New Developments in Kidney Transplantation In the Current Decade

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Relevant Financial Relationship Disclosure Statement

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I have financial relationship(s) within the last 12 months relevant to my presentation with:

1. Grant Support relationship with Alexion
2. Grant Support relationship with Astellas
3. Grant Support relationship Quark Pharmaceuticals
4. Grant support relationship with Care Dx
5. Honorarium with CareDx

AND

My presentation may include discussion of off-label or investigational use
Outline of Topics

- FDA meetings and successes
- Banff Pathology updates in AMR, CAMR
- Scientific updates in brief in kidney Tx
  - DSA and outcomes
  - IFTA + I, i-IFTA, cTCMR
  - New Immunosuppressants
  - Genomics/Biomarkers
- Nonadherence
- The new importance of HLA mismatches
- Kidney Allocation
FDA Public Workshops

- **2010**: Antibody Mediated Rejection
- **2011**: Ischemia Reperfusion Injury
- **2012**: Clinical Endpoints in Kidney Transplantation
- **2012**: Meeting with Generics Group
- **2015**: Surrogate Endpoints in Clinical Kidney Transplantation
- **2016**: Patient-Focused Drug Development Who Have Received an Organ Transplant (PDUFA)
Kidney Transplant v1.0 Standard: TAUG-KT

- Therapeutic Area Data Standards User Guide for Kidney Transplant (TAUG-KT) [aka Kidney Transplant v1.0 standard]
  - a compilation of terms and processes focused on studies of therapeutic interventions to prevent rejection of transplanted kidneys in adult recipients. Published October 2016.

- With funding from FDA, the standard was developed through the Coalition for Accelerating Standards and Therapies (CFAST), a joint initiative of CDISC (Clinical Data Interchange Standards) and C-Path (Critical Path), ASN KHI, AST

- Goal: to accelerate clinical research and medical product development by creating and maintaining data standards, tools, and methods for conducting research in transplantation.
Banff and Cultural Changes: Multiple Phenotypes

- Acute cellular rejection
  - Acute T cell mediated rejection
  - Acute antibody mediated rejection
- Chronic rejection
  - Chronic antibody mediated rejection
  - Chronic T cell mediated rejection
- Mixed cellular and antibody mediated rejection
- Mixed acute and chronic rejections (antibody / cellular)
Revised AMR Criteria: Banff 2013 Revisions

Hence C4d is NOT required but there must be evidence of endothelial interaction

Sis et al. Am Jnl Transplant 2009; 9:2312—endothelial gene expression in kidney allograft with alloantibody indicates antibody mediated injury regardless of C4d status
Changes in Morphologic Criteria of CAMR (Banff 2013)

• Banff 2007: 1 or more of the following
  - Transplant glomerulopathy \((cg\geq1)\)
  - Peritubular capillary basement membrane multilayering
  - Fibrosis intimal thickening of arteries
    - IFTA now deleted

• Banff 2013: 1 or more of the following
  - Transplant glomerulopathy \((cg>0)\)
  - Severe peritubular capillary basement membrane layering by EM
  - Arterial intimal fibrosis of new onset
Impact of New Banff Criteria

• De Serres et al. AM Jnl Transplant 2016: 123 biopsies
  - Looked at impact of diagnosis of AbMR on death-censored graft survival or doubling of serum creatinine
  - By 2007 criteria, 18% had AbMR
  - By 2013 criteria, 36% had AbMR
  - 2013 criteria were associated with worse outcomes
  - When looking at individual components, the key change was the C4d staining requirement.

