Update on the Banff Classification

Michael Mengel
Department of Laboratory Medicine and Pathology
The Banff Process

Consensus communication in transplantation pathology

The Banff community
Pathologists
Nephrologists
Tx-Surgeons
Lab-Medicine

Banff Working Groups

Banff meetings
thesis-antithesis-synthesis
participate

The Banff lesions
g, l, t, v - score

moderated

refinement

The Banff classification
Current consensus for diagnostics

Feedback concerning weaknesses and strengths by results from independent research

New members
Biostaticians
Molecular Biologists
“Omics”-specialists

Off-springs
Liver
Pancreas
Lung, Heart
CTA
2015 BANFF-CST Joint Scientific Meeting
October 5 - 10, 2015 | Vancouver, British Columbia

Banffap@ualberta.ca
www.banfffoundation.org

admin@cst-transplant.ca
www.cst-transplant.ca
Major revision to Banff criteria for ABMR diagnosis in 2013

Meeting Report


18Department of Pathology and Laboratory Medicine, Division of Nephropathology, University of North Carolina at Chapel Hill, Chapel Hill, NC
19Department of Internal Medicine, University of Manitoba Health Sciences Centre, Winnipeg, Manitoba, Canada
20Department of Laboratory Medicine and Pathology, University of California, Los Angeles, CA
*Corresponding author: Mark Haas, mark.haas@cshs.org

The 12th Banff Conference on Allograft Pathology was held in Comandatuba, Brazil, from August 19–23, 2013, and was preceded by a 2-day Latin American
Clinical Relevance of Pretransplant Donor-Specific HLA Antibodies Detected by Single-Antigen Flow-Beads.
Amico, Patrizia; Honger, Gideon; Mayr, Michael; Steiger, Jurg; Hopfer, Helmut; Schaub, Stefan;

The significance of anti HLA antibodies

% Probability of AMR [%]
P<0.0001

De Novo Donor-Specific Antibody at the Time of Kidney Transplant Biopsy Associates with Microvascular Pathology and Late Graft Failure
L. G. Hidalgo* 1, P. M. Campbell* 2, B. Sie*, G. Emecke*, M. Mangol*, J. Chang*, J. Sellanes*, J. Reeve* and P. F. Halloran*
American Journal of Transplantation 2009; 9: 2532-2541

Significance of the Positive Crossmatch Test in Kidney Transplantation
Ramon Patel, M.R.C.P., and Paul I. Terasaki, Ph.D.
Diagnosis of ABMR

C4d positive acute ABMR

- Serological evidence:
  Donor specific antibody present.

- Immunopathologic evidence:
  IF: Diffuse positive C4d in PTC
  IHC: Diffuse or focal positive C4d in PTC

- Histological evidence:
  - ATN like changes; and/or
  - Peritubular capillaritis; and/or
  - Glomerulitis; and/or
  - Thrombotic microangiopathy; and/or
  - Arterial fibrinoid necrosis;
  - No evidence for chronic capillary injury
    (reduplication and/or multilayering of
    glomerular and peritubular capillary
    basement membranes)

C4d positive chronic active ABMR

- Serological evidence:
  Donor specific antibody present.

- Immunopathologic evidence:
  IF: Diffuse positive C4d in PTC
  IHC: Diffuse or focal positive C4d in PTC

- Histological evidence:
  - Transplant glomerulopathy; and/or
  - PTC basement membrane multilamination; and/or
  - Interstitial fibrosis with tubular atrophy; and/or
  - Fibrous intimal thickening of arteries
  - Glomerulitis and/or capillaritis may accompany

Important Consensuses Reached in the Development of Banff 2013 ABMR Criteria

ABMR (both acute/active and chronic, active) may now be diagnosed in the absence of C4d deposition.

However, in the absence of C4d additional evidence of current or recent antibody interaction with the vascular endothelium must be present; this will help avoid overdiagnosis of ABMR. Such evidence may be

morphologic, in the form of at least moderate microvascular inflammation,

or

molecular in the form of respective changes in the expression of transcripts associated with antibody-mediated tissue injury.

