New trends in Stem Cell Transplantation:

Tolerance induction

Urs Schanz, Division of Hematology, University Hospital Zurich
Outline

• The history of tolerance

• Concepts of tolerance induction by HSCT in solid organ transplantation

• The Zurich project
The history of tolerance

Transplantation tolerance is as old as manhood is

Recurrent abortion

Immunotolerance

Choriocarcinoma

Current Opinion in Immunology 2000, 12:731–737
The modern history of tolerance in the 20th century

IMMUNOGENETIC CONSEQUENCES OF VASCULAR ANASTOMOSES BETWEEN BOVINE TWINS

Ray D. Owen

DICYGOTIC (= non identical) cattle twins sharing one placenta have

- Mixed blood groups

Starting point of research in immunotolerance
Acquisition of tolerance in the early stages of life

spleen cells from neonatal A strain
\[ \downarrow \]
neonatal CBA \[ \rightarrow \] adulthood

graft from A strain
\[ \downarrow \]
accepted

graft from third strain
\[ \downarrow \]
rejected

(1) Mice and chickens never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells with which they have been inoculated in fetal life. Animals so treated are tolerant not only of the foreign cells of the original inoculum, but also of skin grafts freshly transplanted in adult life from the original donor or from a donor of the same antigenic constitution.

(2) Acquired tolerance is immunologically specific: mice and chickens made tolerant of homografts from one donor retain the power to react against grafts transplanted from donors of different antigenic constitutions.

(3) Acquired tolerance is due to a specific failure of the host’s immunological response. The antigenic properties of a homograft are not altered by residence in a tolerant host, and the host itself retains the power to give effect to a passively acquired immunity directed against a homograft which has until then been tolerated by it.

(4) The fertility of tolerant mice is unimpaired.
Main, J. M. & Prehn, R. T. Successful skin homografts after the administration of high dosage X radiation and homologous bone marrow. J. Natl Cancer Inst. 1023–1028 (1955)

Figure 1 | Timeline of selected milestones in the development of the mixed chimerism approach. Abbreviations: BM, bone marrow; BMT, bone marrow transplantation; CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen 4–immunoglobulin; HLA, human leukocyte antigen.

Immunologic Tolerance to Renal Allografts after Bone Marrow Transplants from the Same Donors

Mohamed H. Sayegh, MD; Neil A. Fine, MD; John L. Smith, MD; Helmut G. Rennke, MD; Edgar L. Milford, MD; and Nicholas L. Tilney, MD.
LIVING DONOR LIVER TRANSPLANTATION AND TOLERANCE: A POTENTIAL STRATEGY IN CHOLANGIOCARCINOMA

Zakiyah Kadry, Beat Mullhaupt, Eberhard L. Renner, Peter Bauerfeind, Urs Schanz, Bernhard C. Pestalozzi, Gabriella Studer, Rolf Zinkernagel, and Pierre-Alain Clavien

—

1987  BMT for ALL CR1
12/2000  diagnosis of cholangiocarcinoma
03/2001  systemic neoadjuvant chemotherapy and local radiotherapy
04/2001  remission
04/2001  living donor liver transplantation (HLA-id brother, BM-donor)
07/2001  stop short term immunosuppression
10/2014  patient well and alive, showed never signs of liver rejection
Conclusion:

• Conventional allogeneic HSCT leads to long term tolerance against the donor

but

• it is associated with a considerable mortality (TRM, 20-30%) and morbidity (cGvH, 50%)

therefore

• not suitable in this form for tolerance induction in solid organ transplantation
Novel concepts of tolerance induction by HSCT in solid organ transplantation

- Conditioning regimens with only minor toxicities
  - no TRM
  - no aGvHD or cGvHD
  - no late effects i.e. secondary carinomas

- Allowing stable long-term engraftment with mixed chimerism

- Leading to long-term immunotolerance without the need of prolonged (toxic) immunosuppression
Immunosuppression Medication Side Effects

- Infection
- Cancer
- Diabetes
- High Blood Pressure
- Neurotoxicity
- NEPHROTOXICITY
Long-Term Results in Recipients of Combined HLA-Mismatched Kidney and Bone Marrow Transplantation Without Maintenance Immunosuppression

