Immunology in Solid Organ Transplantation

„Selected Topics in Clinical Immunology“
26. April 2018

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Klinik für Nephrologie und Hypertonie, Inselspital Bern

Reference
- Abbas AK, Lichtman AH und Pillai S: Cellular and Molecular Immunology, 8th Edition
- CTS Database, www.ctstransplant.org
- Swiss Transplant Annual Report, www.swisstransplant.ch
- Original References available upon request
Content

- Epidemiology of Solid Organ Transplantation
- Concepts of Anti-allograft Immunity
- Clinical Assessment of Allograft Immunity
- Strange Things in Solid Organ Transplantation
- Future in Solid Organ Transplantation
Epidemiology of Solid Organ Transplantation

Warteliste\(^1,2\)  
Transplantationen\(^1\)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Warteliste</th>
<th>Transplantationen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herz</td>
<td>148 (\uparrow 16)</td>
<td>40 (\text{Herz})</td>
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<tr>
<td>Lunge</td>
<td>82 (\uparrow 4)</td>
<td>32 (\text{Lunge})</td>
</tr>
<tr>
<td>Leber</td>
<td>400 (\uparrow 30)</td>
<td>143 (\text{Leber})</td>
</tr>
<tr>
<td>Niere</td>
<td>1556 (\uparrow 26)</td>
<td>360 (\text{Niere})</td>
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<tr>
<td>Pankreas</td>
<td>101 (\uparrow 2)</td>
<td>19 (\text{Pankreas})</td>
</tr>
<tr>
<td>Dünndarm</td>
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<td>0 (\text{Dünndarm})</td>
</tr>
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</table>

Total:

- Warteliste: 2288
- Transplantationen: 594

Jahresbericht 2017, 17.04.18
Epidemiology of Solid Organ Transplantation

Nierentransplantationen und Warteliste

- Warteliste
- Transplantationen (exkl. Lebendspenden)
- Lebendspender

Lebertransplantationen und Warteliste

- Warteliste
- Transplantationen (exkl. Lebendspenden)
- Lebendspender

\[1556^1\]

\[134/16^2\]
Organ Transplantation in Bern

Kidney Transplantation

**Bern**
- Kidney 50-60
- LDT 50%
- Liver 20-30
- Heart 10-20
- BMT -
Figure 1: Overall Survival post-OLT: Survival was 92%, 90% and 88% at 1, 3 and 5 years.

Kidney Transplantation

Liver Transplantation

**Overall Survival**
«Allograft Immunity for Dummies»: 6 Key Points

- Allogenic transplanation induces rejection of the graft

- A major gene complex for histocompatibility (MHC) is on chr 17 (mus) or chr 6 (human)
«Allograft Immunity for Dummies»: 6 Key Points

- HLA Genes are polymorphic...

<table>
<thead>
<tr>
<th>HLA Class</th>
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<tr>
<td>HLA-A</td>
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<tr>
<td>H2 Class II</td>
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«Allograft Immunity for Dummies»: 6 Key Points

- HLA Genes are polymorphic...

**H2 Class I**  7 alleles  
**H2 Class II**  4 alleles

<table>
<thead>
<tr>
<th>HLA-A</th>
<th>&gt; 800 alleles</th>
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<tr>
<td>HLA-B</td>
<td>&gt; 800 alleles</td>
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<tr>
<td>HLA-DQ</td>
<td>&gt; 400 alleles</td>
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**Switzerland**

<table>
<thead>
<tr>
<th>Allele</th>
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<tr>
<td>A2</td>
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<tr>
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<td>A3</td>
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</tr>
<tr>
<td>A24</td>
<td>9%</td>
</tr>
<tr>
<td>A11</td>
<td>6%</td>
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<tr>
<td>75%</td>
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<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>B7</td>
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<td>B8</td>
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<td>B44</td>
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<td>B15</td>
<td>7%</td>
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<tr>
<td>B35</td>
<td>6%</td>
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<td>48%</td>
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**US**

<table>
<thead>
<tr>
<th>Allele</th>
<th>European</th>
<th>African Am.</th>
<th>Asian Pacific</th>
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<tbody>
<tr>
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<td>7%</td>
<td>2%</td>
<td>15%</td>
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<tr>
<td>B8</td>
<td>13%</td>
<td>4%</td>
<td>9%</td>
<td>21%</td>
</tr>
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<td>9%</td>
<td>2%</td>
<td>17%</td>
<td>32%</td>
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<td>11%</td>
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<tr>
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<td>6%</td>
<td>6%</td>
<td>3%</td>
<td>5%</td>
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<table>
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<tr>
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</tr>
<tr>
<td>A11</td>
<td>6%</td>
</tr>
<tr>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>
MHC molecules are highly expressed on solid organs and immunogenic...

