ABO-incompatible Kidney Transplantation

-Overcoming Immunological Barrier of ABO-carbohydrate antigen-

Kazuhide Saito, MD, Ph.D
Department of Urology,
Graduate School of Medical and Dental Sciences,
Niigata University,
Niigata, JAPAN.
The author have no financial conflicts of interest to disclose concerning the presentation.
History of Kidney Transplantation
## History of Kidney Transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Name</th>
<th>Type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Wien, Austria</td>
<td>Ullman</td>
<td>Experimental kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1902</td>
<td>Lyon, France</td>
<td>Carrel</td>
<td>Vascular anastomosis Experimental</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1910</td>
<td>Kyoto, Japan</td>
<td>Yamanouchi</td>
<td>Experimental kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1933</td>
<td>Ukraine</td>
<td>Voronoy</td>
<td>Deceased kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1945</td>
<td>Boston, USA</td>
<td>Hume</td>
<td>Deceased kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td>Chicago, USA</td>
<td>Lawler</td>
<td>Deceased Kidney transplant</td>
<td>functioned for 53 days</td>
</tr>
<tr>
<td>1951</td>
<td>Paris, France</td>
<td>Kuss</td>
<td>Living Free kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Paris, France</td>
<td>Dobust</td>
<td>Deceased kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Strasbourg, France</td>
<td>Marceau</td>
<td>Deceased kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Toronto, Canada</td>
<td>G. Murray</td>
<td>Deceased kidney transplant</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Paris, France</td>
<td>Hamburger</td>
<td>Living related kidney transplant</td>
<td>functioned for 21 days</td>
</tr>
<tr>
<td>1954</td>
<td>Boston, USA</td>
<td>Hume</td>
<td>Deceased kidney transplant</td>
<td>functioned for 5 months</td>
</tr>
<tr>
<td>1954</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1954.12.23</td>
<td>Boston, USA</td>
<td>Murray, Merrill &amp; Harrison</td>
<td>Living kidney transplant between identical twins</td>
<td>functioned for over 8 years</td>
</tr>
</tbody>
</table>
The first successful kidney transplantation in the World

1954. 12. 23.
The first successful kidney transplant between identical twins.

Peter Bent Brigham Hospital, Boston, MA.

Successful Homotransplantation of the Human Kidney Between Identical Twins. John P. Merrill, MD; Joseph E. Murray, MD; J. Hartwell Harrison, MD; and Warren R. Guild, MD

*JAMA. 1956;160(4):277-282*

Murray, Merrill and Harrison
Richard and Ronald Herrick, Recipient and Donor.
11th April, 1956.

Only after 1 year and 4 months,

Free graft kidney extirpated because of idiopathic renal bleeding was transplanted into left femoral space of acute renal failure patient due to bichloride mercury intoxication at Niigata University.

The first successful kidney transplant in JAPAN

Clinical Allogeneic Kidney transplantation.

Takamitsu Kusunoki, Hikohachiro Inoue.
Renal Transplantation: Experimental Study and Clinical Experience

Renal homotransplantation, the first description of which was made by Ullmann and by Carrel independently in 1902, has no difficulties in technical problems. But as to functional problems the results obtained from a great many experiences have revealed that the homotransplanted kidney always lost its functions and was rejected and destroyed within a few days as a result of immune reaction between the transplant and the recipient. In human cases the rejection and destruction were also inevitable for renal homotransplantation, though the immune reactions appeared to be gradual and mild as compared with those of experimental animals. Therefore homotransplantation of the kidney is far from clinical application in case that permanent kidney substitution is required. But as the homotransplanted kidney can secret urine for a few days after transplantation, renal homotransplantation can be applied in case of acute reversible renal insufficiency which necessitates some temporal substitution. However, whether the transplanted kidney functions sufficiently immediately after transplantation, has not been thoroughly known as yet. If the transplanted kidney begins functioning several days after the transplantation, renal homotransplantation has no significance in treating acute renal insufficiency. It is of clinical importance to investigate the renal function just after the transplantation.
CONCLUSION AND SUMMARY

Table 1
Findings of the Transplant Urine

<table>
<thead>
<tr>
<th></th>
<th>April 12</th>
<th>April 13</th>
<th>April 14</th>
<th>April 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour output (cc.)</td>
<td>65</td>
<td>58</td>
<td>150</td>
<td>220</td>
</tr>
<tr>
<td>Na concentration (mEq/L)</td>
<td>125</td>
<td>126</td>
<td>198</td>
<td>190</td>
</tr>
<tr>
<td>Cl concentration (mEq/L)</td>
<td>105</td>
<td>89.5</td>
<td>87.5</td>
<td>69</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.022</td>
<td>1.032</td>
<td>1.028</td>
<td>1.026</td>
</tr>
</tbody>
</table>