Haploidentical transplants, related
Table 3: Posttransplant complications in conventional immunosuppression versus tolerance

**A. Conventional immunosuppression**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at Tx</th>
<th>Sex</th>
<th>Survival</th>
<th>Creat</th>
<th>HTN</th>
<th>Hyper-lipid</th>
<th>De novo DM</th>
<th>Malignancy</th>
<th>Infection</th>
<th>No. of drugs IS + others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>F</td>
<td>&gt;11.6 years</td>
<td>1.1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>3 + 5</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>F</td>
<td>&gt;11 years</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 7</td>
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<td>3</td>
<td>36</td>
<td>F</td>
<td>&gt;10.8 years</td>
<td>1.4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 + 12</td>
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<tr>
<td>4</td>
<td>38</td>
<td>F</td>
<td>&gt;10.8 years</td>
<td>2.3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>2 + 8</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>F</td>
<td>&gt;10.7 years</td>
<td>1.2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>3 + 5</td>
</tr>
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<td>F</td>
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<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>直属 SCC BCC</td>
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<tr>
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<td>26</td>
<td>M</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 + 6</td>
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<td>23</td>
<td>M</td>
<td>&gt;9.7 years</td>
<td>1.3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 2</td>
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<tr>
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<td>M</td>
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<td>+</td>
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<td>-</td>
<td>-</td>
<td>直属 Melanoma, SCC</td>
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<tr>
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<td>M</td>
<td>&gt;9.2 years</td>
<td>1.9</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 9</td>
</tr>
<tr>
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<td>20</td>
<td>M</td>
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<td>1.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>M</td>
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<td>2.1</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>2 + 2</td>
</tr>
<tr>
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<td>32</td>
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<td>1.3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2 + 9</td>
</tr>
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<td>42</td>
<td>F</td>
<td>&gt;8.1 years</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 3</td>
</tr>
<tr>
<td>16</td>
<td>43</td>
<td>M</td>
<td>&gt;7.9 years</td>
<td>1.2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 5</td>
</tr>
<tr>
<td>17</td>
<td>31</td>
<td>M</td>
<td>&gt;7.7 years</td>
<td>1.6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 + 5</td>
</tr>
</tbody>
</table>

**Graft loss**

- 18: 37 F, 29 days, reTx, NA, NA, NA, NA, NA, NA, NA, NA
- 19: 44 M, 3.9 years, On HD, +, -, -
- 20: 45 M, 6.3 years, On HD, +, +, -
- 21: 22 M, 7.1 years, On HD, +, +, -

Incidences of complications (p-value): 85% (p = 0.04), 65% (p = 0.005), 35% (ns), 10% (ns), 25% (ns)

**B. Tolerance protocol**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at Tx</th>
<th>Sex</th>
<th>Survival</th>
<th>Creat</th>
<th>HTN</th>
<th>Hyper-lipid</th>
<th>De novo DM</th>
<th>Malignancy</th>
<th>Infection</th>
<th>No. of drugs IS + others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>&gt;11 years</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0 + 1</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>F</td>
<td>&gt;10.5 years</td>
<td>2.2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 + 1</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>F</td>
<td>&gt;8.8 years</td>
<td>2.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 + 2</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>F</td>
<td>&gt;7.8 years</td>
<td>2.5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 + 1</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>F</td>
<td>&gt;4.8 years</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0 + 1</td>
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<td>F</td>
<td>&gt;4.6 years</td>
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<td>M</td>
<td>&gt;4.2 years</td>
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<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Incidences of complications: 45%, 0%, 0%, 0%, 0%, 0%

Inacceptable rate of early graft loss!
Tolerance and Withdrawal of Immunosuppressive Drugs in Patients Given Kidney and Hematopoietic Cell Transplants

HLA identical transplants, related
Only 25% need continued immunosuppression, no aGvHD, no cGvHD, no severe short or long-term effects, no graft lost so far, excellent graft function

