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

established by consensus in 1991

Banff meetings
thesis-antithesis-synthesis

refinement

Banff lesions
g, f, t, v - score

tentative thresholds

Feedback concerning weaknesses and strengths by results from independent research

The Banff classification
Current consensus for diagnostics

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

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Major revision to Banff criteria for ABMR diagnosis in 2013

Meeting Report


M. Haas\textsuperscript{1,*}, B. Sis\textsuperscript{2}, L. C. Racusen\textsuperscript{3}, K. Solez\textsuperscript{2}, D. Glotz\textsuperscript{4}, R. B. Colvin\textsuperscript{5}, M. C. R. Castro\textsuperscript{6}, D. S. R. David\textsuperscript{7}, E. David-Neto\textsuperscript{6}, S. M. Bagnasco\textsuperscript{3}, L. C. Cendales\textsuperscript{8}, L. D. Cornell\textsuperscript{9}, A. J. Demetriss\textsuperscript{10}, C. B. Drachenberg\textsuperscript{11}, C. F. Farver\textsuperscript{12}, A. B. Farris III\textsuperscript{13}, I. W. Gibson\textsuperscript{14}, E. Kraus\textsuperscript{15}, H. Liapis\textsuperscript{16}, A. Loupy\textsuperscript{17}, V. Nickeleit\textsuperscript{18}, P. Randhawa\textsuperscript{10}, E. R. Rodriguez\textsuperscript{12}, D. Rush\textsuperscript{19}, R. N. Smith\textsuperscript{5}, C. D. Tan\textsuperscript{12}, W. D. Wallace\textsuperscript{20} and M. Mengel\textsuperscript{2} as the Banff meeting report writing committee

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\textsuperscript{19}Department of Internal Medicine, University of Manitoba Health Sciences Centre, Winnipeg, Manitoba, Canada
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\textsuperscript{*}Corresponding author: Mark Haas, mark.haas@cshs.org

The 12th Banff Conference on Allograft Pathology was held in Comodatuba, 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

Dr. Paul I. Terasaki
1929 - 2016
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 intimal 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 \( (g > 0) \) and/or ptc > 0
   - Intimal or transmural arteritis \( (v > 0) \)
   - 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 \([g + ptc \geq 2])\)
   - 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.

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**Banff 2013 Meeting Report**: Haas et al. AJT 2014; 14: 272-283
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

\(^h\) \(\geq7\) layers in 1 cortical peritubular capillary and \(\geq5\) in 2 additional capillaries, avoiding portions cut tangentially

\(^i\) In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc \(\geq2\) alone is not sufficient to define moderate microvascular inflammation and g must be \(\geq1\).
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

De Serres et al., AJT; 2016: in press
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)
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 de novo
  - History of C4d+ or microvascular inflammation (g, ptc) in a previous biopsy
- All biopsies ≥ 6 months (≥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 = 50)</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 (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>0.1254</td>
</tr>
<tr>
<td>Recipient ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>69%</td>
<td>68%</td>
<td>69%</td>
<td>71%</td>
<td>76%</td>
<td>0.0034</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>18%</td>
<td>18%</td>
<td>23%</td>
<td>20%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>11%</td>
<td>13%</td>
<td>14%</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>HLA-AMER/D/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>Nonmatch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemic time</td>
<td>7.4 ± 5.6</td>
<td>6.9 ± 5.4</td>
<td>8.6 ± 6.6</td>
<td>8.3 ± 5.9</td>
<td>8.9 ± 5.5</td>
<td>0.0025</td>
</tr>
<tr>
<td>Delay graft function</td>
<td>14%</td>
<td>12%</td>
<td>25%</td>
<td>9%</td>
<td>26%</td>
<td>0.0396</td>
</tr>
<tr>
<td>Nondiagnosis</td>
<td>15%</td>
<td>15%</td>
<td>18%</td>
<td>24%</td>
<td>96%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellular rejections 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>0.6 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months to dDSA detection (IGR)</td>
<td>58 ± 19</td>
<td>60 ± 20</td>
<td>53 ± 17</td>
<td>60 ± 17</td>
<td>57 ± 20</td>
<td>0.3699</td>
</tr>
<tr>
<td>eGFR 6 months posttransplant</td>
<td>56 ± 14</td>
<td>52 ± 16</td>
<td>56 ± 14</td>
<td>52 ± 16</td>
<td>56 ± 14</td>
<td>0.3694</td>
</tr>
<tr>
<td>eGFR at dDSA development</td>
<td>55 ± 15</td>
<td>34 ± 23</td>
<td>55 ± 15</td>
<td>34 ± 23</td>
<td>55 ± 15</td>
<td>0.0004</td>
</tr>
<tr>
<td>eGFR 1 year post-dDSA</td>
<td>52 ± 17</td>
<td>25 ± 19</td>
<td>52 ± 17</td>
<td>25 ± 19</td>
<td>52 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR 2 years post-dDSA</td>
<td>48 ± 16</td>
<td>18 ± 13</td>
<td>48 ± 16</td>
<td>18 ± 13</td>
<td>48 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR 3 years post-dDSA</td>
<td>46 ± 22</td>
<td>16 ± 11</td>
<td>46 ± 22</td>
<td>16 ± 11</td>
<td>46 ± 22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR 5 years posttransplant</td>
<td>55 ± 23</td>
<td>42 ± 21</td>
<td></td>
<td>55 ± 23</td>
<td>42 ± 21</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

IQR, interquartile range; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); dDSA, de novo donor-specific antibody.