Fig. 1. Schema of renal transplantation in the upper thigh.
Orthotopic Kidney Transplant Operation Procedure into Iliac Fossa Established by Joseph E. Murray, A Novel Prize Winner.
Kidney Transplantation

“Bench surgery” on the bactable

Transplant Operation
ABO-incompatible Kidney Transplantation
Contents

◆ History of ABO-incompatible Kidney transplantation

◆ The Battle against ABO-incompatibility
  Antibody-Mediated Rejection (AMR)
  Splenectomy
  Antibody removal

◆ Induction of the concept of “Desensitization“

◆ What is “Immunological Accommodation”?

◆ Achievement and future perspectives.
Discovery of ABO blood type

Aus dem pathologisch-anatomischen Institute in Wien.

Über Agglutinationserscheinungen normalen menschlichen Blutes.

Von Dr. Karl Landsteiner, Assistenten am pathologisch-anatomischen Institute.

Vor einiger Zeit habe ich beobachtet und mitgetheilt ¹), dass öfters Blutserum von normalen Menschen rothe Blutkörperchen anderer gesunder Individuen zu verklumpen im Stande ist. Ich hatte damals den Eindruck,

¹) Centralblatt für Bacteriologie. XXVII. S. 361. v. 10. Februar 1900.
Generation of H-, A-, and -B Histo-Blood Antigen

Gal(β1→3 or 4)GlcNAc

HDP-Fuc

UDP

Fuc transferase

(H-enzyme)

Gal(β1→3 or 4)GlcNAc

O (H) antigen

Fuc α↑

GalNAc transferase

(A-enzyme)

GalNAc(α1→3)Gal(β1→3 or 4)GlcNAc

UDP-GalNAc

UDP

Gal transferase

(B-enzyme)

Gal(α1→3)Gal(β1→3 or 4)GlcNAc

A antigen

B antigen

Fuc α↑
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell type</td>
<td><img src="image1" alt="A antigen" /></td>
<td><img src="image2" alt="B antigen" /></td>
<td><img src="image3" alt="A and B antigens" /></td>
<td><img src="image4" alt="None" /></td>
</tr>
<tr>
<td>Antibodies in Plasma</td>
<td><img src="image5" alt="Anti-B" /></td>
<td><img src="image6" alt="Anti-A" /></td>
<td>None</td>
<td><img src="image7" alt="Anti-A and Anti-B" /></td>
</tr>
<tr>
<td>Antigens in Red Blood Cell</td>
<td><img src="image1" alt="A antigen" /></td>
<td><img src="image2" alt="B antigen" /></td>
<td><img src="image3" alt="A and B antigens" /></td>
<td>None</td>
</tr>
</tbody>
</table>
ABO-Histo-Blood type Carbohydrate Antigens are Expressed on Endothelial Cell Surface

Expression of A-antigen in the kidney

“Natural antibody”
anti-A/anti-B antibody
ABO-incompatible organ transplantation

Landsteiner’s “classic blood transfusion principle”

- **Type O**: Universal Donor
- **Type AB**: Universal Recipient
History of ABO incompatible kidney transplantation
Renal homografts in patients with major donor-recipient blood group incompatibilities

Addendum Table II. Direction of acceptable mismatched tissue transfer*

<table>
<thead>
<tr>
<th></th>
<th>Safe</th>
<th>Safe</th>
<th>Relatively safe</th>
<th>Dangerous</th>
<th>Dangerous</th>
<th>Dangerous</th>
</tr>
</thead>
<tbody>
<tr>
<td>O to non-O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rh- to Rh+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rh+ to Rh-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A to non-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B to non-B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB to non-AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*O is universal donor; AB is universal recipient.
ABO-incompatibility tends to increase the incidence of transplants which never function.
What happens when ABO-incompatible kidney transplanted?