Table 1: Patient characteristics, conditioning and donor cell composition

<table>
<thead>
<tr>
<th>Patients¹</th>
<th>Age/Gender</th>
<th>ESRD cause</th>
<th>Total dose TLI (cGy)</th>
<th>CD34+ cell dose (×106/kg)</th>
<th>CD3+ cell dose (×106/kg)</th>
<th>Serum creatinine at last observation (mg/dL)</th>
<th>Duration off drugs⁴</th>
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<tbody>
<tr>
<td>1 (42 months)</td>
<td>48/M</td>
<td>Unknown</td>
<td>800</td>
<td>8.0</td>
<td>1</td>
<td>1.3</td>
<td>36 months</td>
</tr>
<tr>
<td>2 (72 months)</td>
<td>39/F</td>
<td>FSGS</td>
<td>800</td>
<td>8.4</td>
<td>1</td>
<td>0.9</td>
<td>–</td>
</tr>
<tr>
<td>3 (68 months)</td>
<td>24/M</td>
<td>Dysplasia</td>
<td>800</td>
<td>12.5</td>
<td>1</td>
<td>1.6</td>
<td>–</td>
</tr>
<tr>
<td>4 (50 months)</td>
<td>52/M</td>
<td>Unknown</td>
<td>1,200²</td>
<td>4.9</td>
<td>1</td>
<td>1.4</td>
<td>32 months</td>
</tr>
<tr>
<td>5 (48 months)</td>
<td>34/M</td>
<td>IgA</td>
<td>1,200</td>
<td>12.8</td>
<td>1</td>
<td>1.2</td>
<td>40 months</td>
</tr>
<tr>
<td>6 (47 months)</td>
<td>61/F</td>
<td>DM</td>
<td>1,200</td>
<td>12.2</td>
<td>1</td>
<td>1.2</td>
<td>–</td>
</tr>
<tr>
<td>7 (43 months)</td>
<td>23/F</td>
<td>SLE</td>
<td>1,200</td>
<td>16.5</td>
<td>10³</td>
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<td>8 (49 months)</td>
<td>33/M</td>
<td>Reflux</td>
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<td>1</td>
<td>0.9</td>
<td>34 months</td>
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<td>9 (34 months)</td>
<td>29/F</td>
<td>Unknown</td>
<td>1,200</td>
<td>17.5</td>
<td>1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>10 (33 months)</td>
<td>52/F</td>
<td>PKD</td>
<td>1,200</td>
<td>14.4</td>
<td>1</td>
<td>0.9</td>
<td>21 months</td>
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<tr>
<td>11 (25 months)</td>
<td>37/F</td>
<td>IgA</td>
<td>1,200</td>
<td>14.4</td>
<td>1</td>
<td>1.0</td>
<td>16 months</td>
</tr>
<tr>
<td>12 (22 months)</td>
<td>36/F</td>
<td>PKD</td>
<td>1,200</td>
<td>10.1</td>
<td>1</td>
<td>1.4</td>
<td>16 months</td>
</tr>
<tr>
<td>13 (14 months)</td>
<td>26/M</td>
<td>Unknown</td>
<td>1,200</td>
<td>6.6</td>
<td>1</td>
<td>1.0</td>
<td>1 month</td>
</tr>
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<td>14 (13 months)</td>
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<td>Unknown</td>
<td>1,200</td>
<td>14.4</td>
<td>1</td>
<td>0.8</td>
<td>1 month</td>
</tr>
<tr>
<td>15 (12 months)</td>
<td>40/F</td>
<td>IgA</td>
<td>1,200</td>
<td>10.0</td>
<td>1</td>
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<td>1 month</td>
</tr>
<tr>
<td>16 (4 months)</td>
<td>42/M</td>
<td>DM</td>
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<td>6.0</td>
<td>1</td>
<td>1.5</td>
<td>TE</td>
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</tbody>
</table>

ESRD = end-stage renal disease; FSGS = focal segmental glomerulosclerosis; IgA = IgA nephropathy; DM = diabetes mellitus; SLE = systemic lupus erythematosus; PKD = polycystic kidney disease.

