

SUCCESSFUL HAND TRANSPLANTATION

One-Year Follow-up

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ABSTRACT

Background On the basis of positive results in studies of the transplantation of pig extremities and the information exchanged at an international symposium on composite-tissue transplantation, we developed a protocol for human hand transplantation.

Methods After a comprehensive pretransplantation evaluation and informed-consent process, the left hand of a 58-year-old cadaveric donor, matched for size, sex, and skin tone, was transplanted to a 37-year-old man who had lost his dominant left hand 13 years earlier. Immunosuppression consisted of basiliximab for induction therapy and tacrolimus, mycophenolate mofetil, and prednisone for maintenance therapy.

Results The cold-ischemia time of the donor hand was 310 minutes. There were no intraoperative or early postoperative complications. Moderate acute cellular rejection of the skin of the graft developed 6, 20, and 27 weeks after transplantation. All three episodes resolved completely after treatment with intravenous methylprednisolone and topical tacrolimus and clobetasol. Temperature, pain, and pressure sensation had developed in the hand and fingers by one year. At one year, the patient could perform many functional activities with his left hand that he had not been able to perform with his prosthesis, such as throwing a baseball, turning the pages of a newspaper, writing, and tying his shoelaces.

Conclusions Early success has been achieved in hand transplantation with the use of currently available immunosuppressive drugs. (N Engl J Med 2000; 343:468-73.)

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IN 1996, the Louisville Hand Transplant Team was formed to examine the possibility of performing a human hand transplantation. One of our first goals was to develop procedures for the transplantation of allografts of extremities in large animals.^{1,2} In contrast to prior studies of hand transplantation in primates, in which very high doses of cyclosporine and prednisone did not prevent rejection episodes and had many adverse effects,³⁻⁵ we found that in pigs that received extremity transplants, rejection could be delayed with a regimen of cyclosporine, mycophenolate mofetil, and prednisone or a regimen of tacrolimus, mycophenolate mofetil, and prednisone.^{6,7} These results strengthened our belief that hand transplantation was feasible in humans.

In November 1997, we organized an international

symposium to discuss the scientific, clinical, and ethical barriers to performing hand transplantation in humans. Although some participants expressed reservations about the high level of immunosuppression that might be required to prevent rejection, the majority felt that, on the basis of the data presented,⁸ limb transplantation in humans should be attempted, provided an appropriate experimental protocol was strictly adhered to. We therefore decided to proceed with clinical hand transplantation, but only after we had obtained the approval of the Human Studies Committee at the University of Louisville Medical School in Louisville, Kentucky, and of an ethics committee composed of people not related in any way to the institutions involved in the Louisville Hand Transplant Team. We also made public and professional disclosure of our intention to proceed, invited local as well as national commentary from the lay and medical communities before the procedure, and assessed the risk-benefit ratio for the procedure.⁹ Finally, on January 24, 1999, four months after the performance of the first human hand transplantation in France,¹⁰ a hand transplantation was performed at the Jewish Hospital of Louisville. In this article, we present the results at one year.

METHODS

Selection and Evaluation of the Patient

Our initial screening criteria specified that eligible patients should be in good health, 18 to 65 years of age, with amputation of one or both hands at or above the wrist, and with no evidence of viral hepatitis or human immunodeficiency virus infection. A complete history was obtained, and patients underwent a physical examination; routine laboratory studies; determination of blood group and HLA type; tests for cytomegalovirus, Epstein-Barr virus, and panel-reactive antibodies in serum; electromyography; angiography; testing of nerve conduction velocity; and extensive psychological testing.

If the patient remained a candidate after these evaluations, informed consent was obtained. During this process, which was filmed with the patient's consent, we addressed the risks associated with surgery and immunosuppressive therapy, including death, rejec-

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tion of the graft, serious infection, cancer, adverse drug effects, and graft amputation. In addition, the patient was asked to identify a patient advocate in his or her community. The advocate was a person not connected with the Louisville Hand Transplant Team and its member institutions, who would counsel the patient on the advisability of continuing with hand transplantation. Finally, the patient was presented to a patient-selection committee modeled after that used for solid-organ transplantation; this committee was composed of people with medical, surgical, psychiatric, and social-services expertise.

The patient selected for the initial procedure was a 37-year-old man who had lost his dominant left hand and lower forearm in a fireworks accident 13 years earlier (Fig. 1A). He had a myoelectric prosthesis that permitted him to work as a paramedic. He had had type 1 diabetes mellitus for 11 years, which was treated with twice-daily doses of intermediate- and short-acting insulin, with good glycemic control. The patient was a nonsmoker. He had no evidence of diabetic retinopathy, neuropathy, nephropathy (his serum creatinine concentration was 1.0 mg per deciliter [$88 \mu\text{mol per liter}$], with no microalbuminuria), gastroenteropathy, or cardiovascular disease. Serum panel-reactive and cytomegalovirus antibodies were not detected, but antibodies to Epstein-Barr virus were present.

The patient was advised of the increased risk of cytomegalovirus infection and the need for specific prophylaxis to prevent that infection if he should receive a graft from a cytomegalovirus-positive donor. He was also told that the postoperative administration of tacrolimus and cyclosporine might cause renal dysfunction and that we would discontinue these drugs if his renal function was in jeopardy. The patient clearly understood these potential risks and wished to proceed.