Banff 2013 Meeting Report: Haas et al. AJT 2014; 14: 272-283
Acute/Active ABMR; all 3 features must be present for diagnosis

1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation \((g > 0^b\text{ and/or } ptc > 0)\)
   - Intimal or transmural arteritis \((v > 0)^c\)
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation \(([g + ptc] > 2)^d\)
   - Molecular markers, such as increased expression of endothelial-associated transcripts

3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

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*a These lesions may be clinically acute, smoldering, or subclinical. Biopsies showing two of the 3 features may be designated as “suspicious” for acute/active ABMR.

*b Recurrent/de novo glomerulonephritis should be excluded

*c These lesions may be indicated of ABMR, TCMR, or mixed ABMR/TCMR

*d In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc > 2 alone is not sufficient to define moderate microvascular inflammation and g must be >1.
Chronic, Active ABMR; all three features must be present for diagnosis

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   - Transplant glomerulopathy (cg >0)\(^g\), if no evidence of chronic TMA
   - Severe peritubular capillary basement membrane multilayering (requires EM)\(^h\)
   - Arterial intimal fibrosis of new onset, excluding other causes

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation (\([g + ptc] >2\)\(^i\))
   - Molecular markers (e.g., incr. expression of endothelial-associated transcripts)

3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

---

\(f\) In the absence of evidence of current/recent antibody interaction with the endothelium (those features in section 2), the term active should be omitted; in such cases DSA may be present at the time of biopsy or at any previous time post-transplantation.

\(g\) Includes GBM duplication by electron microscopy only (cg1a) or GBM double contours by light microscopy

\(h\) \(\geq 7\) layers in 1 cortical peritubular capillary and \(\geq 5\) in 2 additional capillaries, avoiding portions cut tangentially

\(i\) In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc \(\geq 2\) alone is not sufficient to define moderate microvascular inflammation and g must be \(\geq 1\).
Important Consensuses Reached in the Development of Banff 2013 ABMR Criteria (3)

Intimal arteritis (v1 and v2) should be included among lesions satisfying histologic criteria for ABMR, based on findings of Le Faucheur, Loupy, Glotz et al, Lancet 381: 313-9, 2013; and presented at the 2013 Banff meeting.

In ABMR intimal arteritis is associated with an inferior prognosis, however these lesions are more commonly associated with mixed ABMR/TCMR than with “pure” ABMR, and may also be seen in pure TCMR in the absence of donor-specific antibodies.
Presentation of active, chronic-active, and chronic ABMR post renal transplantation

Halloran et al AJT 2016; in press
Increased microcirculation inflammation is associated with increased gene expression.
Clinical impact of 2013 Banff revisions

18% of patients

36% of patients
Transplant-Glomerulitis-Glomerulopathy
TG is usually a late pathology lesion in patients with DSA

Gloor et al, AJT 7: 2124-32, 2007
Early glomerular Endothelial Changes precede overt TG

- Endothelial Cell Swelling with Vacuolization, Loss of Fenestrations
- Subendothelial Electron-Lucent Widening
- Early GBM Duplication

Seen as early as 1 month post-transplant in grafts that developed TG 2-5 years later (Wavamunno et al, AJT 7: 1-12, 2007)
Proposal for standard definition and scoring system of Glomerular Double Contours

Chronic glomerulopathy (transplant glomerulopathy) is defined as presence of glomerular basement membrane duplications observed using PAS and/or silver stained sections in the absence of significant IC deposits along capillary walls by IF and/or EM studies.

cg0 – NO double contours of the GBM (0%) in any glomeruli using LM PAS/silver or EM.

cg1 – double contours of the GBM in 1-25% of capillaries in the most involved glomerulus by LM (cg1b) or EM (cg1a – see criteria below)

cg2 – double contours of the GBM in 26-50% of capillaries in the most involved glomerulus

cg3 – double contours of the GBM in >50% of capillaries in the most involved glomerulus

This new definition/threshold had better inter-observer agreement and better correlations with anti-class II DSAs and ENDATs than the current definition/threshold for cg

Banff 2013 Meeting Report: Haas et al. AJT 2014; 14: 272-283
Banff now recommends that tissue be taken for EM from renal allograft biopsies:

