科学は技術と伴にある
ーラット小腸移植モデルの展開ー
世界の臨床小腸移植の年次推移

Numbers of intestinal/multivisceral transplantation
(OPTN/SRTR data)
Difficulties, guidelines and review of developing an acute rejection model after rat intestinal transplantation.


Pediatric Surgery Department, La Paz University Hospital, Paseo La Castellana, 261, 28046 Madrid, Spain
### Table: Average surgical times.

<table>
<thead>
<tr>
<th></th>
<th>Learning curve (n = 160)</th>
<th>Rejection study group* (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor surgery</td>
<td>38 ± 8 min</td>
<td>32 ± 6 min</td>
</tr>
<tr>
<td>Venous anastomosis</td>
<td>18 ± 6 min</td>
<td>15 ± 6 min</td>
</tr>
<tr>
<td>Arterial anastomosis</td>
<td>16 ± 4 min</td>
<td>14 ± 3 min</td>
</tr>
<tr>
<td>Warm ischemia</td>
<td>38 ± 9 min</td>
<td>35 ± 7 min</td>
</tr>
<tr>
<td>Recipient surgery</td>
<td>98 ± 20 min</td>
<td>86 ± 15 min</td>
</tr>
<tr>
<td>Total transplantation</td>
<td>152 ± 23 min</td>
<td>138 ± 20 min</td>
</tr>
</tbody>
</table>

*異所性に植えて術後6日以上生きたもの

（Andres MA, et al. Transplant Immunol 2016）
オーバーナイトしない例
オーバーナイトした例

（Andres MA, et al. Transplant Immunol 2016）
動脈吻合時間

（Andres MA, et al. Transplant Immunol 2016）
静脈吻合時間

（Andres MA, et al. Transplant Immunol 2016）
Teaching intestinal transplantation in the rat for medical student.  
Galvão FH, Bacchella T, Cerqueira, Machado M  
Experimental Microvascular Laboratory of Transplant and Liver Surgery Discipline, 
Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Abstract  
Technical difficulties hamper the widespread use of intestinal transplantation in rats. We evaluated the feasibility in training this microsurgical model for medical students. Thirty eight students were assessed. After information about intestinal transplantation in rats, they spontaneously agreed to be trained for this procedure. The course consisted of 4-h weekly lessons during 4-month period. The teaching process includes assessment in four phases:  
I) conception of intestinal transplantation and rat anatomy;  
II) basic microsurgery training;  
III) donor operation;  
IV) donor/recipient operation. Wistar rats were used as donors and recipients in one-step small bowel transplantation. All students (100%) reached phase II, seven students (18.42%) reached phase III and two students (5.26%) reached phase IV. Decreased interest about the theme, lack of time and patience, frustration and/or inability were all reasons given by the student that may have contributed to the low rate of success. Medical students achieved a low rate of completion for training in rat intestinal transplantation microsurgical procedures.
Microsurgery Room in Kobayashi’s Labo (2000 – 2009)

Cuff Method

Hand-Suture Method
Prevention by Liver transplantation of the Graft-Versus-Host Reaction and Allograft Rejection in a Rat Model of Small Bowel Transplantation

(Kobayashi E, et al. Transplantation 1994)
Impact of graft length on surgical damage after intestinal transplantation in rats

Table 1
Survival of cervical SBT rat

<table>
<thead>
<tr>
<th>Group</th>
<th>Cuff size</th>
<th>Graft length</th>
<th>N</th>
<th>Survival (days)</th>
<th>Lethality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>20 G</td>
<td>Segment (15 cm)</td>
<td>10</td>
<td>&gt;100, &gt;100, &gt;100, &gt;100, &gt;100, &gt;100, &gt;100</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>18 G</td>
<td>Whole (700 cm)</td>
<td>11</td>
<td>7*, 8*, 9*, 11*, 16*, &gt;100, &gt;100, &gt;100, &gt;50, &gt;50</td>
<td>45.6</td>
</tr>
</tbody>
</table>

* The rats showed severe weight loss with intact graft.

**Immunologic Benefits of Longer Graft in Rat Allogenic Small Bowel Transplantation**

**TABLE 1. Effect of graft length on recipient survival after orthotopic small-bowel transplantation (SBT) in two different models**

<table>
<thead>
<tr>
<th>Group</th>
<th>Model</th>
<th>Donor</th>
<th>Recipient</th>
<th>Graft length</th>
<th>n</th>
<th>Recipient survival (days)</th>
<th>Mean ± SD (days)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A^f</td>
<td>M&amp;R^a</td>
<td>BN</td>
<td>LEW</td>
<td>Whole (70 cm)</td>
<td>5</td>
<td>16, 63, 71, 72, &gt;80</td>
<td>60.4 ± 25.5</td>
<td></td>
</tr>
<tr>
<td>B^f</td>
<td>M&amp;R^a</td>
<td>BN</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>7</td>
<td>7, 7, 8, 8, 9, 14, 14^d</td>
<td>9.6 ± 3.1</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>C</td>
<td>M&amp;R^a</td>
<td>LEW</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>4</td>
<td>&gt;80, &gt;80, &gt;80, &gt;80</td>
<td>&gt;80</td>
<td></td>
</tr>
<tr>
<td>D^f</td>
<td>Combined^b</td>
<td>BN</td>
<td>LEW</td>
<td>Whole (70 cm)</td>
<td>8</td>
<td>44, 45, 51, 55, 62, 63, 67</td>
<td>54.3 ± 8.9</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>E^f</td>
<td>Combined^b</td>
<td>BN</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>7</td>
<td>29, 43, 49, 52, 54, 56</td>
<td>45.4 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Combined^b</td>
<td>LEW</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>6</td>
<td>&gt;100, &gt;100, &gt;100, &gt;100, &gt;100</td>
<td>&gt;100</td>
<td></td>
</tr>
</tbody>
</table>

^a Orthotopic SBT were performed using classical microsurgical technique reported by Monchik and Russell (M&R).
^b Cuff technique was used for venous reconstruction.
^c Tacrolimus (0.64 mg/kg/day) was administered intramuscularly from 0 to 13 postoperative days.
^d Recipients died with intact graft.
BN, Brown Norway; LEW, Lewis.