¹Parentheses show duration of follow-up from kidney transplant.
²Dose increased to facilitate persistent chimerism.
³Dose used to facilitate persistent chimerism in SLE patient.
⁴Duration off antirejection drugs at last observation, dashes indicate patients on maintenance drugs; TE, too early to evaluate.
Tolerance Induction in HLA Disparate Living Donor Kidney Transplantation by Donor Stem Cell Infusion: Durable Chimerism Predicts Outcome

Joseph Leventhal,1 Michael Abecassis,1 Joshua Miller,1 Lorenzo Gallon,1 David Tollerud,2,3 Mary Jane Elliott,2 Larry D. Bozulic,3 Christopher Houston,2 Nedjema Sustento-Reodica,4 and Suzanne T. Ildstad2,3,5

Transplantation 2013;95: 169-176

5/6 to 0/6 HLA identical transplants, related and unrelated
### TABLE 2. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Highest historic PRA</th>
<th>PRA</th>
<th>αβ T cells</th>
<th>CD34</th>
<th>FC total</th>
<th>% Chimerism at 1 month</th>
<th>Anti-donor alloantibody after transplantation</th>
<th>Time off all immunosuppression</th>
<th>Durability of chimerism</th>
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<td>NW1</td>
<td>0</td>
<td>0.963</td>
<td>0.896</td>
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<td>3.80</td>
<td>2.53</td>
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<td>3.06</td>
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<td>2.29</td>
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*All cell dosing is # × 10^6/kg recipient body weight.
Chimerism testing was performed by molecular analysis of short tandem repeats; sensitivity 2% to 5%.
IC, iliac crest; PRA, panel reactive antibody.

35% off immunosuppression, no GvHD
Tolerance and Chimerism after Renal and Hematopoietic-Cell Transplantation

John D. Scandling, M.D., Stephen Busque, M.D., Sussan Dejvakhsh-Jones, M.S., Claudia Berntke, B.S., Maria T. Millan, M.D., Judith A. Shizuru, M.D., Ph.D., Richard T. Hoppe, M.D., Robert Lowoky, M.D., Edgar G. Engleman, M.D., and Samuel Strober, M.D.

SUMMARY

We describe a recipient of a combined kidney and hematopoietic-cell transplantation from an HLA-matched donor. A post-transplantation conditioning regimen of total lymphoid irradiation and antithymocyte globulin allowed engraftment of the donor's hematopoietic cells. The patient had persistent mixed chimerism, and the function of the kidney allograft has been normal for more than 28 months since discontinuation of all immunosuppressive drugs. Adverse events requiring hospitalization were limited to a 2-day episode of fever with neutropenia. The patient has had neither rejection episodes nor clinical manifestations of graft-versus-host disease.

IMMUNE TOLERANCE OF ORGAN TRANSPLANTS HAS BEEN INDUCED IN LABORATORY ANIMALS WHEN PERSISTENT MIXED BLOOD AND IMMUNE-CELL CHIMERISM HAS BEEN ACHIEVED BY INFUSING HEMATOPOIETIC CELLS FROM THE ORGAN DONOR BEFORE OR AFTER TRANSPLANTATION OF THE ORGAN.3,4 THE CONTINUOUS PRESENCE OF THE ORGAN DONOR'S IMMUNE CELLS IN THE RECIPIENT'S RHYTHMS AND PERIPHERAL LYMPHOID TISSUE PROMOTES AND MAINTAINS IMMUNE TOLERANCE BY ELIMINATING T-CELL CLONES THAT CAN REACT TO ALLOGENICANTIGENS OF THE GRAFT.5

We have attempted to achieve persistent mixed chimerism and tolerance in humans after transplantation of combined HLA-matched kidney and hematopoietic cells, using a low-intensity conditioning regimen of total lymphoid irradiation and antithymocyte globulin. This regimen can induce tolerance of organ allografts in laboratory animals.6,7 It also provides protection against graft-versus-host disease when used in patients with hematologic malignancies conditions who are given HLA-matched hematopoietic-cell transplants. Total lymphoid irradiation can facilitate tolerance of kidney transplants in some patients without the administration of donor hematopoietic cells.8

CASE REPORT

The patient was a 47-year-old man with end-stage renal disease of unknown origin at the time of preemptive kidney transplantation. The kidney donor was his 49-year-old brother, who shared the HLA type A1, Bw38, Bw4:40, DR1:01, DQ1:04,12 with the patient. On the day of kidney transplantation (day 0), the patient received the
The goal is to reproduce the results of the Stanford team.
A quote from Dr Strober:

“If we were able to make organ transplantation a reality in the 20th century, the goal for the 21st should be to do it without drugs.”
Combined kidney and hematopoietic stem cell transplantation to cure end-stage renal disease