- If any clinical suspicion of recurrent or de novo glomerular disease
- If any significant proteinuria
- If specific risk factors for TG:
  - Pre-sensitized patients with positive crossmatch
  - History of DSA+, preformed or \textit{de novo}
  - History of C4d+ or microvascular inflammation (g, ptc) in a previous biopsy
- All biopsies $\geq 6$ months ($\geq 3$ months for indication biopsies) post-transplantation, looking for ultrastructural features of early TG & PTCBMML

Proposal by Ian Gibson, University of Manitoba
DSA alone is not bad, only for those allografts which develop ABMR.
Prevalence of de novo DSA in non pre-sensitized patients

Wiebe et al. AJT 2015; 15: 2921 - 2930
### Table 1: Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>All (n=508)</th>
<th>No dDSA (n = 388)</th>
<th>No dDSA (n = 56)</th>
<th>Subclinical dDSA (n = 45)</th>
<th>Clinical dDSA (n = 19)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First transplant</td>
<td>97%</td>
<td>97%</td>
<td>96%</td>
<td>98%</td>
<td>96%</td>
<td>0.9691</td>
</tr>
<tr>
<td>Recipient age at transplant (years)</td>
<td>43 ± 16</td>
<td>45 ± 15</td>
<td>37 ± 15</td>
<td>36 ± 18</td>
<td>29 ± 18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>39 ± 14</td>
<td>40 ± 15</td>
<td>42 ± 13</td>
<td>36 ± 14</td>
<td>36 ± 15</td>
<td>0.1265</td>
</tr>
<tr>
<td>Recipient ethnicity</td>
<td>69%</td>
<td>68%</td>
<td>59%</td>
<td>80%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>18%</td>
<td>18%</td>
<td>23%</td>
<td>14%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Aboriginal</td>
<td>11%</td>
<td>13%</td>
<td>14%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
<td>0%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>HL-A/AB/DR/DO</td>
<td>4.0 ± 2.0</td>
<td>4.0 ± 2.1</td>
<td>3.7 ± 2.2</td>
<td>4.5 ± 1.3</td>
<td>3.9 ± 1.4</td>
<td>0.3134</td>
</tr>
<tr>
<td>Mismatch</td>
<td>7.4 ± 5.6</td>
<td>6.9 ± 5.4</td>
<td>9.5 ± 6.6</td>
<td>8.3 ± 5.9</td>
<td>8.9 ± 5.5</td>
<td>0.0025</td>
</tr>
<tr>
<td>Cold ischemic time (hours)</td>
<td>14%</td>
<td>12%</td>
<td>25%</td>
<td>9%</td>
<td>26%</td>
<td>0.0386</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>15%</td>
<td>5%</td>
<td>18%</td>
<td>24%</td>
<td>90%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cell rejection 0–12 months</td>
<td>0.2 ± 0.5</td>
<td>0.1 ± 0.3</td>
<td>0.4 ± 0.8</td>
<td>0.3 ± 0.6</td>
<td>0.8 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months to dDSA detection (months)</td>
<td>58 ± 19</td>
<td>60 ± 20</td>
<td>53 ± 17</td>
<td>60 ± 17</td>
<td>57 ± 20</td>
<td>0.3069</td>
</tr>
<tr>
<td>eGFR 6 months postrx</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>eGFR 6 months postrx</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>eGFR at dDSA development</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>eGFR 1 year post-dDSA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>eGFR 2 years post-dDSA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>eGFR 3 years post-dDSA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>eGFR 5 years posttransplant</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Univariate clinical predictors</th>
<th>Multivariate clinical predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (per year)</td>
<td>0.99 (0.95–0.99)</td>
<td>0.0465</td>
</tr>
<tr>
<td>Donor age (per year)</td>
<td>1.00 (0.97–1.02)</td>
<td>0.7745</td>
</tr>
<tr>
<td>Decreased versus living donor</td>
<td>1.81 (0.9–4.4)</td>
<td>0.1500</td>
</tr>
<tr>
<td>HLA-AB/DR/DO mismatch (per mismatch)</td>
<td>0.87 (0.6–1.3)</td>
<td>0.3633</td>
</tr>
<tr>
<td>Cold ischemic time (per hour)</td>
<td>1.06 (0.99–1.03)</td>
<td>0.0674</td>
</tr>
<tr>
<td>Delayed graft function (yes vs. no)</td>
<td>3.78 (1.2–10.0)</td>
<td>0.0250</td>
</tr>
<tr>
<td>TCMR episodes ≤12 months (per episode)</td>
<td>1.74 (1.0–2.9)</td>
<td>0.0505</td>
</tr>
<tr>
<td>Nonadherence (yes vs. no)</td>
<td>5.51 (3.3–15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>dDSA phenotype (clinical vs. subclinical)</td>
<td>4.96 (2.2–11.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MFI urea (per 1000 MFI)</td>
<td>1.01 (1.0–1.03)</td>
<td>0.0993</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Univariate histologic predictors</th>
<th>Multivariate histologic predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>g</td>
<td>1.53 (0.9–2.9)</td>
<td>0.2015</td>
</tr>
<tr>
<td>i</td>
<td>1.77 (1.2–2.9)</td>
<td>0.0083</td>
</tr>
<tr>
<td>v</td>
<td>2.73 (1.6–5.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>v</td>
<td>0.95 (0.2–1.3)</td>
<td>0.9240</td>
</tr>
<tr>
<td>ptc</td>
<td>1.11 (0.7–1.6)</td>
<td>0.6663</td>
</tr>
<tr>
<td>C4d</td>
<td>3.3 (0.4–2.4)</td>
<td>0.6203</td>
</tr>
<tr>
<td>eq</td>
<td>2.14 (0.9–4.4)</td>
<td>0.0575</td>
</tr>
<tr>
<td>dp</td>
<td>1.38 (0.8–2.1)</td>
<td>0.2753</td>
</tr>
<tr>
<td>ct</td>
<td>1.36 (0.8–2.4)</td>
<td>0.2940</td>
</tr>
<tr>
<td>cv</td>
<td>1.11 (0.6–2.1)</td>
<td>0.7434</td>
</tr>
</tbody>
</table>

