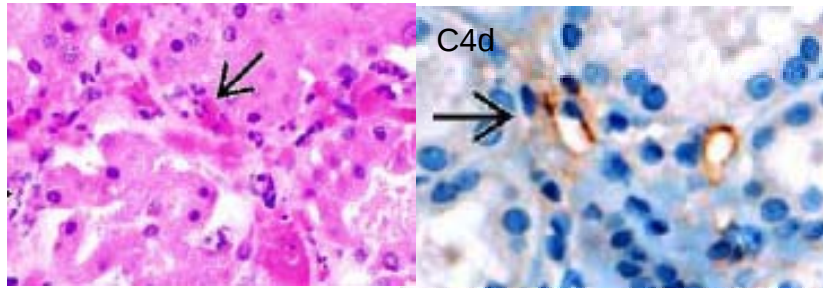
IFN γ related transcripts



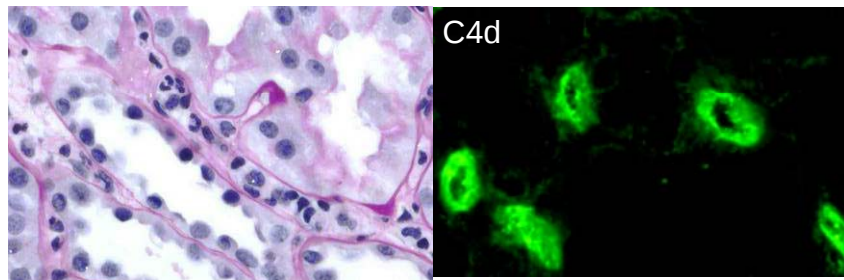
Aubert et al (Paris) JASN 2017

Why Different Effects of Antibody?