Experimental Models of Rat Small Intestinal Transplantation: Cuff Method and Suture Method

(Cuff method) (Suture method) (Combined method)

# Immunologic Benefits of Longer Graft in Rat Allogenic Small Bowel Transplantation

## TABLE 1. Effect of graft length on recipient survival after orthotopic small-bowel transplantation (SBT) in two different models

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<th>Recipient</th>
<th>Graft length</th>
<th>n</th>
<th>Recipient survival (days)</th>
<th>Mean ± SD (days)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>M&amp;R</td>
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<td>LEW</td>
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<td>5</td>
<td>16, 63, 71, 72, &gt;80</td>
<td>60.4 ± 25.5</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>B</td>
<td>M&amp;R</td>
<td>BN</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>7</td>
<td>7, 8, 8, 9, 14, 14</td>
<td>9.6 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>M&amp;R</td>
<td>LEW</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>4</td>
<td>&gt;80, &gt;80, &gt;80, &gt;80</td>
<td>&gt;80</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Combined</td>
<td>BN</td>
<td>LEW</td>
<td>Whole (70 cm)</td>
<td>8</td>
<td>44, 45, 51, 55, 62, 63, 67</td>
<td>54.3 ± 8.9</td>
<td>p = 0.10</td>
</tr>
<tr>
<td>E</td>
<td>Combined</td>
<td>BN</td>
<td>LEW</td>
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<td>29, 35, 43, 49, 52, 54, 56</td>
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</tr>
<tr>
<td>F</td>
<td>Combined</td>
<td>LEW</td>
<td>LEW</td>
<td>Segment (15 cm)</td>
<td>6</td>
<td>&gt;100, &gt;100, &gt;100, &gt;100</td>
<td>&gt;100</td>
<td></td>
</tr>
</tbody>
</table>

* Orthotopic SBT were performed using classical microsurgical technique reported by Monchik and Russell (M&R).
* Cuff technique was used for venous reconstruction.
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* Recipients died with intact graft.
* BN, Brown Norway; LEW, Lewis.

（Fujishiro J, et al. Transplantation 2005）
(Fujishiro J, et al. Transplantation 2005)
Immunologic Benefits of Longer Graft in Rat Allogenic Small Bowel Transplantation

**TABLE 2.** Onset of rejection and suffering period after whole or segmental orthotopic SBT (BN to LEW)

<table>
<thead>
<tr>
<th>Group</th>
<th>Graft length</th>
<th>Onset of rejection (days)</th>
<th>Mean ± SD (days)</th>
<th>Suffering period (days)</th>
<th>Mean ± SD (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Whole</td>
<td>30, 33, 35, 37, 37, 39, 41, 60</td>
<td>39.0 ± 9.1</td>
<td>5, 7, 8, 14, 20, 21, 21, 26</td>
<td>15.3 ± 7.9</td>
</tr>
<tr>
<td>E</td>
<td>Segment</td>
<td>27, 29, 35, 41, 43, 52</td>
<td>37.4 ± 8.6</td>
<td>0, 2, 5, 6, 8, 8, 17</td>
<td>6.6 ± 5.5</td>
</tr>
</tbody>
</table>

The characteristics of group D and E are shown in Table 1.

* Onset of rejection was defined by the day when recipients body weight start decreasing.

* Suffering period was defined by the period from the onset of rejection to recipient death.

SBT, small-bowel transplantation; BN, Brown Norway; LEW, Lewis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Short Graft (5 cm)</th>
<th>Long Graft (40 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis</td>
<td>0; None</td>
<td>0; None</td>
</tr>
<tr>
<td>Width of villi</td>
<td>1; Longitudinal/transverse ratio &gt; 1</td>
<td>0; Normal</td>
</tr>
<tr>
<td>Width of proliferating zone</td>
<td>2; Focal disappearance</td>
<td>0; Normal</td>
</tr>
<tr>
<td>Inflammation</td>
<td>2; Moderate</td>
<td>1; Mild</td>
</tr>
<tr>
<td>Total score</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

(Fujishiro J, et al. Transplantation 2005)
Generation of functional gut-like organ from mouse induced pluripotent stem cells

( Ueda T, et al. BBRC 391;38-42,2010)
Directed differentiation of human pluripotent stem cells into intestinal tissue in vitro

An *in vivo* model of human small intestine using pluripotent stem cells

A rat decellularized small bowel scaffold that preserves villus-crypt architecture for intestinal regeneration

Effect of FK 506 on growth of transplanted newborn rat intestine.
Ogasa N, Maeda K, Nakamura K, Itoh H.

Successful transplantation of newborn rat intestine as a free graft.
Ogasa N, Maeda K, Nakamura K, Itoh H, Schwartz MZ.

Experimental Small Bowel Transplantation Using Newborn Intestine in Rats:
I. Lipid Absorption Restored After Transplantation of Nonvascularized Graft

II. Revascularization of Newborn Intestine Is Independent of Vascular Endothelial Growth Factor

III. Long-Term Cryopreservation of Rat Newborn Intestine

IV. Effect of Cold Preservation on Graft Neovascularization
Regeneration of the Rat Neonatal Intestine in Transplantation

Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche

(Sato T, et al. Nature 459;262,2009)
謝辞

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