Percent of biopsies with each Banff score in 10,12,23. Hazard ratio (HR) per Banff score increase; CI, confidence interval; c, chronic glomerulopathy; ci, interstitial fibrosis; ct, tubular atrophy; cv, chronic vasculopathy; dDSA, de novo donor-specific antibody; g, glomerular inflammation; i, interstitial inflammation; pts, peritubular capillaritis; TCMR, T cell-mediated rejection; t, tubulitis; v, interstitial.
Adoption of molecular ABMR diagnostics
Three Pathways to Antibody Mediated Injury

Antibody Alone
- MHC or other antigens
- SRC-RHO
- PI3K-AKT
- Proliferation
- Resistance to complement
- ↑ vWF
- ↑ P-selectin
- ↑ BCL-XL
- ↑ BCL-2
- ↑ CD59
- ↑ FGFR

Complement Mediated
- C3a
- C5a or C3a receptor
- Sublytic C5b-9
- C4d
- Chemotactic cytokines and chemokines (IL-1α, IL-8, CCL2 and CCL5)
- ↑ Tissue factor
- ↑ PDGF
- ↑ DAF
- Leukocyte migration
- Thrombosis
- Proliferation
- Resistance to complement

Cell Mediated (FcR)
- Macrophage
- NK
- FcγRI
- FcγRIII
- Poly
- FcγRIIIB
- IFN-γ
- TNF
- Granzyme B
- ↑ Adhesion molecules (VCAM-1, ICAM-1, E-selectin)
- ↑ Chemotactic cytokines and chemokines (IL-1β, IL-6, IL-8 and CCL5)
- Leukocyte migration and adhesion

Farkash and Colvin, Nat Rev Nephrol 8:255, 2012
Transcripts selectively associated with DSA: Endothelial and NK cell transcripts

A 132 DSA-associated transcripts

DSA+ ▶ DSA neg

Rejection classified biopsies (n = 78)

23 transcripts (FDR < 0.05)

B

NK

C

endothelial

D

Hidalgo et al. AJT 2010; 10: 1812–1822
Endothelial stress accelerates graft loss in transplant glomerulopathy (TG) despite lack of C4d staining

Cumulative survival

Post-biopsy time (months)

TG with no ENDAT, n=13
TG with ENDAT and no C4d, n=17
TG with ENDAT and C4d, n=10

Sis et al. abstract ATC 2013
Routine Formalin-fixed, paraffin-embedded (FFPE) NanoString gene expression assay workflow for assessing the molecular signature of ABMR.

