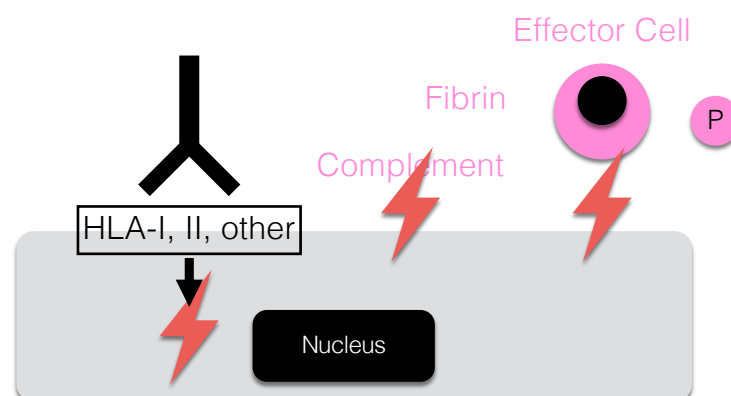# Histopathology of antibody-mediated rejection - Banff and beyond

PD Dr. med. Jan U. Becker
Institute of Pathology
University Hospital of Cologne
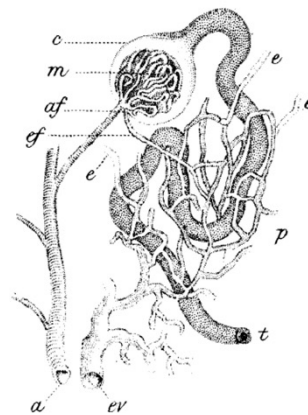Germany

Theory of ABMR

Effector Cell

Fibrin

P

Complement

HLA-I, II, other

Nucleus

Multidisciplinary approach

The Nephron by Bowman

16 Plan – Proportions as in Man.

Arteries

Activity

Activity

2079 transplanted patients from Paris
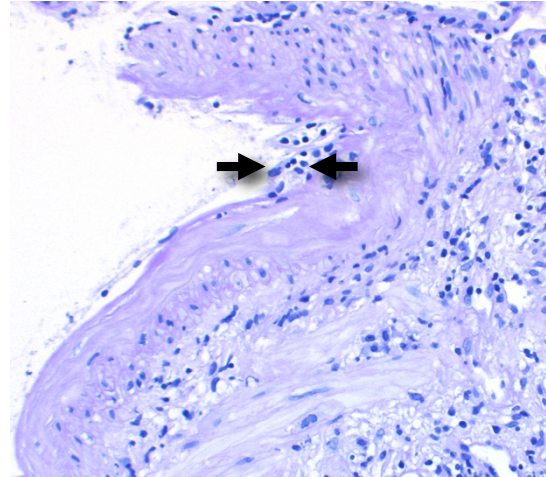
302 with rejection

90 with Arteritis

64/90 (71%) with ABMR
Lefaucheur, Lancet 2013
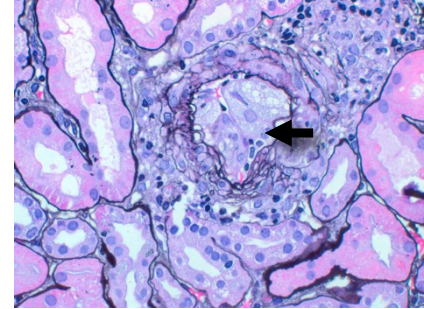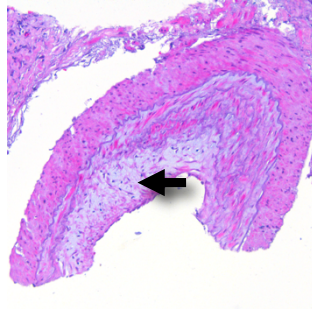
Inclusion in Banff 2013
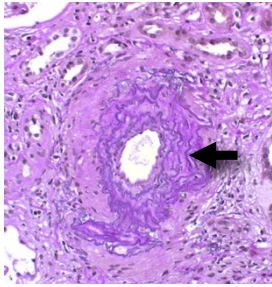Haas, Am J Transplant 2013

Chronicity

Transplant Vasculopathy

Defined as „accelerated atherosclerosis"[Hill, JASN 2011]

Transplant Vasculopathy

Hybrid lesion, recognised as chronicity parameter of ABMR if TCMR excluded, but only for „chronic active ABMR", not „chronic ABMR"

Can it not be recognised as both ABMR and TCMR, just like arteritis?