• Gimeno et al. Nephrol Dial Transplant 2016
  - 73 biopsies for chronic allograft dysfunction, proteinuria, or presence of de novo DSA
  - With 2007 criteria, 40% with AbMR
  - With 2013 criteria, 74% with AbMR (P=0.006)
  - Main differences were inclusion of microvascular inflammation (g+ptc>2) and EM diagnosis
| Post-Tx TSG Method | Post-Tx TSG Kit configuration | Post-Tx TSG Serum initiation | Post-Tx TSG Serum dilution | Post-Tx TSG testing | Post-Tx TSG C+H | Post-Tx TSG C+ | Post-Tx TSG C+H dilutions | Pathology | Induction therapy | Maintenance therapy | Surveillance (CCy+R1) | DSA-detected | Rejection (TN) | TCMR (TN) | AMR (TN) | n/a | Patient survival | Graft survival | Main conclusions/Recommendations |
|-------------------|-----------------------------|-----------------------------|---------------------------|-------------------|----------------|----------------|--------------------------|-----------|---------------------|----------------------|-----------------------|----------------|----------------|-------------|---------|-----------------|-----------------|---------------------------------|
| not-reported      | not-reported                | not-reported                | not-reported              | not-reported      | not-reported   | not-reported   | not-reported             | not-reported | not-reported        | not-reported         | not-reported         | not-reported | not-reported   | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported | not-reported |
| Sensitization in Transplantation: Assessment of Risk (STAR) - North American 2017 Working Group |

**Literature Review of dnDSA**

**Sensitization in Transplantation: Assessment of Risk (STAR)** - North American 2017 Working Group
## Frequency of De Novo DSA Development Varies from 2-27%

<table>
<thead>
<tr>
<th>Group</th>
<th>1st Tx</th>
<th>Pre-Txp Technique</th>
<th>1st Month</th>
<th>1st Year</th>
<th>&gt;1st Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper</td>
<td>NA</td>
<td>FCXM</td>
<td>15.6%</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td>DeVos</td>
<td>93%</td>
<td>&gt;2000 MFI</td>
<td>8.0%</td>
<td>20%</td>
<td>5% / y</td>
</tr>
<tr>
<td>Heilman</td>
<td>91%</td>
<td>&gt;1000 MFI</td>
<td>8.2%</td>
<td>17.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Everly</td>
<td>100%</td>
<td>&gt;1000 MFI</td>
<td>3.0%</td>
<td>11.0%</td>
<td>2.3% / y</td>
</tr>
<tr>
<td>Wiebe</td>
<td>95%</td>
<td>&gt;500 MFI</td>
<td>0.0%</td>
<td>2.0%</td>
<td>2.0% / y</td>
</tr>
</tbody>
</table>

Frequency varies based on measuring technique, frequency of measures, baseline immunosuppression and patient type.
Rates and Determinants of Progression to Graft Failure in Kidney Allograft Recipients With De Novo Donor-Specific Antibody

76% Stable

9% Subclinical DSA

11% Dysfunction/no DSA

4% Clinical DSA

11% Other =

- GN+IFTA (n=20)
- TCMR+IFTA (n=10)
- IFTA (n=8)
- BKPVN (n=2)
- Other (n=6)
- Not bx (n=10)

Clinical DSA Outcome Worse than Subclinical DSA:
- Loupey JASN 2015;
- Orandi Transplantation 2015

DNDSA and therapy conversion or minimization – the other adherence

- Liefeldt Am Jnl Transplantation 2012; 12(5): 1192 :: CSA conversion to mTORi
- Hricik et al. JASN 2015; 26:3114 :: tac minimization/withdrawal
- Shapiro Transplantation 2008; 85:1125 :: tac weaning
- Hoshino Transplantation 93: 1173 :: LD with clonal deletion protocol
- Dorje C Transplantation 2013; 96:79 :: Late AbMR with MNZA or physician minimization
- Gupta G Transplantation 2014; 97:1240 :: Late AbMR with MNZA or physician minimization
Other considerations about DSAs: C1q Binding

C1q binding of DSA associated with worse outcomes (Loupey NEJM 2013; 369:1215)
Death Censored Kidney Allograft Survival According DSA IgG Subclass

Carmen Lefaucheur et al. JASN 2016;27:293-304
Natural History of Alloantibody Injury

Banff ti Score Defined in Banff 2007 Revisited in Banff 2017

- Should the ti score be included in the classification for TCMR diagnosis?
  - As a replacement for the i score
  - As part of a new category of chronic/active TCMR
  - Recommend inclusion of ti score in the diagnosis line, possibly with a comment as to its prognostic significance, but do not change the current TCMR classification

Table 4: Quantitative criteria for mononuclear cell interstitial inflammation (‘ti’) in total parenchyma (scarred and unscarred) scores—to be evaluated over next two years. Not incorporated into classification yet.