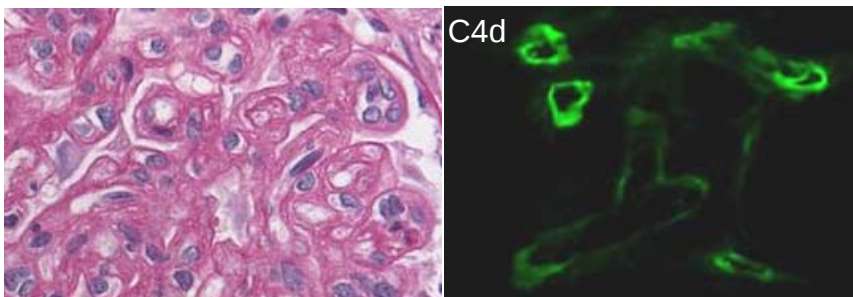
Hyperacute AMR



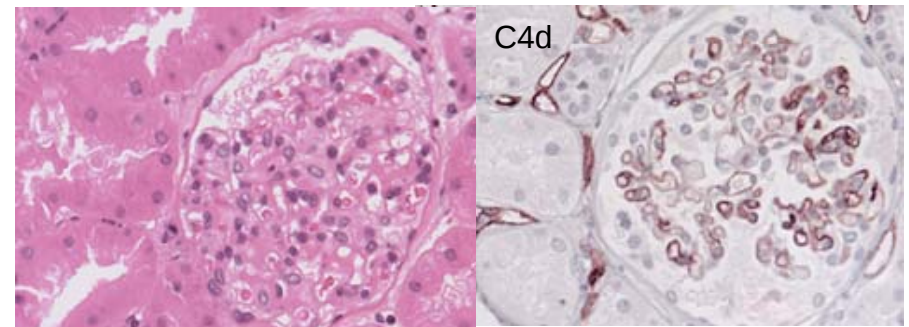
Acute AMR



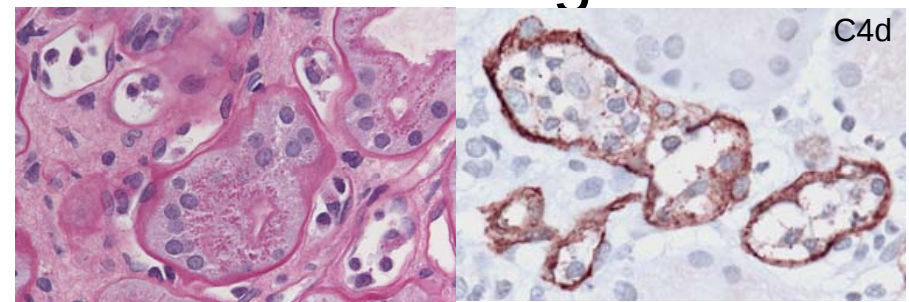
Chronic AMR



Accommodation

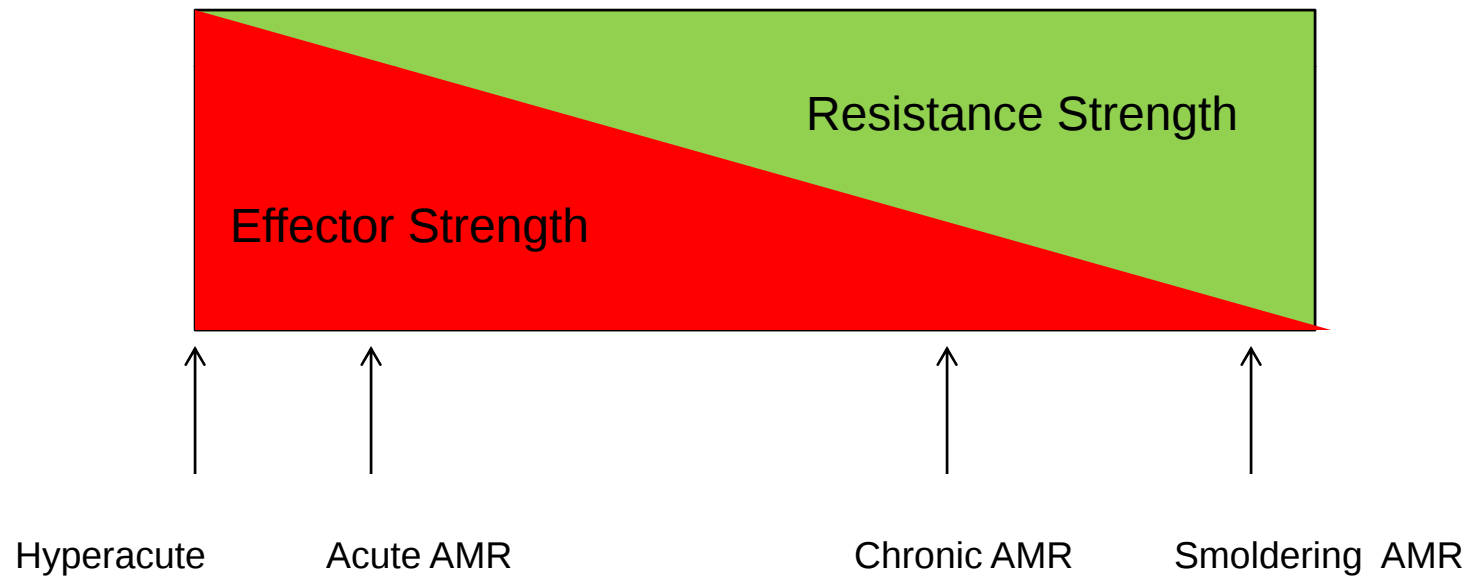


“Smoldering” AMR



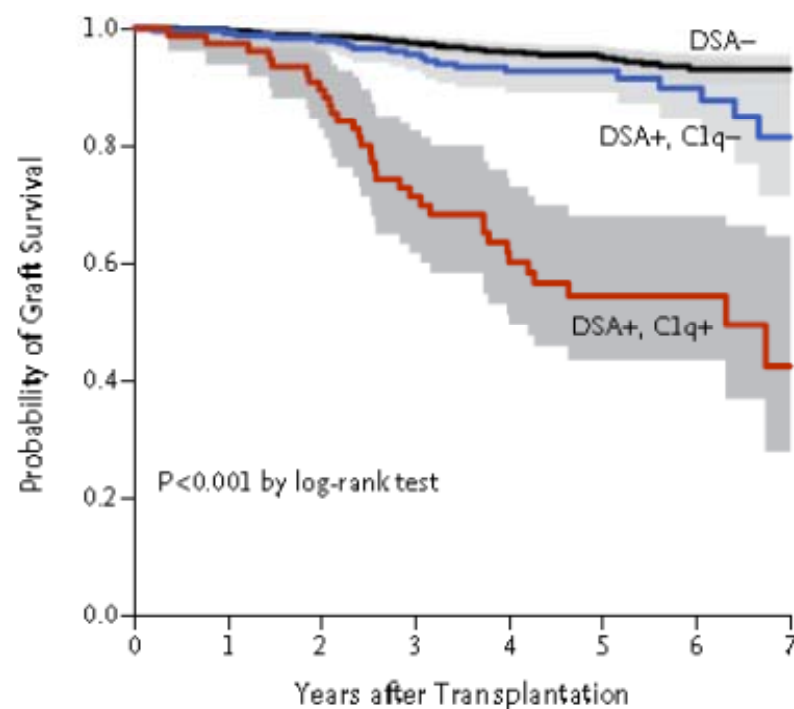
AMR = antibody mediated rejection