Phenotype/DSA association?

Correlation with microvascular manifestations?

Prognosis?

Arterioles

Arterioles

Manifestations of
active and chronic ABMR not
officially recognised

TMA, arteriolitis and
vasculopathy occur

Arteriolitis carries „poor
prognosis" Bellamy, Histopathology 2000

In practice, arteriolitis often
reported as arteritis

Glomerulus

Activity

Transplant glomerulitis
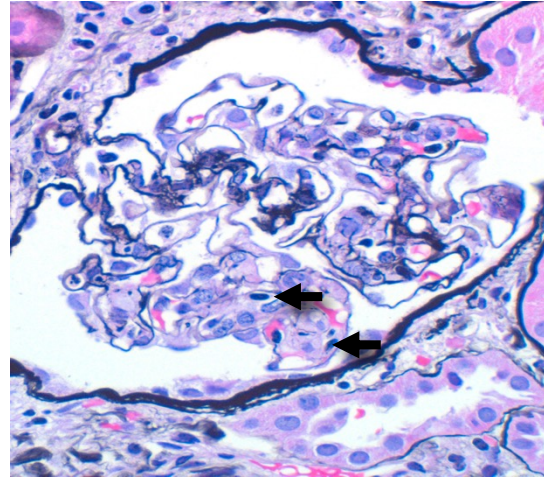
Indicator for rejection
Richardson, NEJM 1981

Broad definition in Banff 1997
Racusen, Am J Transpl 1999

Grading of 111 biopsies; currently best definition:
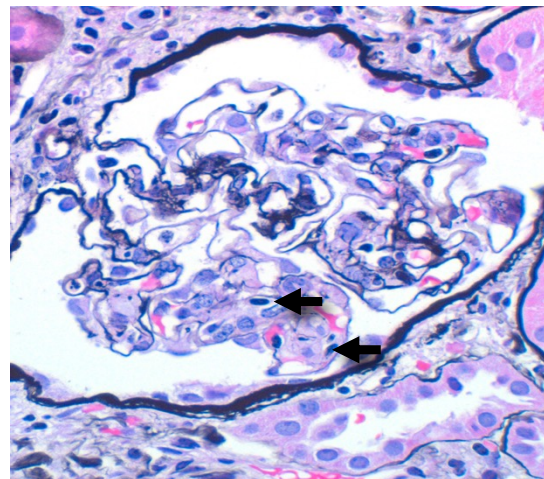≥5 leukocytes/glomerulus
Batal, Am J Transpl 2009

Transplant Glomerulitis- Changes with Banff 2013

Redefinition by Banff WG based on 47 cases without correlating outcome, just DSA and C4d
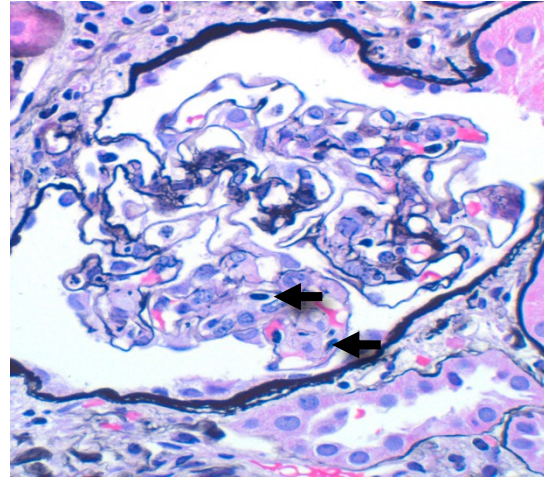Haas, Am J Transpl 2014

Improvement with IHC?