«Allograft Immunity for Dummies»: 6 Key Points

A Direct alloantigen recognition

T cell recognizes unprocessed allogeneic MHC molecule on graft APC

B Indirect alloantigen presentation

Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule
«Allograft Immunity for Dummies»: 6 Key Points

... and induce effector mechanisms of anti-allograft immunity ...

[Diagram showing the processes of sensitization and rejection in allograft immunity]
«Allograft Immunity for Dummies»: 6 Key Points

Cellular Response
- T cells
  - Cytokines
  - Chemokines

Innate immunity Tissue Responses
- Monoc./Macrophages
  - Neutrophils
  - Endothelial cells
  - Fibroblasts
  - Cytokines
  - Chemokines

Humoral Response
- Complement-mediated Cytotoxicity
  - AICD
  - Cytokines
  - Chemokines
«Allograft Immunity for Dummies»: 6 Key Points

**Innate immunity**

**Tissue Responses**
Monoc./Macrophages

- Neutrophils
- Endothelial cells
- Fibroblasts

**Humoral Response**
Complement-mediated
Cytotoxicity
AICD

**Cellular Response**

- T cells
- Cytokines
- Chemokines

**Tubulitis Infiltration**

**Capillaritis**
Endothelialitis Arteritis

**Fibrosis Atrophy**
Past, current and future strategies to prevent graft loss.

Kidney Transplantation
In Bern

death-censored
Graft Survival (%)
Goals of Transplantation Immunology

- (induce tolerance towards the allograft)
- Recognize preformed Donor Specific Memory Immunity
- Match the Donor to the Recipient
- Prevent Allogenic Immunization and Memory Formation
- Block Effector Mechanisms Allograft Immunity
- Reverse Chronic Fibrotic Responses and Atrophy
Goals of Transplantation Immunology

- (induce tolerance towards the allograft)
- Match the Donor to the Recipient
- Recognise preformed Donor Specific Memory Immunity
- Inhibit naive allogen-specific Immunity
- Block Effector Mechanisms Allograft Immunity
- Reverse Chronic Fibrotic Responses and Atrophy
#1: Match the Donor to the Recipient: «Bloodgroup»

<table>
<thead>
<tr>
<th>Empfänger</th>
<th>Spender</th>
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<tbody>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Rh and other blood group factors do not matter.
#2: Match Donor and Recipient: «HLA Matching»

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-Klasse I:</td>
<td></td>
</tr>
<tr>
<td>A1, A11</td>
<td>A1, A31(19)</td>
</tr>
<tr>
<td>B27, B44(12)</td>
<td>B7, B60(40)</td>
</tr>
<tr>
<td>Cw2, Cw5</td>
<td></td>
</tr>
<tr>
<td>HLA-Klasse II:</td>
<td></td>
</tr>
<tr>
<td>DR4/DR53</td>
<td>DR4/DR53, DR15(2)/DR51</td>
</tr>
<tr>
<td>DQ7(3), DQ8(3)</td>
<td>DQ8(3), DQ6(1)</td>
</tr>
</tbody>
</table>

3/6 matches or 3/6 mismatches
#3: Match Donor and Recipient: «HLA Matching»

Success of HLA-matching is dependent on donor pool

USA: 10’000 NTx/y  15%
CH:   300 NTx/y   2%

#3: Match Donor to Recipient: «It’s mostly, but not entirely HLA-dependent»

HLA-Identical Renal Transplant Recipients: Immunosuppression, Long-Term Complications, and Survival