<table>
<thead>
<tr>
<th>ti0</th>
<th>No or trivial interstitial inflammation (&lt;10% of parenchyma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ti1</td>
<td>10–25% of parenchyma inflamed</td>
</tr>
<tr>
<td>ti2</td>
<td>26–50% of parenchyma inflamed</td>
</tr>
<tr>
<td>ti3</td>
<td>&gt;50% of parenchyma inflamed</td>
</tr>
</tbody>
</table>
Inflammation in Areas of Atrophy: Strong Negative Predictor of Outcome

DeKAF Study:
289 recipients in cohort
59 with graft loss
89 with i=0, and iatr>1

“iatr”—inflammation in areas of tubular atrophy
0 = inflammation in less than 10% of atrophic regions
1 = inflammation in 10-25% of atrophic regions;
2 = inflammation in 26-50% of atrophic regions;
3 = inflammation in >50% of atrophic regions.

Mannon RB. Am Jnl Transplant 2010; 10: 2066-2073
i + IFTA is Bad News

- Tubulointerstitial inflammation in early surveillance biopsies is associated with progression of IF and decreased allograft survival [Nankivell et al. Transplantation 2004; Choi et al. AJT 2005].

- Surveillance biopsies with i in nonscarred areas and IFTA [i+IFTA ] are associated with shorter graft survivals [Shishido et al. JASN 2003; Moresco et al. AJT 2006; Park et al. JASN 2010]

- Surveillance biopsy at 6w with i+IFTA is an independent risk factor for dnDSA development with an incidence of 9% at 1y [Garcia-Carro et al. Transplantation 2016; PMID 27163535]
Molecular Classifiers of Inflammation/Injury

- **PBMC**
  - Transplant Genomics Inc: Tx status (Peripheral blood; transplant excellence)
  - Immuncor—15 gene transcripts indicating acute cellular rejection
  - AlloSure™ Cell Free DNA measurements

- **Urine**
  - Urinary markers of acute rejection (mRNA expression of CD3ε chain, perforin, granzyme B, proteinase inhibitor 9, CD103, interferon-inducible protein 10 (IP-10), and the chemokine receptor CXCR3)

- **Cell Free DNA**
  - AMR and CAMR discrimination from TCMR [Bloom et al. JASN 2017; in press.]
Belatacept Approved 2012
Vincenti et al. NEJM 2016; 374:333
Complement Inhibition as Potential New Therapy for Antibody-Mediated Rejection

HLA I LDTx
DGF
AMR
Risk of Nonadherence on Outcomes

![Image of a table and pie charts related to the risk of nonadherence on outcomes.]

**Table 2**: Clinical pathologic course before dNDSA detection

<table>
<thead>
<tr>
<th></th>
<th>No dNDSA (n = 268)</th>
<th>Total dNDSA (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adherence</td>
<td>8%</td>
<td>49%***</td>
</tr>
<tr>
<td>DGF requiring dialysis</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Clinical rejection, 0–6 months</td>
<td>13%</td>
<td>28%*</td>
</tr>
<tr>
<td>Subclinical rejection, 0–6 months</td>
<td>15%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Patients whose biopsies showed histologic changes highly suggestive of polyoma virus nephropathy, although the iQEmite hybridization was reported either inconclusive (n=1) or negative (n=2).