Effector/Resistance Theory



Complement Fixation Theory

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

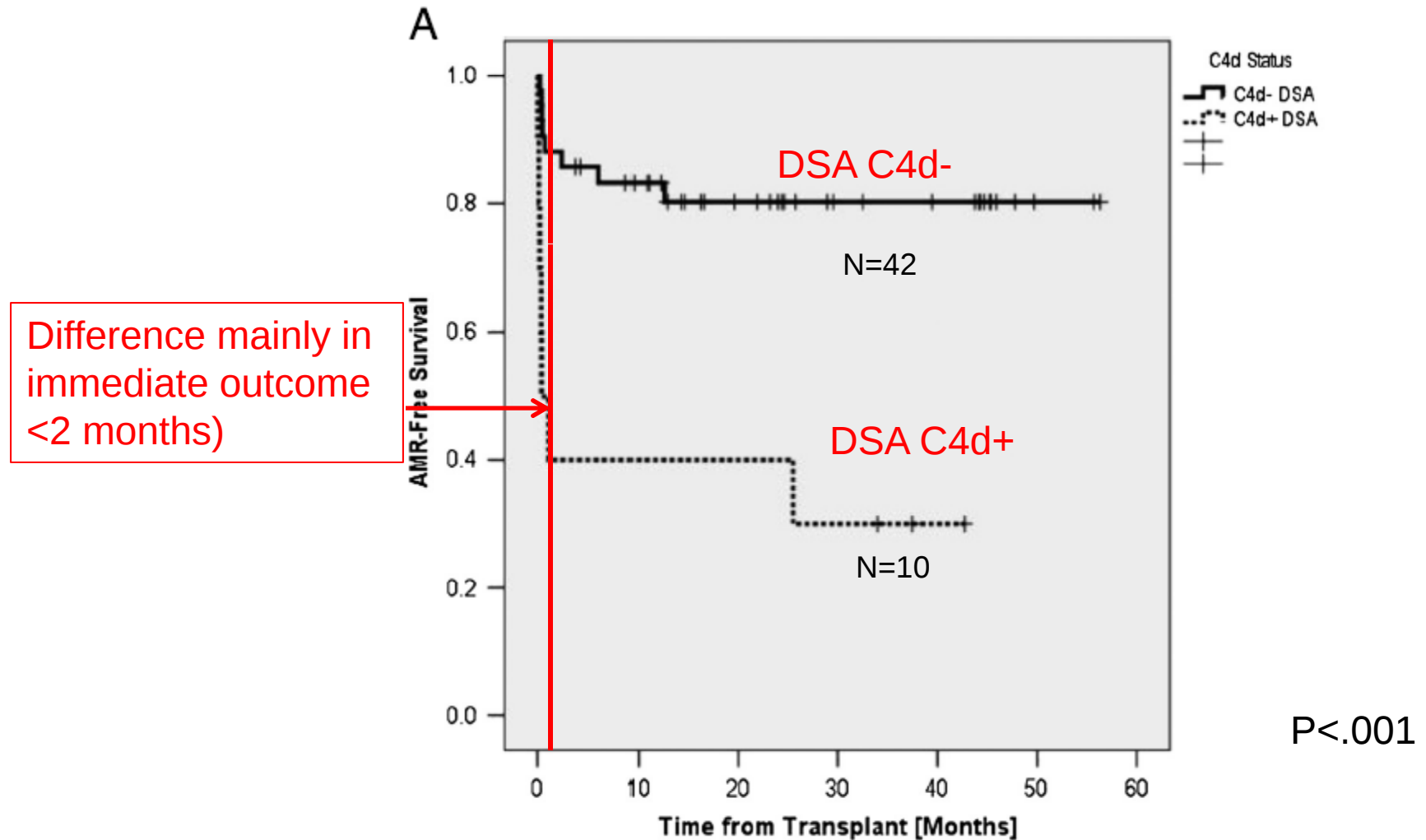


No. at Risk								
DSA-	700	698	667	612	504	338	164	38
DSA+, C1q-	239	237	227	181	139	80	44	14
DSA+, C1q+	77	75	68	48	37	20	12	5

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



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.”

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

B. J. Orandi¹, N. Alachkar², E. S. Kraus²,
F. Naqvi², B. E. Lonze¹, L. Lees³,
K. J. Van Arendonk¹, C. Wickliffe¹,
S. M. Bagnasco⁴, A. A. Zachary², D. L. Segev^{1,*}
and R. A. Montgomery¹