Antigen-antibody reaction

Complement activation

Endothelial cell injury

Micro thrombosis

Interstitial Hemorrhage

Graft Thrombosis

Kidney Graft would be destroyed by severe antibody-mediated rejection.
ABO-incompatible kidney transplantation was considered as Immunologically “contra-indication”
The Battle against the immunological barrier of ABO-incompatibility in Kidney Transplantation
## History of ABO-incompatible Kidney Transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Researcher</th>
<th>Procedure/finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1901</td>
<td>Landsteiner</td>
<td>ABO blood type discovered</td>
</tr>
<tr>
<td>1952</td>
<td>Hume</td>
<td>Procedure first performed ; graft rejected</td>
</tr>
<tr>
<td>1964</td>
<td>Starzl</td>
<td>Long-term graft survival in one out of two kidney transplant patients</td>
</tr>
<tr>
<td>1965</td>
<td>Inou, Ota</td>
<td>Graft rejected</td>
</tr>
<tr>
<td>1967</td>
<td>Sonoda</td>
<td>Long-term graft survival in one kidney transplant patient in Japan</td>
</tr>
<tr>
<td></td>
<td>Gleason, Murray</td>
<td>ABO incompatibility grafts tends to Never Function</td>
</tr>
<tr>
<td>1981</td>
<td>Slapak</td>
<td>Posttransplant plasma exchange was effective ; graft survival</td>
</tr>
<tr>
<td>1985</td>
<td>Alexandre</td>
<td>Pretransplant plasma exchange and splenectomy ; graft survival</td>
</tr>
<tr>
<td>1986</td>
<td>Cardella</td>
<td>Pre-and Post- transplant plasma exchange and splenectomy ; graft survival</td>
</tr>
<tr>
<td>1987</td>
<td>Bannett</td>
<td>Pretransplant immunoadsorption and splenectomy ; graft survival</td>
</tr>
<tr>
<td>1989</td>
<td>Takahashi, Ota</td>
<td>Pretransplant DFPP and immunoadsorption, splenectomy ; graft survival</td>
</tr>
</tbody>
</table>
RENAL TRANSPLANT IN A PATIENT WITH MAJOR DONOR-RECIPIENT BLOOD GROUP INCOMPATIBILITY

Reversal of Acute Rejection by the Use of Modified Plasmapheresis

Maurice Slapak, Ramesh B. Naik, and Harry A. Lewis

The Wessex Regional Transplant and Renal Unit, St. Mary's Hospital, Portsmouth, Hants, PO3 6AD England

A+ ⇒ O+
Deceased donor
kidney transplantation
( Accidental)

“AMR”

Plasmapheresis

Graft Survived

Plasmapheresis !!!

Figure 1. This shows the fall in activity, IgG and IgM, drop in total anti-A activity and its IgG component associated with the plasmapheresis. There is a return in the level of both these antibodies seen after plasmapheresis without any deterioration of graft function. Nevertheless, each successive plasmapheresis results in reduced levels of anti-A activity. Overall, the present activity is approximately 80% of the level immediately after transplantation. In each instance IgG levels seem more affected than IgM.
Guy Alexandre MD.
Professor Emeritus,
St. Lukes Hospital, Brussels, Belgium
Plasmapheresis !!!

<table>
<thead>
<tr>
<th>Recipient (Diagnosis)</th>
<th>Secretor Status</th>
<th>Serum Creatinine Follow-up (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>se</td>
</tr>
<tr>
<td>ABO-Incompatible Living Donor Renal Homografts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. V.D.N. (Iga nephropathy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. D.S.A. (Wilms’ tumor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. G.B. (CIN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. V.B.J. (Iga nephropathy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. M.G. (CGN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. C.G. (CGN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. R.C. (CGN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. C.F. (Diabetic nephropathy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. P.C. (CGN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. H.B. (CIN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. R.R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. A.G.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. L.G.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. J.G.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Splenectomy !!!
What is the key for successful ABO incompatible kidney transplant?

Alexandre GPJ. et al.:

Plasmapheresis (PP) and Splenectomy are necessary.
19th January, 1989

The 1st Successful ABO-incompatible Kidney Transplantation in JAPAN

Tokyo Women’s Medical Univ.

Antibody removal by DFPP + Immunoadsorption

Splenectomy
Takahashi K, Saito K, Takahara S, et al.
Excellent long-term outcome of ABO-incompatible living kidney transplantation in Japan.
Am.J.Transplant 2004;4:1089. (441 cases)

Takahashi K, Saito K
Present status of ABO-incompatible kidney transplantation in Japan.
Xenotransplantation 2006;13:118. (578 cases)

Saito K, Takahashi K
ABO-incompatible kidney transplantation in Japan
International Congress Series 2006, Elsevier Science. (685 cases)
Prof. Emeritus, Guy Alexandre
St. Luc Univ. Hospital, Brussel, Belgium

Prof. Emeritus, Kota Takahashi,
Niigata University, Niigata, Japan.