V.R. Peddi, P. Weiskittel, J.W. Alexander, E.S. Woodle, and M.R. First

28/506 KTx from 1985-1996 in Cincinnati
- No induction therapy
- 1985-1990 Im+PDN
- 1990-1996 CsA/Im/PDN

Episodes of Rejection
- Acute Rejection in 7/15 (46%) (first phase)
- Acute Rejection in 2/13 (15%) (second phase)
  (after CsA-Withdrawal, even after 4 yrs)

Maintenance IS
- PDN-free in 61%
- 50% on monotherapy (mostly Imurek, rare CsA)

Transplantation Proceedings, 33, 3411–3413 (2001)
#4: Recognize preformed donor-specific memory

**Pre-formed anti-HLA antibodies**
- Previous Whole-Blood Transfusions
- Previous Transplantations
- Pregnancies
- Autoimmune Diseases
- Unknown
#4: Recognize preformed donor-specific memory

Pre-formed anti-HLA antibodies
- Previous Whole-Blood Transfusions
- Previous Transplantations
- Pregnancies
- Autoimmune Diseases
- Unknown
#4: Recognize preformed donor-specific memory

---

**The New England Journal of Medicine**

-significance of the positive crossmatch test in kidney transplantation*

**Ramon Patel, M.R.C.P., and Paul I. Terasaki, Ph.D.**

<table>
<thead>
<tr>
<th>Graft Survival</th>
<th>Recipients with Antibodies</th>
<th>Recipients without Antibodies</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive Crossmatch</td>
<td>No Crossmatch</td>
</tr>
<tr>
<td>Immediate failures</td>
<td>24 (80.0%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Failure within &lt;3 mo</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Failure after &gt;3 mo</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Survival for &lt;3 mo</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Survival after &gt;3 mo</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>23</td>
</tr>
</tbody>
</table>

**PPV 24/30: 80%**  
**NPV 23/27: 86%**
#4: Recognize preformed donor-specific memory «Luminex or Solid Phase Antigen Bead Assay»

Pre-formed anti-HLA antibodies
- Previous Whole-Blood Transfusions
- Previous Transplantations
- Pregnancies
  - Autoimmune Diseases
- Unknown

Luminex Multiplex Assay
(Solid Phase Single Antigen Beads)
#4: Recognize preformed donor-specific memory

**Frequency and Determinants of Pregnancy-Induced Child-Specific Sensitization**

Immunization with child (father) antigens…
#4: Recognize preformed donor-specific memory

**Recipient**
(female, 60 J, 3 children, BG A)

- HLA-Klasse I:
  - A2, A24(9)
  - B7, B62(15)
  - Cw5(w3), Cw7

- HLA-Klasse II:
  - DR11(5)/DR52, DR15(2)/DR51
  - DQ7(3), DQ6(1)

- T-Zell X-Match: negativ

- B-Zell X-Match: negativ

**Donor**
(male, 62 J, 3 children, BG A)

- HLA-Klasse I:
  - A1, A11
  - B27, B44(12)
  - Cw2, Cw5

- HLA-Klasse II:
  - DR4/DR53
  - DQ7(3), DQ8(3)

**Blood Group compatible (A>A)**
1/8 matches (1xDQ)
Crossmatch negativ pre-formed DSA
#4: Recognize preformed donor-specific memory

Recipient
(female, 58j, 2 children, BG AB)

Donor
(male, 62j, 2 children, BG 0)

**HLA-Klasse I:**

Recipient: A1, A24(9)  
B7, B56(22)  
Cw1, Cw7

Donor: A2, A3  
B35, B60(40)  
Cw10(w3), Cw4

**HLA-Klasse II:**

Recipient: DR4/DR53, DR8  
DQ7(3), DQ4

Donor: DR7/DR53, DR9/DR53  
DQ2, DQ9(3)

**T-Zell X-Match:** negativ

**B-Zell X-Match:** negativ

**AK-Spezifität Klasse II**

DR7: 3718

Blood Group compatible (0>AB)

0/8 matches

Crossmatch negativ

pre-formed DSA anti DR7
#5: «Inhibit the Naive Allogen-Specific Immunity.»