Transplant Glomerulitis- Changes with Banff 2013

For Banff g≥1 graft survival worse, regardless of DSA and C4d Nabokov, Transplantation 2015

(Glomerular) TMA

Definition varies widely
e.g. arterial or glomerular thrombi plus endothelial damage and/or glomerular or preglomerular wall remodeling Meehan, cJASN 2011

Subject of Banff WG

9/25 caused by ABMR, diminished glomerular ADAMTS13-mRNA
Agustian, Transplantation 2013

7/24 patients with *de novo* TMA had mutation in CFH or CFI
Le Quintrec, Am J Transpl 2008
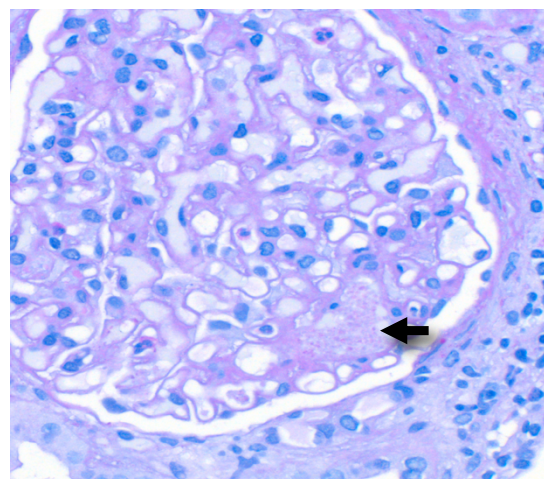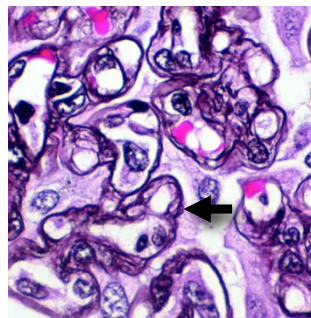
Chronicity

Transplant glomerulopathy

Transplant-glomerulopathy:
62% transplant loss
within 54 months ±19
Issa,Transplantation 2008

5.3fold increase in risk of graft
loss or doubling serum
creatinine
Lesage, Transplantation 2105

Immune complexes in ABMR

55 patients with TxG, after exclusion of de novo GN, immune complex GN as primary disease and Hepatitis C:
8 patients, 1/6 HLA-DSA+

Similar to F344 to Lewis kidney transplantation with multiple non-MHC-alloantibodies
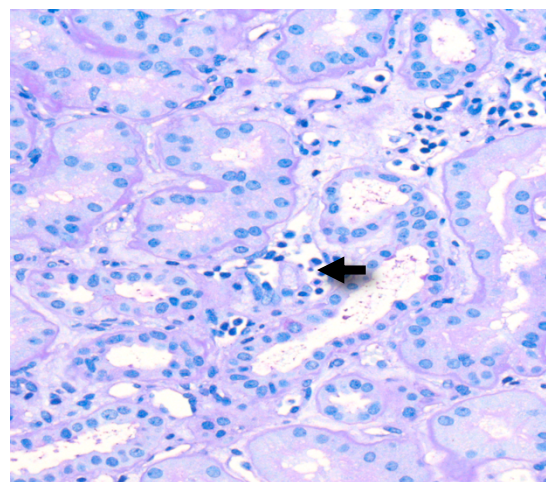Grau, Transplantation 2016
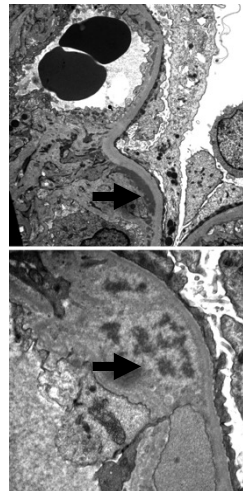
Peritubular Capillaries

Activity

Peritubular Capillaritis

Old criterion for ABMR
Halloran, Transplantation 1990

Banff Lesion Score ptc
Solez, Am J Tranpl 2008

Peritubulocapillary C4d
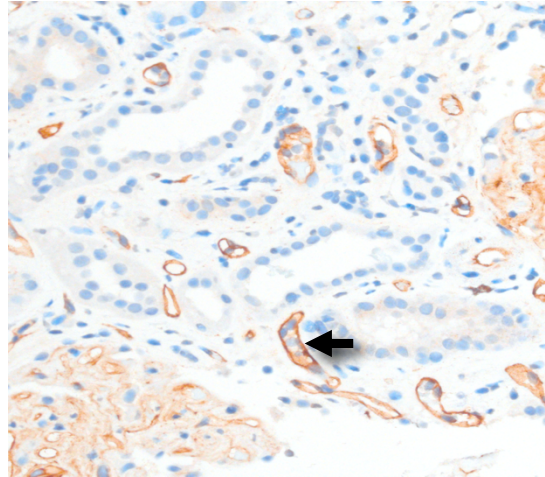
Medullary vasa recta also count