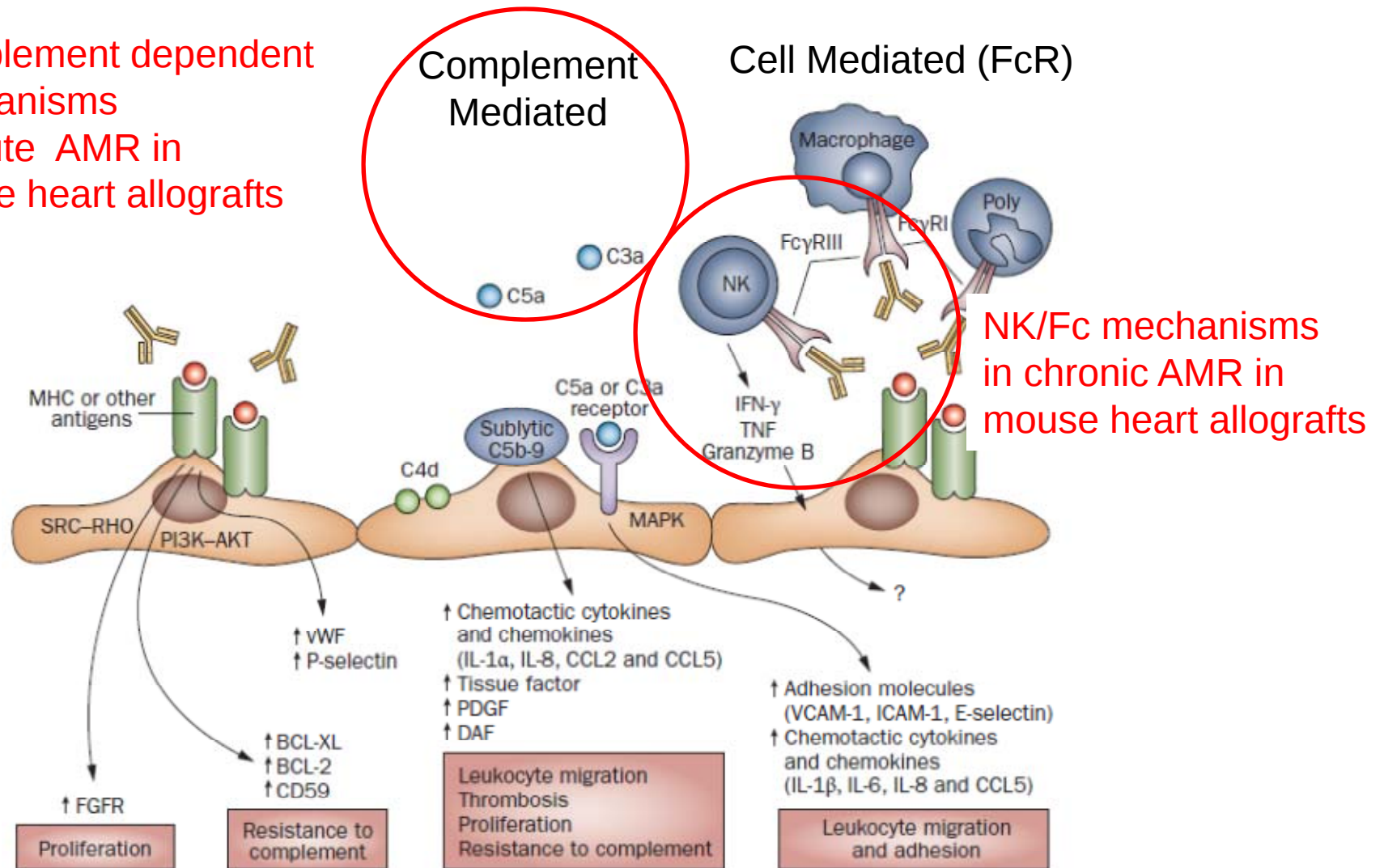
	C4d+	C4d-
N	156	51
Onset	14 d (8-32)	46 d (20-191)*
Graft dysfunction	85%	55%*
Graft loss at 1 yr	13.2%	6.6%
Risk of graft loss (vs no AMR)	3.7	2.56