### Table 4: Predictors of allograft failure from the time of dDSA development

<table>
<thead>
<tr>
<th></th>
<th>Univariate clinical predictors</th>
<th>Multivariate clinical predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>0.98 (0.99–1.00)</td>
<td>0.0468</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>1.00 (0.97–1.03)</td>
<td>0.7745</td>
</tr>
<tr>
<td>Deceased versus living</td>
<td>1.81 (0.84–4.4)</td>
<td>0.1500</td>
</tr>
<tr>
<td>HLA-AMER/D/DO mismatch (per mismatch)</td>
<td>0.87 (0.56–1.3)</td>
<td>0.2022</td>
</tr>
<tr>
<td>Cold ischemic time (per hour)</td>
<td>1.06 (0.99–1.03)</td>
<td>0.6674</td>
</tr>
<tr>
<td>Delayed graft function (yes vs. no)</td>
<td>3.78 (1.2–10.5)</td>
<td>0.0250</td>
</tr>
<tr>
<td>Necroaemia (yes vs. no)</td>
<td>5.11 (2.3–15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>dDSA phenotype (clinical vs. subclinical)</td>
<td>4.98 (2.3–11.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MPR (per 1000 MPR)</td>
<td>1.01 (3.5–1.63)</td>
<td>0.0681</td>
</tr>
</tbody>
</table>

1Percent of biopsy with each Banff score 0(1-2,3,4)
2Hazard ratio (HR) per Banff score increase; 95% confidence interval; g, chronic glomerulopathy; cl, interstitial fibrosis; ct, tubular atrophy; cv, chronic vasculopathy; dDSA, de novo donor-specific antibody; g, glomerular inflammation; i, interstitial inflammation; pt, peritubular infiltrates; TCMR, T cell-mediated rejection; t, tubulitis; v, inter alia.
Adoption of molecular ABMR diagnostics
Three Pathways to Antibody Mediated Injury

Antibody Alone  
- Complement Mediated  
- Cell Mediated (FcR)

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

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

p=0.67
p=0.03
p=0.67

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

Association between ABMR gene set expression and corresponding serohistologic features in 194 renal allograft biopsies.

<table>
<thead>
<tr>
<th>Serologic/histologic feature</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor specific antibodies</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>ABMR-related lesions</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>TCMR-related lesions</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>ABMR and TCMR-related lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimal arteritis (v)</td>
<td>0.055</td>
<td>0.456</td>
</tr>
<tr>
<td>Scarring/atrophy-related lesions</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>
</tr>
<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>
</tr>
<tr>
<td>Immunopathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4d-positive¹</td>
<td>0.123</td>
<td>0.094</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCBML²</td>
<td>0.421</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adam et al Clin. Transplant 2016 in press
Where do we need consensus?

### 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
The Path toward adoption of molecular pathology by the Banff classification: prospect for companion to standard histopathology

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

## Antibody-mediated rejection

<table>
<thead>
<tr>
<th>Gap Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of sub-clinical ABMR versus clinical ABMR</td>
</tr>
<tr>
<td>Comparison of TCMR with and without DSA, but no glomerulitis or TG (note: ptc-itis is often seen with TCMR)</td>
</tr>
<tr>
<td>Comparison of DSA-negative biopsies versus DSA-positive biopsies in sequence from the same patient</td>
</tr>
<tr>
<td>Comparison of matched biopsies from adherent versus non-adherent patients</td>
</tr>
<tr>
<td>Comparison of histologically similar biopsies from patients with anti-HLA versus anti-non-HLA DSA</td>
</tr>
<tr>
<td>Comparison of ABMR biopsies with TMA to TMA in native kidneys</td>
</tr>
<tr>
<td>Comparison of consensus gene sets to diagnostic ABMR classifiers</td>
</tr>
</tbody>
</table>

## T-Cell mediated rejection

<table>
<thead>
<tr>
<th>Gap Addressed</th>
</tr>
</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>
</tr>
</tbody>
</table>

## Mixed rejection

<table>
<thead>
<tr>
<th>Gap Addressed</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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# Ongoing activities through Banff Working Groups

<table>
<thead>
<tr>
<th>Working Group</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>
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<tbody>
<tr>
<td>Leaders</td>
<td>Volker Nieckel, Parnjeet Randhawa</td>
<td>Lynn Cornell, Ed Kraus</td>
<td>Banu Sis, Michael Mengel</td>
<td>Candice Roufosse, Sharan Singh</td>
<td>Marjan Afruzzian, Helen Liapis</td>
<td>TBD</td>
<td>Nada Alachkar, Pathologist TBD</td>
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<td>Issues to Address</td>
<td>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</td>
<td>Define criteria for highly sensitized patients (HS), determine consensus for what personnel and facilities are needed for centers to perform transplantation in HS recipients</td>
<td>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</td>
<td>Inter-observer variability and clinical correlations in cg1a lesions and gfbm1 Criteria for amount of immune complex deposit allowable in cg1a</td>
<td>TBD; seek possible funding from Alexion</td>
<td>Immuno-phenotyping of leukocytes in biopsies before and after treatment for TCMR and possibly ABMR in clinical responders and non-responders to distinguish those cells mediating injury vs. those involved in repair, and those cells that disappear or persist following different therapies. Seek possible sources of funding.</td>
<td>TBD</td>
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<td>Group Findings/Plans</td>
<td>Group currently collecting cases of &quot;pure&quot; TCMR (no DSA or CAD) for pathologic evaluation and clinic-pathologic correlation</td>
<td>Survey results presented by L. Cornell at 2015 Banff conference; expanded survey; future discussions to address core issues. Prepare consensus paper for publication</td>
<td>Single center data using Nanosting method on FFPE tissue presented by Banu Sis at Banff 2015 conference; validation needed on biopsies from additional centers</td>
<td>New WG</td>
<td>New WG</td>
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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