Sensitivity for DSA+ 35%, specificity 98%;
No independent predictor for graft loss
Sis, Am J Transpl 2012

With peritubular capillaritis, C4d irrelevant for prognosis
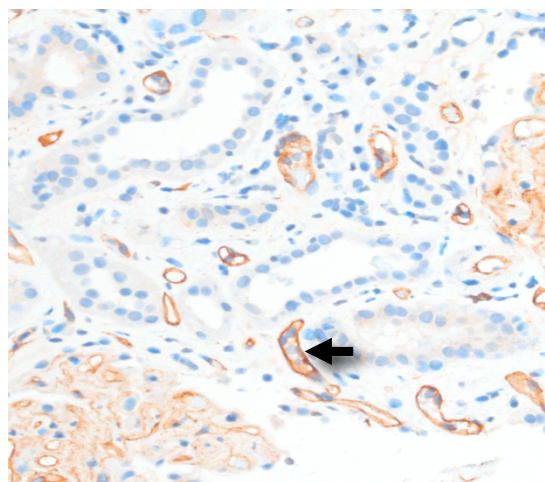de Kort, Am J Transpl 2013

Peritubulocapillary C4d

C4d usually negative with anti-AT1R-antibodies Banasik, Transplant Int 2014; Philogene, Transplantation 2017

C4d-negative ABMR is a fact

MVI vs. C4d

Glomerulitis and peritubular capillaritis can be summarized as MVI
Sis, AM J Transpl 2010, de Kort, Am J Transpl 2013

MVI most sensitive parameter for DSA+
Sis, AM J Transpl 2012

MVI correlates with graft loss within 4 years independently of C4d
de Kort, Am J Transpl 2013

The Return of C4d?

Initially, C4d-positivity with sensitivity and specificity for DSA+ of >90% with triple-layer IF Mauiyyeddi, JASN 2002

825 patients: Independent prognostic factor for graft survival
Kikic, cJASN 2015

Chronicity

Splitting of PTC Basement Membranes

Long known
Monga, Ultrastructural Pathology 1990

Barely visible by LM
Ivanyi, Human Pathology 2000

Indicates early chronic ABMR

Roufosse, Transplantation 2012

Precisely defined in Banff 2013
Haas, Am J Transplant 2012

Subject of Banff WG
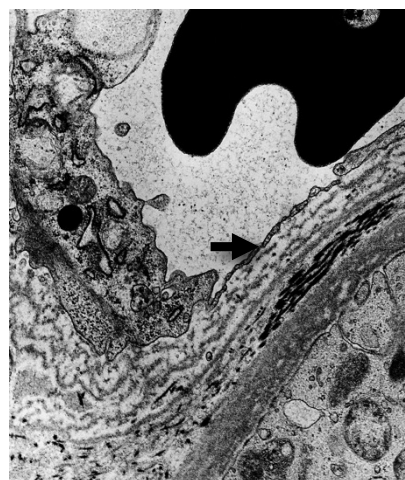
Tubulointerstitium

Tubulointerstitial Infiltrates

Concurrent acute TCMR (without Borderline) associated with worse prognosis in C4d+ ABMR Matignon, Transplantation 2012

Infiltrates in ABMR: mostly equivalent to Borderline acute TCMR
unpublished data

Do infiltrates concurrent with ABMR have a specific pattern?

Molecular Microscope

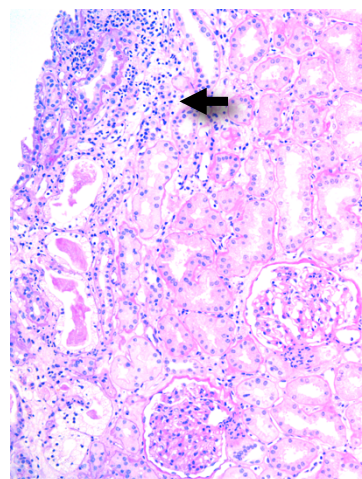One core for RNA-hybridisation array

Transcripts from largely unpublished data

DSASTs (DARC, ICAM-1, ROBO4, VE-Cadherin, MALL, COL13A1, H-Cadherin, TEK, SRY)

ENDATs (among others VWF, PECAM1, SELE, CD34, VE-Cadherin)

ENDATs validated in multicenter studies (INTERCOM-Study) Halloran, Am J Transpl 2013

The new gold standard?