<table>
<thead>
<tr>
<th>Serologic/histologic feature</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor specific antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I or II</td>
<td>0.587</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class II</td>
<td>0.483</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class I</td>
<td>0.320</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ABMR-related lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritubular capillaritis (ptc)</td>
<td>0.507</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transplant glomerulopathy (cg)</td>
<td>0.442</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerulitis (g)</td>
<td>0.421</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TCMR-related lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial inflammation (i)</td>
<td>0.315</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tubulitis (t)</td>
<td>0.199</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>ABMR and TCMR-related lesion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimal arteritis (v)</td>
<td>0.055</td>
<td>0.456</td>
</tr>
<tr>
<td><strong>Scarring/atrophy-related lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesangial matrix increase (mm)</td>
<td>0.379</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interstitial fibrosis (ci)</td>
<td>0.342</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tubular atrophy (ct)</td>
<td>0.275</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arteriolar hyalinosis (ah)</td>
<td>0.266</td>
<td>&lt;0.001</td>
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<tr>
<td>Total interstitial inflammation (ti)</td>
<td>0.388</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial intimal thickening (cv)</td>
<td>0.189</td>
<td>0.009</td>
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<tr>
<td><strong>Immunopathology</strong></td>
<td></td>
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<tr>
<td>C4d-positive</td>
<td>0.123</td>
<td>0.094</td>
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<tr>
<td>Electron microscopy</td>
<td></td>
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<tr>
<td>PTCBMML²</td>
<td>0.421</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Indications

- **Diagnosis**
  - TCMR
  - ABMR
  - Injury, acute
  - Injury, chronic

- **Prediction (prognosis)**
  - Failure
  - Initial function / DGF
  - Response to treatment (Companion Diagnostic)

- **Treatment monitoring**
  - Response to treatment (post treatment)
  - Side effects / dosing

## Applications

- **Tissue / biopsy**

- **Body fluids**
  - Urine
  - Blood
  - bile

## Methods

- **Targets**
  - mRNA
  - miRNA
  - free DNA
  - Proteins
  - metabolites

- **Platforms**
  - PCR
  - Microarrays
  - ELISA
  - Flow
  - NanoString
  - Luminex
  - IHC
  - ........
Defining a diagnostic threshold on a continuous disease scale

Costs:
- Treatment
- Health Care
- Society

Benefits:
- Survival
- Health Care
- Society

Overtreated

Undertreated

Diagnostic Assay Threshold
Outcome Banff 2015 meeting:
A path towards adoption of molecular pathology into Banff

<table>
<thead>
<tr>
<th>The Path toward adoption of molecular pathology by the Banff classification: prospect for companion to standard histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The main area of application should focus on rejection diagnosis</td>
</tr>
<tr>
<td>• The primary effort should be on applying molecular studies to biopsies</td>
</tr>
<tr>
<td>• Reference data sets should be well annotated and studied (anti HLA DSA)</td>
</tr>
<tr>
<td>• Accurate phenotypes for all biopsies are needed</td>
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<tr>
<td>• Pathology spectrum needs to be comprehensive: i.e. ABMR subtypes, AKI, GN, TCMR, ABMR, mixed, PVN</td>
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<td>• Pathogenesis based transcript strategy appears useful and can be completed by classifier approaches</td>
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<tr>
<td>• No single gene is specific for a disease</td>
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<tr>
<td>• Proper methodological approaches are needed (for both assay performance and data analysis,)</td>
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<tr>
<td>• Quality Assurance is mandatory (inter-laboratory, inter-platform and inter-assay reproducibility; development of standardized positive and negative controls and quantitative diagnostic reference standard)</td>
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# Outcome Banff 2015 meeting:
Knowledge gaps to be addressed before Banff can fully adopt molecular diagnostics