**Wiebe et al. Am Jnl Transplant 2012; 12: 1157**

**Sellares et al Am Jnl Transplant 2012; 12: 368**
HLA Mismatch Has a Graded Effect on Transplant Survival

Hazard Ratio for First Kidney Failure Time as a Function of HLA Mismatch Permutations in the Full Cox Model. Deceased Donors, N = 189,141

<table>
<thead>
<tr>
<th>HLA mismatch</th>
<th>Reduced model</th>
<th>$P$</th>
<th>Full model</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.17</td>
<td>&lt;0.0001</td>
<td>1.13</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td></td>
<td>1.10, 1.25</td>
<td>&lt;0.0001</td>
<td>1.06, 1.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.38</td>
<td>&lt;0.0001</td>
<td>1.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.31, 1.46</td>
<td>&lt;0.0001</td>
<td>1.30, 1.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.51</td>
<td>&lt;0.0001</td>
<td>1.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.44, 1.58</td>
<td>&lt;0.0001</td>
<td>1.30, 1.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.69</td>
<td>&lt;0.0001</td>
<td>1.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.61, 1.77</td>
<td>&lt;0.0001</td>
<td>1.41, 1.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.84</td>
<td>&lt;0.0001</td>
<td>1.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.75, 1.92</td>
<td>&lt;0.0001</td>
<td>1.49, 1.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.98</td>
<td>&lt;0.0001</td>
<td>1.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.88, 2.08</td>
<td>&lt;0.0001</td>
<td>1.56, 1.73</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjustment for recipient age, recipient sex, transplant era.
*Adjustment for recipient age, donor age, donor sex, transplant era, recipient ethnicity, recipient diabetes, cold ischemia time, recipient peak PRA, recipient education, recipient BMI, donor BMI, recipient working for income at transplant, recipient COPD, recipient dialysis type, induction and immunosuppression at discharge.

PRA, panel-reactive antibody.
The Synergistic Effect of Class II HLA Epitope-Mismatch and Non-adherence on Acute Rejection and Graft Survival

• Changed prior algorithm from first-come, first-serve, to a scheme where balanced equitable distribution of deceased donor kidneys with maximal utility.
• Improvement in utility: kidney donor risk index (KDRI) based on donor age, height, weight race/ethnicity, hypertension, diabetes, cause of death, serum creatinine, hepatitis C status, and donation after circulatory death status and converted to KD Profile Index of 0-100% (KDPI).
• Kidneys in 20% of expected post-transplant allograft survival are offered first to recipients in the highest 20% of estimated post-transplant survival (EPTS)[age, duration dialysis, prior transplant, diabetes].
• Equity is addressed by increased national and regional sharing, and priority given to those waiting for multi-organ transplants, calculated panel-reactive antibody (cPRA) of 98% or higher (more sensitized), zero-HLA mismatched kidneys, pediatric candidates and prior living donors.
  - Listing after dialysis still accrues time on dialysis!
Pre and Post KAS Deceased Donor Kidney Transplant Recipient Characteristics 01/01/2014-05/31/015

And impacts on AA recipients, peds, DGF, and graft survival
Other New Concepts in Kidney Transplantation

• Use of HIV positive donor organs

• Hepatitis C treatment: before or after kidney transplantation
  - Use of HepC\(^+\) kidneys in high EPTS recipients

• Potential role of APOL1 mutations in either living donor or recipient outcomes
Conclusion

Since 2010, there has been remarkable progress in the field of AMR and CAMR.

• We have yet to develop consensus on monitoring (close), or validated biomarkers.

• These will assist in endpoint development and facilitate the identification of new therapeutics in this unmet need in solid organ transplantation.
De Novo DSA is Associated with Worse Kidney Allograft Survival

DSA free Survival

All

A 1.0
0.8
0.6
0.4
0.2
0.0

0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

0 1 2 3 4 5 6 7 8 9 10 11 12

2% 10% 19% 27%

B 1.0
0.8
0.6
0.4
0.2
0.0

0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

0 1 2 3 4 5 6 7 8 9 10 11 12

p<0.0001 19% 72%

Non-Adherent
Adherent