ABMR according to Banff

Chronicity Parameters
Transplant vasculopathy, transplant glomerulopathy, severe peritubular capillary basement membrane multilayering

Activity Parameters
Arteritis, TMA, microvascular inflammation (glomerulitis and peritubular capillaritis, acute tubular damage)

Antibody Interaction with tissue
Microvascular inflammation (MVI)
C4d-positivity
Transcriptome

Donor-specific Antibodies or equivalents
anti-HLA or non-HLA
C4d-positivity
Transcriptome

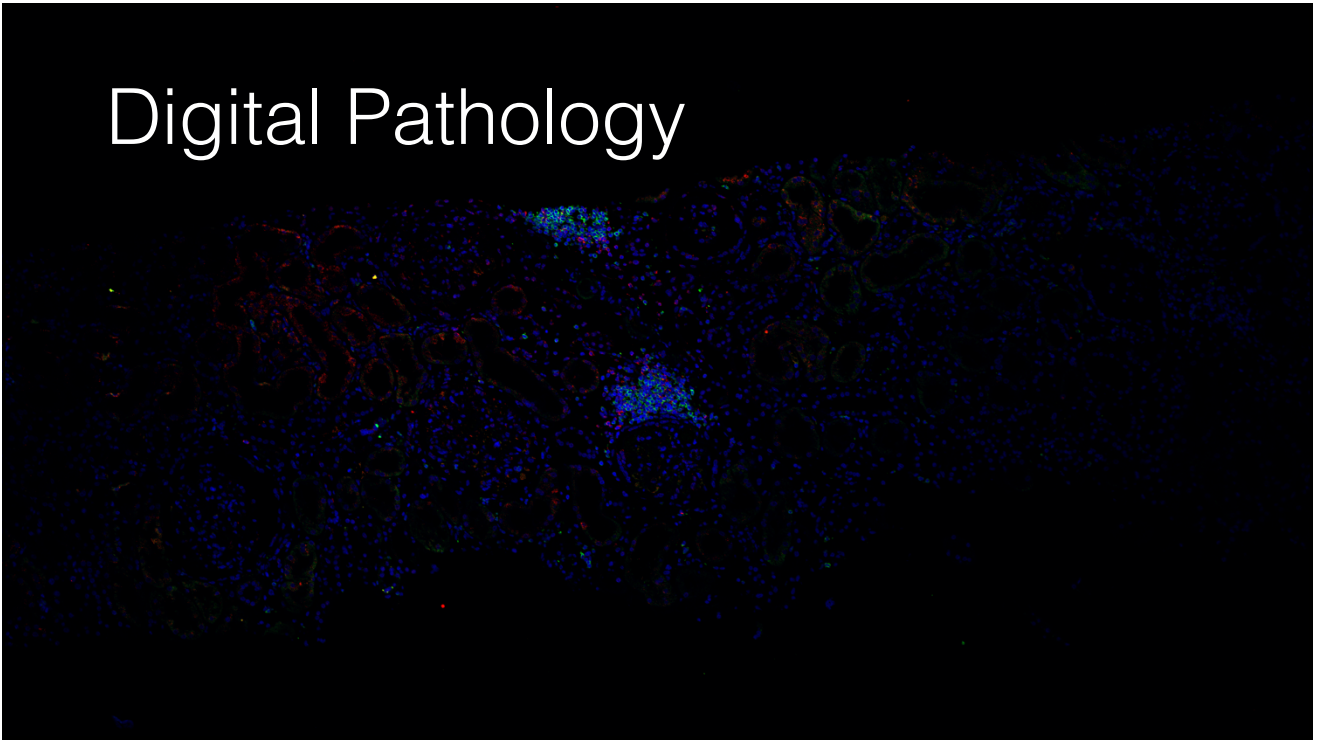# No method officially recognised by Banff
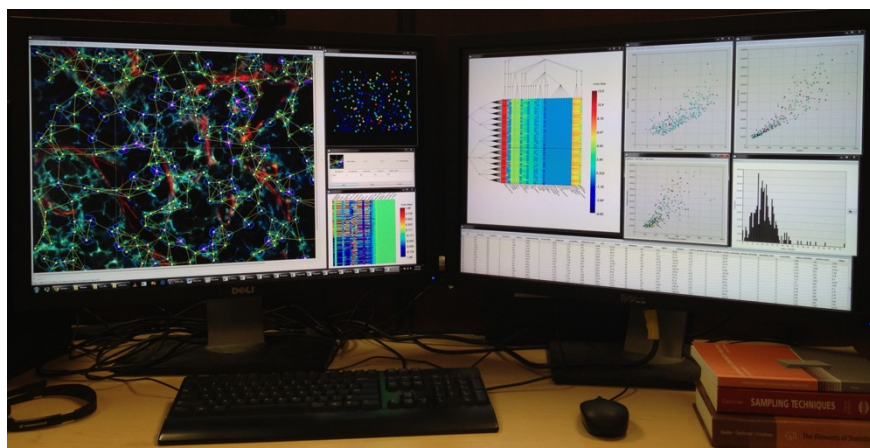
Novel ancillary Techniques