<table>
<thead>
<tr>
<th>Antibody-mediated rejection</th>
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<tbody>
<tr>
<td>Comparison of sub-clinical ABMR versus clinical ABMR</td>
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<tr>
<td>Comparison of TCMR with and without DSA, but no glomerulitis or TG (note: ptc-itis is often seen with TCMR)</td>
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<tr>
<td>Comparison of DSA-negative biopsies versus DSA-positive biopsies in sequence from the same patient</td>
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<tr>
<td>Comparison of matched biopsies from adherent versus non-adherent patients</td>
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<tr>
<td>Comparison of histologically similar biopsies from patients with anti-HLA versus anti-non-HLA DSA</td>
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<tr>
<td>Comparison of ABMR biopsies with TMA to TMA in native kidneys</td>
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<tr>
<td>Comparison of consensus gene sets to diagnostic ABMR classifiers</td>
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</tbody>
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<thead>
<tr>
<th>T-Cell mediated rejection</th>
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</thead>
<tbody>
<tr>
<td>Comparison of early versus late TCMR with different levels of Banff i, t, and i-IFTA score</td>
</tr>
<tr>
<td>Define the molecular phenotype of borderline cases in the current clinical context, (i.e., after elimination of ABMR and mixed cases)</td>
</tr>
<tr>
<td>Comparison of consensus gene sets to diagnostic TCMR classifiers</td>
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<thead>
<tr>
<th>Mixed rejection</th>
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<tr>
<td>Should be a focus since recent data suggest that most cases of ABMR (at least in non-sensitized, non-adherent patients) are mixed rejection</td>
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<tr>
<td>Testing the utility of one common rejection gene signature or classifier versus two separate classifiers for ABMR and TCMR in mixed cases</td>
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</table>
# Ongoing activities through Banff Working Groups

<table>
<thead>
<tr>
<th>Working Group Leaders</th>
<th>TCMR</th>
<th>Highly Sensitized</th>
<th>Molecular</th>
<th>Electron Microscopy</th>
<th>TMA</th>
<th>Repeat Biopsy</th>
<th>Recurrent Glomerular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volker Nickeleit</td>
<td>Lynn Cornell, Ed Kraus</td>
<td>Banu Sis, Michael Mengel</td>
<td>Candice Roufosse, Sharan Singh</td>
<td>Marjan Afrouzian, Helen Liapis</td>
<td>TBD</td>
<td>Nada Alachkar, Pathologist TBD</td>
<td></td>
</tr>
</tbody>
</table>

## Issues to Address
- Possible incorporation of I-IFTA into classification; possible elimination of borderline category; re-evaluate thresholds for i and t and possible addition of other findings (e.g., edema) to TCMR diagnostic criteria
- Define criteria for highly sensitized patients (HS), determine consensus for what personnel and facilities are needed for centers to perform transplantation in HS recipients
- Develop consensus guidelines for circumstances under which it is advisable to molecular analysis on renal biopsy tissue and/or serum/urine collected at the time of biopsy.
- Determine what are the best molecular studies to perform under specific circumstances.
- Standardize diagnostic criteria for "molecular microscope"
- Inter-observer variability and clinical correlations in cgt1a lesions and ptcbmi
- Criteria for amount of immune complex deposit allowable in cgt1a
- TBD; seek possible funding from Alexion

## Group Findings/Plans
- Group currently collecting cases of "pure" TCMR (no DSA or C4d) for pathologic evaluation and clinic-pathologic correlation
- Survey results presented by L. Cornell at 2015 Banff conference; expanded survey, future discussions to address core issues. Prepare consensus paper for publication
- Single center data using Nanostring method on FFPE tissue presented by Banu Sis at Banff 2015 conference; validation needed on biopsies from additional centers
- New WG
- New WG
- New WG
- New WG
- TBD
Main topics:

• New end-points for Next-Generation Clinical Trials
• Up-dates on BWG: EM scoring, PVN, TCMR/borderline, etc.
• Significance and scoring of i-IFTA
• Integrated Diagnosis: pathology + DSA