1. Signal 1: Antigen signal
2. Signal 2: Co-stimulation
3. Signal 3: Cytokines
4. Signal 4: «What we always do»
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

Biological Function

Allograft Histopathology

Allogen-specific Immune Response

Rejection-specific gene Transcripts
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

Biological Function

Allograft Histopathology

Allogen-specific Immune Response

Rejection-specific gene Transcripts

Kreatinin
Clinical Assessment
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

Biological Function

Allograft Histopathology

Allogen-specific Immune Response

Rejection-specific gene Transcripts

Kreatinin
Clinical Assessment
Histopathology
Immunofluorescence
Electron Microscopy
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

- Biological Function
- Allograft Histopathology
- Allogen-specific Immune Response
- Rejection-specific gene Transcripts

Kreatinin
Clinical Assessment
Histopathology
Immunofluorescence
Electron Microscopy
Donor-specific AB
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

Biological Function

Allograft Histopathology

Allogen-specific Immune Response

Rejection-specific Gene Transcripts

Kreatinin
Clinical Assessment
Histopathology
Immunofluorescence
Electron Microscopy
Donor-specific AB
DNA Array

Molecular Diagnosis of T Cell-Mediated Rejection in Human Kidney Transplant Biopsies

**Methods**
- 403 biopsies, 8 reference samples
- 2 centers (Alberta, Chicago)
- Array with 54675 probes
- Prospectively collected, pooled analysis

---

**FINDING THE GENE SIGNATURE**

<table>
<thead>
<tr>
<th>Affymetrix ID</th>
<th>Description</th>
<th>Common gene name</th>
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<td>208783_at</td>
<td>CD95 antigen</td>
<td>CD95</td>
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<td>220348_s_at</td>
<td>signal-regulatory protein beta 2</td>
<td>SIRPβ2</td>
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<tr>
<td>238733_at</td>
<td>tumor necrosis factor ligand I</td>
<td>TNFSF8</td>
</tr>
<tr>
<td>236220_at</td>
<td>B and T lymphocyte associated</td>
<td>BTLA</td>
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<tr>
<td>238629_s_at</td>
<td>Similar to Dofactory receptor 322</td>
<td>OR2G1P</td>
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<td>237735_at</td>
<td>interleukin 21 receptor</td>
<td>IL21R</td>
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<td>227030_at</td>
<td>IKAROS family zinc finger 3 (Aiolos)</td>
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<td>SLAMF5</td>
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<td>AGAM-like, death domain 1</td>
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<td>CHX10</td>
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<tr>
<td>2037601_s_at</td>
<td>Slug-like cadherin</td>
<td>SLA</td>
</tr>
</tbody>
</table>

1TCMR: samples collected TCMR by both pathologists excluding isolated inflammation.
2Left out cases with mixed rejection (n = 22), intimal arteritis and no inters of the pathologists (n = 40).
3Others; all other biopsies for clinical indications.

**Accuracy of 89%**
- Low sensitivity
- High specificity
- High NPV

---

Strange Things: «ABO-incompatible Kidney Transplantation»

«ABO-incompatible Transplantation»
Karolinska-Protokoll

Rituximab Tac MMF PDN Immuno-Adsorption 2-6x

d-30 d-15 d-5 d0
Strange Things: Advantage of Double Organ Transplantation

Double Organ Transplants
Kidney Transplant Survival Matched With Three Controls

% Grafts Surviving

0 50 60 70 80 90 100

Years

0 1 2 3 4 5 6 7 8

Kidney + Liver  n=255

Kidney Only  n=867
Strange Things: «non-immunological factors in allograft survival»
Outlook

- **Reduced Toxicity**
- **Tolerance-Induction**
- **Treatment of Chronic Lesions**

<table>
<thead>
<tr>
<th>Reduced Toxicity</th>
<th>Belatacept (CTLA4-Ig)</th>
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</thead>
<tbody>
<tr>
<td>Tolerance-Induction</td>
<td>combined BM/KT</td>
</tr>
<tr>
<td>Treatment of Chronic Lesions</td>
<td>Tocilizumab (sIL6R)</td>
</tr>
<tr>
<td></td>
<td>Eculizumab (αC5-AB)</td>
</tr>
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