Pioneer of ABO-incompatible kidney transplantation
Cassical Strategy for Successful ABO-incompatible Kidney Transplantation

1. Antibody removal
2. Immunosuppression (antibody production)
3. Splenectomy
4. Anticoagulation therapy

Strategy has been established in 1990s.
Excellent Long-term Outcome of ABO-Incompatible Living Donor Kidney Transplantation in Japan

Kota Takahashi, Kazuhide Saito, Shiro Takahara, Akihiko Okuyama, Kazunari Tanabe, Hiroshi Toma, Kazuharu Uchida, Akira Hasegawa, Norio Yoshimura, Yoriaki Kamiryo and the Japanese ABO-incompatible Kidney Transplantation Committee

Figure 2: Rates of patient survival and graft survival for ABO-incompatible kidney transplantation and for historical controls undergoing living kidney transplantation. The graft survival rate was slightly but not significantly lower for ABO-incompatible kidney transplantation than for historical controls.
No significant difference between A- and B- incompatibility

Figure 6: Graft survival rates for A-incompatible transplantation and B-incompatible transplantation. Graft survival rates were similar for A-incompatible transplantation and B-incompatible transplantation.

Figure 8: Graft survival rate according to the presence or absence of anticoagulation therapy after transplantation. Graft survival rate was significantly better in patients receiving anticoagulation therapy than in those not receiving anticoagulation therapy.
Problems to be solved

1. Achieved fair patient and graft outcome, however, about 5 to 10% grafts are still lost due to AMR in the early period.

2. Splenectomy is considered to be necessary for success, however, still a big surgical burden which sometimes cause severe complication.

( i.e. Postoperative hemorrhage, pancreatitis, ileus • • • etc.)
Graft Outcome and Anti-A, Anti-B Antibody Production.

1. Good Outcome

2. Type I acute AMR

3. Type II acute AMR

AMR: Antibody-mediated rejection
Type I Acute AMR
Type I Acute AMR

40y.o. Female O ← B HLA 1 haplo identical

IA: immunoabsorption  DFPP: double filtration plasma pheresis  ▼: local irradiation
HD: hemodialysis  DSG: deoxyspergualin  OKT3: muromonab CD3  AZ: azathioprine
MP: methylprednisolone  CYA: ciclosporin  ALG: antilymphocyte globulin  AMR: antibody-mediated rejection
Type II
Acute AMR
## Clinical Classification of Acute AMR in ABOi Kidney Transplant

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occurrence in</strong></td>
<td><strong>Early</strong></td>
<td><strong>Late</strong></td>
</tr>
<tr>
<td>Critical period</td>
<td><strong>Highly sensitized</strong></td>
<td><strong>Not highly sensitized</strong></td>
</tr>
<tr>
<td>Recipient</td>
<td><strong>Inadequate</strong></td>
<td><strong>Adequate~ oversuppressed</strong></td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td><strong>ABO histo-blood group Ags</strong></td>
<td><strong>ABO histo-blood group associated Ags</strong></td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td><strong>Re-sensitization</strong></td>
<td><strong>cross reactive</strong></td>
</tr>
<tr>
<td><strong>Sensitization</strong></td>
<td><strong>Second-set</strong></td>
<td><strong>Responsive response</strong></td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td><strong>“Severe”</strong></td>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td><strong>Antibody production</strong></td>
<td><strong>“Explosive”</strong></td>
<td><strong>“Less than type I”</strong></td>
</tr>
<tr>
<td><strong>Antibody class</strong></td>
<td><strong>IgG↑ dominant IgM</strong></td>
<td><strong>“Slowly “</strong></td>
</tr>
<tr>
<td>B cell</td>
<td><strong>B-1a cell</strong></td>
<td><strong>IgM↑ dominant</strong></td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td><strong>Poor</strong></td>
<td><strong>B-1b cell</strong></td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td><strong>Desensitization therapy</strong></td>
<td><strong>Fair</strong></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td><strong>Poor</strong>(graft loss)**</td>
<td><strong>Infection control</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Possible graft survival</strong></td>
</tr>
</tbody>
</table>
Onset of acute antibody-mediated rejection

Recipient: 1989-2001, without rixuimab

Onset of acute antibody-mediated rejection

Silent period  Critical period  Stable period

- Upper low: Splenectomy group
- Lower low: Non-splectomy group

Cases of graft loss
Cases of graft survival

Recipient: 1989-2001, without rixuimab

If we could successfully reached to “stable period” without AMR, Long-term graft survival would be promising.