Endothelial-to-mesenchymal transdifferentiation:
„Strong endothelial neoexpression of vimentin, fascin 1 and HSP47"
Xu-Dubois, JASN 2015

Validation still missing

Digital Pathology

Digital Pathology

Homebrew qRT-PCR

Predictive model based on SH2D1b and MYBL1 correlates with graft survival <small>Dominy, Transplantation 2015</small>

Nanostring Banff Panel

800 mRNA transcripts for TCMR, ABMR, BKVN, IFTA

Currently under development, will be unveiled in Pittsburgh, September 2019 during Banff Meeting

2017 Banff ABMR Diagnoses

C4d-positivity without evidence of rejection

Active ABMR

Chronic active ABMR

Chronic ABMR Haas, Am J Transplant 2017

ABMR according to Banff

Chronicity Parameters
Transplant vasculopathy, transplant glomerulopathy, severe peritubular capillary basement membrane multilayering

Activity Parameters
Arteritis, microvascular inflammation (glomerulitis and peritubular capillaritis), TMA or acute tubular damage in the absence of any other apparent cause

Antibody Interaction with tissue
Moderate microvascular inflammation (MVI)
C4d-positivity
Transcriptome

Donor-specific Antibodies or Equivalents
anti-HLA or non-HLA DSA
C4d-positivity
Transcriptome

ABMR according to Banff

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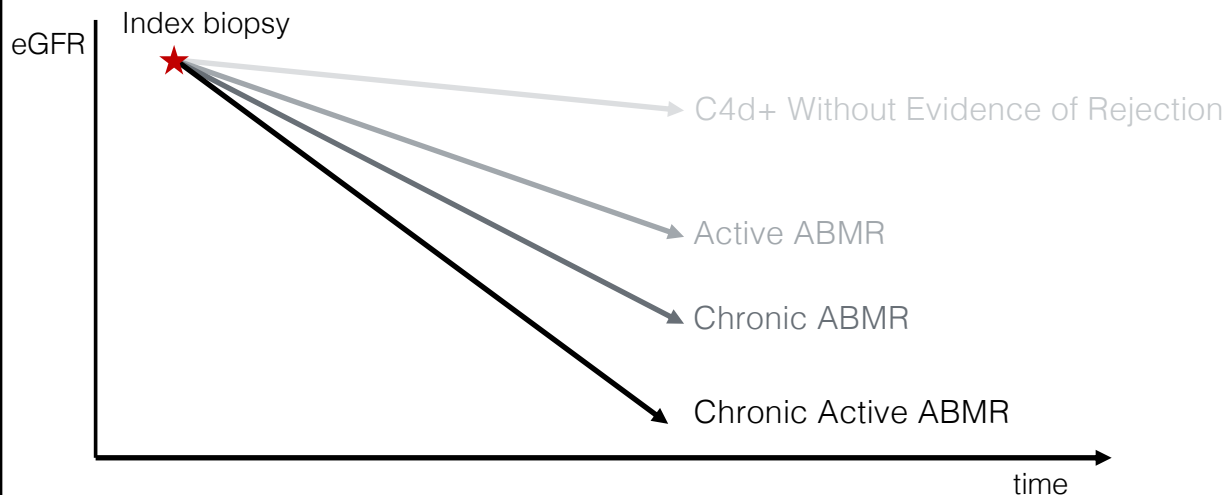
Specificity

Donor-specific Antibodies or Equivalents
anti-HLA or non-HLA DSA
C4d-positivity
Transcriptome

Examples

Data that do not exist

eGFR

Index biopsy

C4d+ Without Evidence of Rejection

Active ABMR

Chronic ABMR

Chronic Active ABMR

time

Considerable changes in the Banff Classification 1999-2017

Older literature lacks current-standard DSA testing

Comparison between studies difficult

Reproducibility issues Smith, Transpl Int 2019

Very little evidence for ABMR diagnoses

Beyond Banff?