*p<.001

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

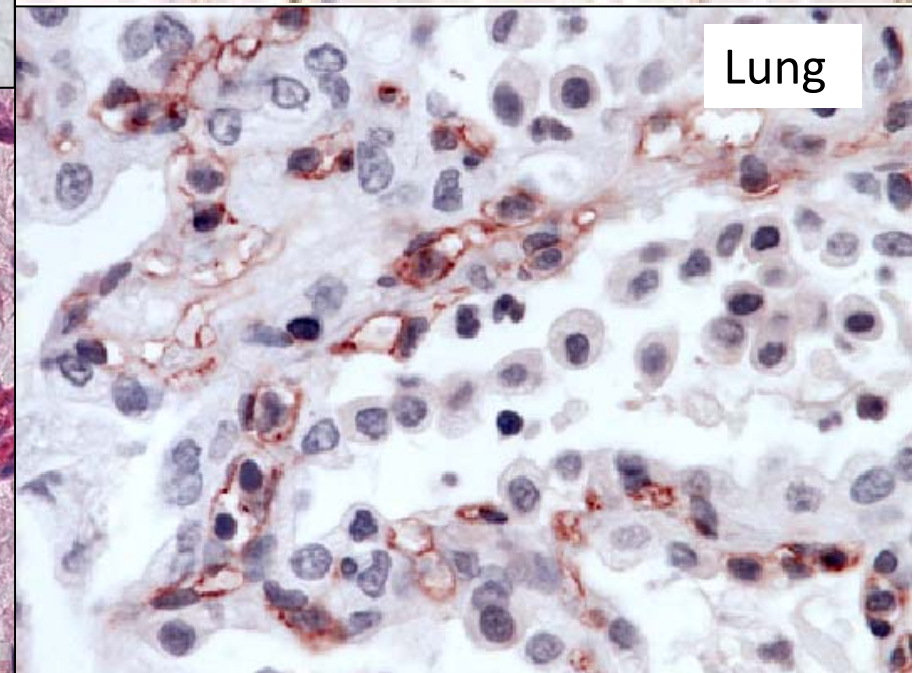
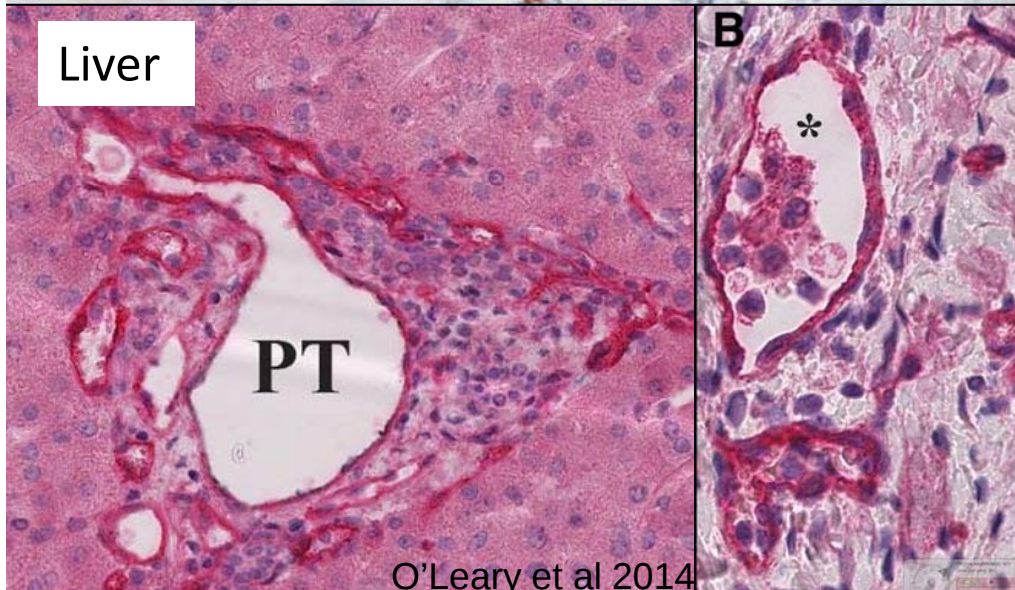
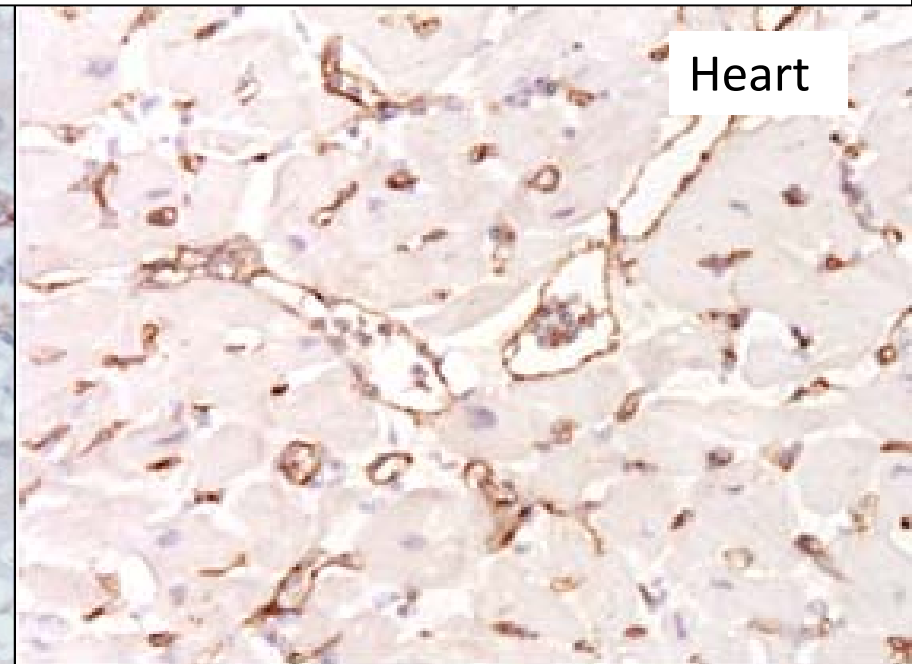
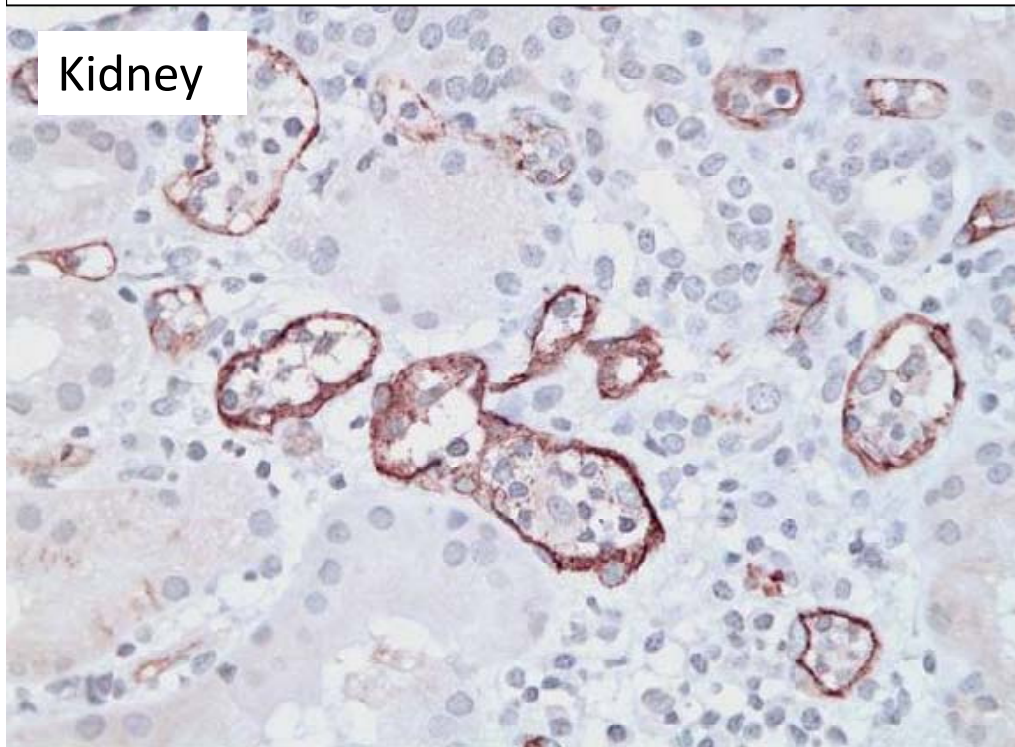
Mechanism Theory

Complement dependent mechanisms in acute AMR in mouse heart allografts



AMR in Other Organs

AMR Common Features: Capillaritis, C4d+, Dilation



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)



Research Group

Sandro Alessandrini
R. Neal Smith
Ivy Rosales
Tricia Della Pelle
Nicole Brousaides
Catherine Adams
Dorothy Ndishibandi
Rebecca White
Bernie Collins
Chao Yang
Paul Russell

Clinical

Nina Tolkoﬀ-Rubin
Ben Cosimi
Tatsuo Kawai
Jim Markman
Win Williams
Elliot Heher
Frank Delmonico
Jay Fishman

Histocompatibility

Susan Saidman

Monkey

Ben Cosimi
Tatsuo Kawai
David Sachs
Gilles Benichou
Joren Madsen

Pig

David Sachs
Akira Shimizu
Kazu Yamada
David Leonard

Edmonton

Michael Mengel
Ben Adam

Grant Support: NIAID, NHBLI