In this stage, “Immunological Accommodation” is likely to occur.
Definition of Immunological Accommodation in ABO-incompatible Kidney Transplantation


Accommodation refers to the lack of reaction between ABO blood group antigens on the surfaces of endothelial cells within the graft and these antibodies in the blood of the recipient, i.e. graft survival without antibody-mediated rejection. Various mechanisms have been proposed for accommodation. The ABO blood group gene, its gene product glycosyltransferase, antigens, and antibodies are implicated in this phenomenon.
How can we avoid AMR?

How can we avoid splenectomy?

And successfully induce Immunological Accommodation?
The Concept of Preoperative Desensitization therapy without Splenectomy!

The answer is

〜Moving toward to the next stage〜
Preconditioning regimen consisting of anti-CD20 monoclonal antibody infusions, splenectomy and DFPP-enabled non-responders to undergo ABO-incompatible kidney transplantation

Tokyo Women’s Medical University, Tokyo, JAPAN.
Plasmapheresis, CMV Hyperimmune Globulin, and Anti-CD20 Allow ABO-Incompatible Renal Transplantation Without Splenectomy

Christopher J. Sonnenday, Daniel S. Warren, Mathew Cooper, Milagros Samaniego, Mark Haas, Karen E. King, R. Sue Shirey, Christopher E. Simpkins and Robert A. Montgomery.

Johns Hopkins University
Baltimore, Maryland, USA.
ABO Incompatible Kidney Transplantations Without Splenectomy, Using Antigen-Specific Immunoabsorption and Rituximab

Gunnar Tydén, Gunilla Kumlien, Helena Genberg, John Sandberg, Torbjörn Lundgren, and Ingela Fehrman

Figure 1: The effect of antigen-specific immunoabsorption (Glycosorb) on antigen titers. The timing of the different components of the immunosuppressive protocol is also shown.
Pinpoint targeted immunosuppression: anti-CD20/MMF desensitization with anti-CD25 in successful ABO-incompatible kidney transplantation without splenectomy


Kazuhide Saito,¹ Yuki Nakagawa,¹ Michihiro Suwa,¹ Naoki Kumagai,¹ Toshiki Tanikawa,¹ Tsutomu Nishiyama,¹ Mitsuhiro Ueno,² Fumitake Gejyo,² Shin-ichi Nishi³ and Kota Takahashi¹


The first successful ABO-incompatible kidney transplantation “without splenectomy” Using “Desensitization” with Rituximab.

Niigata University Hospital.
B-cell maturation to plasma cells

B-cell surface antigen:
- CD19
- CD20
- CD22
- CD52
- CD40
- BAFF-R
- CD27
- CD38
- CD138

-“Rituximab”-
Anti-human CD20
mouse/human chimeric monoclonal antibody
Welcome to Göteborg, Sweden for:

2nd International Symposium on ABO Incompatibility in Transplantation

September 10-11, 2005

Dear Colleagues

Please be aware that The IXA2005 congress is preceded by a 1½ day satellite meeting entitled “The 2nd International Symposium on ABO Incompatibility in Transplantation”, designed to complement the main meeting. The satellite will focus on the clinical aspects of ABO incompatible transplantation, a subject that has gained considerable attention the last few years driven by the increasing global shortage of organs for transplantation. A number of well recognized plenary speakers will lead the proceedings but participation from the wider community is encouraged.

Michael Bremer, Chairman

Scientific programme

Plenary

Renal Transplantation

Kota Takahashi, Niigata, Japan:
Present status of ABO incompatible kidney transplantation in Japan.

Robert Montgomery, John Hopkins, USA:
Anti-CD20 and plasmapheresis in ABO incompatible renal transplantation.

Gunnar Tyden, Stockholm, Sweden:
The use of anti-CD20 mAbs and specific immunoabsorption in ABO incompatible renal transplantation.

Kazuhide Saito, Niigata, Japan:
Pin-Point Targeted Immunosuppression; Desensitization and Anti-CD20, Anti-CD25 mAbs in ABO Incompatible Kidney Transplantation without Splenectomy.

Workshop

The role of anti-CD20 Mab in ABO incompatible transplantation – risks/benefits versus splenectomy

(Chair: T. Cairns, UK)

Ken Smith, Cambridge, UK:
Rituximab and the Suppression of Human Immunity.