Banff is a process with the classification as its product

We need to continuously improve the Banff Classification through introduction of novel techniques, collection of large cohorts, hard evidence (big data) and discussion
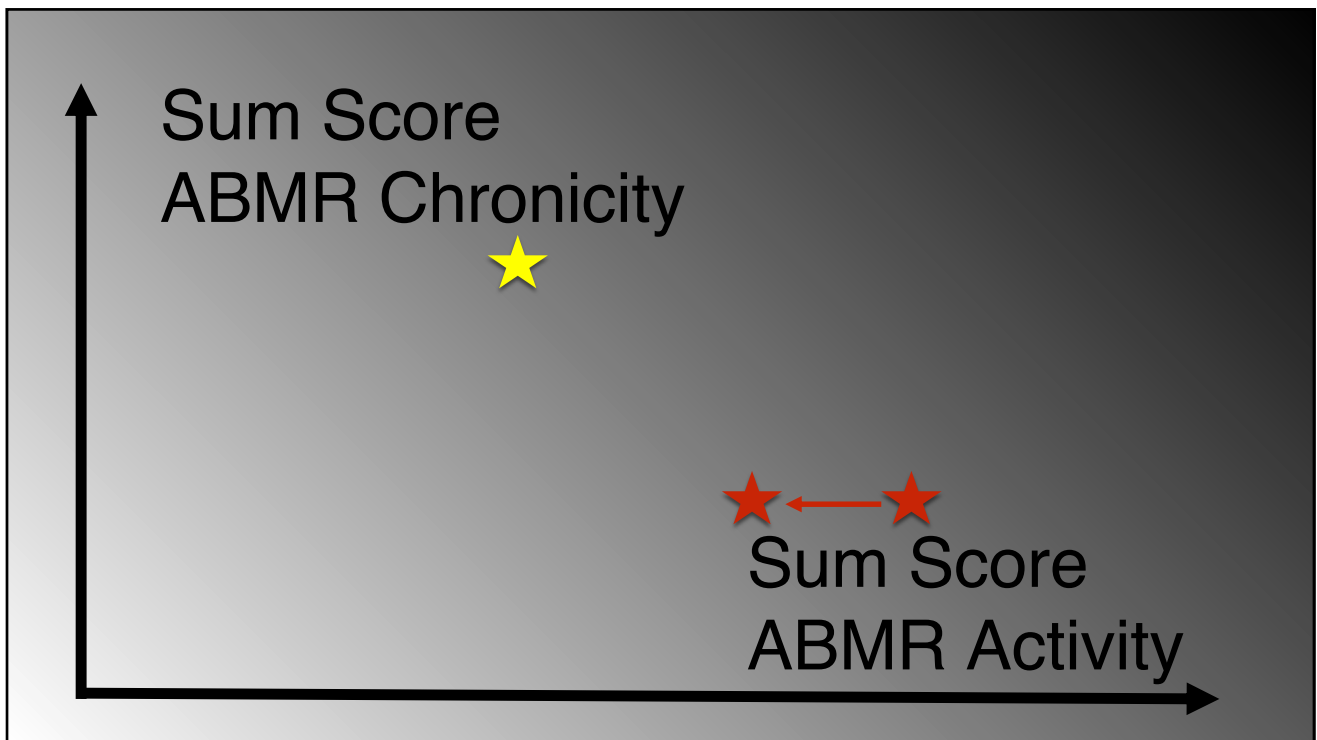
Going it alone is not an option

.. And for now?

Chronic (inactive) ABMR		Chronic active ABMR
No ABMR	C4d+ Without Evidence Of Rejection	Active ABMR

Very little evidence for ABMR diagnoses

Hypothesis

All transplants undergo rejection at all times, just with different activity

All ABMR parameters are independent predictors of worse outcome

Let's collaborate, pathologists!

Contact

Marion Rabant (Paris)
Pediatric Tx WG Nephropathology Panel Chair

or

me

Thank you!