Deckblatt für Prüfprotokoll

Version: 1.00
Datum: [Date]

Prüfer: Prof. Dr. med Thomas Fehr

Institutionen: Interdisziplinäre Studie der folgenden Kliniken:
- Klinik für Nephrologie
- Klinik für Hämatologie
- Klinik für Viszerale- und Transplantationschirurgie
- Klinik für Radio-Onkologie
- Universitätskinderklinik Zürich

Kurztitel: swissTolerance.ch

Ziel: Etablierung eines klinischen Protokolls zur Induktion von immunologischer Toleranz durch eine kombinierte Transplantation von hämatopoetischen Stammzellen und Nieren

Sponsor: Universitätssspital Zürich

Studentyp: Klinische Pilotstudie

Patientenzahl: 5 Patienten

Ort: Universitätssspital Zürich

Zeitperiode: Einschluss von 5 Patienten in 2 Jahren. Mindestens 2 Jahre Follow-up, d.h. maximale Studiendauer ist 4 Jahre

Bericht: Zwischenbericht jährlich nach Einschluss des ersten Patienten
Schlussbericht nach 5 Patienten
Unmittelbare Meldung bei Auftreten von schweren Komplikationen (Nierentransplantatverlust, schwere Graft-versus-host Erkrankung ≥ Grad III, schwere Infektionskomplikationen, Tod eines Patienten)

Mitarbeiter:
Prof. Dr. Thomas Fehr (NEP)
PD Dr. Urs Schanz (HAE)
Dr. Dr. Pietro Cippà (NEP)
PD Dr. Jens Brockmann (VIS)
Prof. Dr. Thomas Müller (NEP ab 1.1.2014)
PD Dr. Oliver Riesterer (Radio ONK)
PD Dr. Tayfun Göngör (Universitäts-Kinderklinik Zürich)

Zürich, den [Date] Prof. Dr. med. Thomas Fehr
5. Selection and withdrawal of subjects and donors

5.1 Study population / Recruitment
All patients aged 18-70 with end-stage renal failure under evaluation for kidney transplantation at the University Hospital Zurich will be considered for this clinical trial. Potential recipients must have uncompromised pulmonary, cardiac and liver function, be free of infection, and have an HLA-identical sibling donor.

5.2 Recipient inclusion criteria
- Patients, who are eligible for kidney transplantation
- Males or females 18 – 70 years of age.
- Subjects must have an HLA-matched sibling donor 18-70 years of age
- Men and women of reproductive potential must agree to use a reliable method of birth control
- Ability to understand and provide informed consent.
5.3 Recipient exclusion criteria
- Evidence of uncontrolled active infection (including replicating HIV, HCV and HBV) as defined by:
  a) clinical syndrome consistent with viral or bacterial infection (e.g., URI, UTI), or
  b) fever with a clinical site of infection identified, or
  c) microbiologically documented infection
- Contraindication to therapy with any one of the proposed agents (e.g., allergy to ATG).
- Serologic positivity to HIV.
- Women of childbearing age in whom adequate contraception cannot be maintained, pregnant women or nursing mothers.
- Malignancy within the past two years, for which waiting time for transplantation is required by PENN registry consult, thereby excluding non-melanoma skin cancer and carcinoma in situ of the cervix.
- AST/ALT > 3 x normal value.
- Cardiac ejection fraction < 50% by radionuclide ventriculography or echocardiograph.
- FEV1 < 50% predicted or postbronchodilator > predicted.
- HLA-ABO blood group incompatibility in the donor-graft direction.
- RA > 10%.
- High risk of primary kidney disease recurrence (i.e. FSGS or HUS).

5.4 Donor inclusion criteria
- Donor must be eligible for kidney donation and hematopoietic stem cell donation according to the transplantation law and local guidelines for living donor kidney transplantation and stem cell donation.
- HLA-matched for A, B, C, DR and DQ loci
- Age ≥ 25 years, ≤ 70 years
- Identical or minor incompatible ABO blood group.
- Ability to understand and provide informed consent.

5.5 Donor exclusion criteria
- Contraindication to therapy with any one of the proposed agents (e.g., allergy to G-CSF).
- Serologic positivity to HIV, HCV or HBV.
- Women of childbearing age in whom adequate contraception cannot be maintained, pregnant women or nursing mothers.