Discussion panel: R. Montgomery, G. Tydén, K. Saito, K. Smith
B1a recognizes
Histo-Blood type carbohydrate Ags

B1b : 
Histo- Blood type associated Ags

B2 : 
Peptide Ags (HLA)
Current Desensitization & Immunosuppression Protocol For ABO-incompatible Kidney Transplantation Niigata University Hospital.

Transplantation

**Rituximab**
- 100mg x 2

**Basiliximab 20mg x 2**

**CNI (Tacrolimus or Ciclosporine)**
- MMF 20mg/kg
- 30mg/kg
- 20mg/kg
- Low Dose Steroid MP 8mg
- DFPP x 2
- MP 125mg div～
- 20mg p.o.
- 4mg ～minimum /off

**Antibody Removal**
- -28d -14d -5d -2d
- Anti-A/B titer

**Accommodation**
- 0 4 1W 2W 4W
- "Critical period"
In Japan, Rituximab has been approved to use under public health insurance for desensitization in 2017.
Achievement
Annual Number of Kidney Transplantation in JAPAN

Total Number

Living Donor Kidney Transplant

Deceased Donor Kidney Transplant

Provided by Prof. T. Yagisawa, Jichi Medical Univ.
Annual Number of ABO-incompatible Kidney Transplant in JAPAN

(1989 - 2016: 4,545)

Provided by Prof. T. Yagisawa, Jichi Medical Univ.
Proportion of ABO-incompatibility in Living donor Kidney Transplantation in JAPAN

Provided by Prof. T. Yagisawa, Jichi Medical Univ.
Japan ABO-incompatible Kidney Transplantation Committee

Overall Patient and Graft Survival

N = 2,434

120 institutes

Observation period
Median 3 yrs 5 m
(1d ~ 23 yrs 7 m)

Patient Survival
Graft Survival

(Kaplan-Meier)
Patient Survival according to the transplanted year period

- **Overall (n = 2,434)**
  - 3 yr: 96%
  - 5 yr: 93%
  - 10 yr: 90%
  - 15 yr: 83%
  - 20 yr: 73%

- **Before 2000 (n= 449)**
  - 3 yr: 89%
  - 5 yr: 86%
  - 10 yr: 83%
  - 15 yr: 77%
  - 20 yr: 67%

- **After 2001 (n = 1,985)**
  - 3 yr: 97%
  - 5 yr: 95%
  - 10 yr: 93%

**Log-rank**

- **P<0.01**

Japan ABO-incompatible Kidney Transplantation Committee
Graft Survival according to the transplanted year period

Overall (n = 2,434)

Before 2000 (n = 449)

After 2001 (n = 1,985)

**P<0.01

(Kaplan-Meier)
Graft Survival according to the preoperative IgG antibody titer (Before 2000)

Graft survival
Significantly worse in IgGAb titre ≥64 folds vs. Ab titre <32 folds
Before 2000.

Japan ABO-incompatible Kidney Transplantation Committee
Graft Survival according to the preoperative IgG antibody titer (After 2001)

No significant difference in Graft survival between IgGAb titre ≥ 64 folds and <32 folds After 2001 era.

Japan ABO-incompatible Kidney Transplantation Committee
Paradigm Shift for Successful ABO-incompatible Kidney Transplantation

Classical

- Antibody Removal (Necessary)
- Immunosuppression
- Splenectomy (Necessary)
- Anti-coagulation therapy

Updated

- Antibody Removal (on demand)
- Preoperative Desensitization Immunosuppression (Necessary)
- Anti-coagulation therapy (On Demand)
Graft Survival ABO compatibility

We have overcome the immunological barrier against ABO incompatibility in kidney transplantation

Provided by Prof. T. Yagisawa, Jichi Medical Univ.
What is the mechanism of the induction and maintenance of “Immunological Accommodation”? 
Graft (Donor) factors

Disparity of the ABO-carbohydrate antigens on the endothelial surface of the kidney graft

Regulatory mechanism of complement activation

Vs.

Host (Recipient) factors

Disparity & regulatory mechanism of B cell immunity against ABO-carbohydrate antigens
Summary

1. ABO-incompatibility was immunologically contraindication for kidney transplant before 1980’s.

2. Splenectomy & Antibody removal was necessary prerequisite for success in late 1980’s~1990’s.

3. Splenectomy has been replaced by Preoperative Desensitization with Rituximab in early 2000’s.

4. The concept of “Immunological Accommodation” against ABO-carbohydrate antigens has become emerged.

5. The mechanism of the induction and maintenance of “Accommodation” must be further examined and elucidated.
Thank You For Attention.