Selection of the Donor and Preparation of the Graft

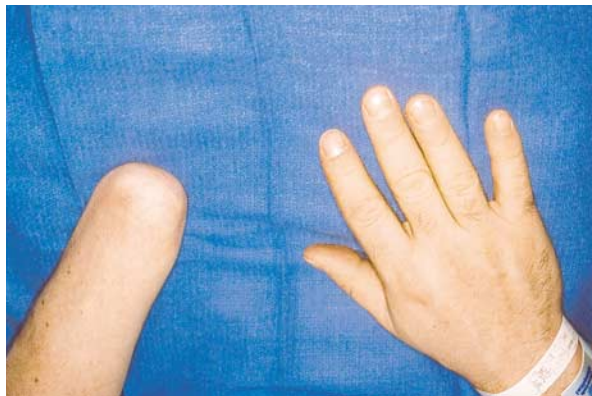
Consent for tissue donation was obtained by the local organ-procurement organization from the family of a 58-year-old male cadaveric donor. The donor was matched to the recipient for bone size and skin tone according to preestablished guidelines. The donor had serum antibodies against cytomegalovirus and Epstein-Barr virus. The donor and recipient were discordant at all six HLA alleles.

During the dissection phase of the procurement procedure, the left upper arm of the donor was disarticulated at the elbow under tourniquet control. The limb was cooled externally by topical application of sterile saline slush and internally by perfusion of the brachial artery with University of Wisconsin solution (ViaSpan, Dupont Merck Pharmaceuticals, Wilmington, Del.) at 4°C . The resected limb was then wrapped in moist sponges, placed in a sterile bag surrounded by ice slush, and transported to another hospital two blocks away.

After removal of excess skin and bone, all arteries, nerves, and tendons to be repaired were identified. The tendons were cut at the level of their respective muscle bellies, and measurements were taken to shorten the bones appropriately. Plates were affixed to the radius and ulna.

Preparation of the Recipient and Transplantation

The skin of the stump of the recipient's left arm was incised, and the tendons, nerves, and vascular structures were freed for joining with those of the donor hand. The patient had a pronation contracture of 70 degrees, requiring release of the pronator teres. Osteotomy was performed to match the graft. The bones were fixed anteriorly with 3.5-mm fixation plates. The arteries of



A



B



C

Figure 1. Photograph of the Patient's Left Forearm Stump and Right Hand before Transplantation (Panel A) and Dorsal and Ventral Views (Panels B and C, Respectively) of the Hands One Year after Transplantation.

the donor and recipient were then joined. The total cold-ischemic time was 310 minutes.

Tendon grafts were harvested from the recipient's feet. These were used to bridge a 4-cm gap between the donor's and recipient's tendons. Recipient-to-donor repair of the tendons of the flexor digitorum profundus of digits 3, 4, and 5 and of the tendons of the extensor pollicis brevis and abductor pollicis longus was performed en masse. Recipient-to-donor repairs of other tendons were performed as follows: brachioradialis to flexor carpi radialis; extensor carpi ulnaris to extensor pollicis longus; extensor carpi radialis brevis to extensor digitorum communis; and extensor carpi radialis longus to the distal ends of the extensor carpi radialis longus and extensor carpi radialis brevis. Recipient-to-donor repair of the tendons of the flexor digitorum profundus to the index finger and the flexor pollicis longus was performed. There was evidence of neuroma, confirmed by biopsy, at the sites of nerve anastomosis in the recipient 15 cm above the wrist. Next, the venous anastomoses were completed. The skin was closed, and an autologous split-thickness skin graft approximately 6 by 10 cm was placed on the dorsal aspect of the forearm. Finally, the hand and arm were placed in a long-arm splint.

Postoperative Care

The patient was cared for in a hand-surgery unit according to protocols already in place for hand replantation.¹¹ The care included digital temperature monitoring and anticoagulant therapy with low-molecular-weight dextran. On postoperative day 4, the arm was placed in a forearm-based, dynamic crane extension outrigger with adjustable metacarpophalangeal block, and active range-of-motion exercises of the graft were begun. The forearm and elbow were placed in a hinged elbow splint, and controlled pronation-supination was initiated. The patient was discharged from the hospital on day 11 after surgery. The rehabilitation program formulated for the recipient while he remained in the Louisville area, until three months after transplantation, is summarized in Table 1.

Immunosuppressive Regimen

The patient received 20 mg of the interleukin-2-receptor antagonist basiliximab (Simulect, Novartis Pharmaceuticals, East Hanover, N.J.) intravenously immediately before surgery and on postoperative day 4. Oral therapy with tacrolimus (Prograf, Fujisawa USA, Deerfield, Ill.), at a dose of 0.15 mg per kilogram of body weight per day, was begun at the same time, with the dose subsequently adjusted to maintain 12-hour whole-blood trough concentrations between 15 and 20 ng per milliliter (as measured with the Incstar ProTrac II enzyme-linked immunosorbent assay [Diasorin, Stillwater, Minn.]).¹² Mycophenolate mofetil, at a dose of 1 g twice daily, was also begun before surgery, with the dose subsequently adjusted to maintain trough plasma concentrations of mycophenolic acid between 3 and 5 ng per milliliter (as measured with the EMIT 2000 assay [Dade Behring, Deerfield, Ill.]),¹³ with a maximal daily dose of 3 g. Five hundred milligrams of intravenous methylprednisolone was administered intraoperatively; tapering doses were given orally, beginning on the first postoperative day (at 2 mg per kilogram per day, which was decreased to 10 mg per day by month 3). Graft-skin biopsies were performed when clinically indicated by visible signs of rejection (maculopapular rash) and according to the protocol on days 0, 5, 7, 10, 14, 21, and 30 and monthly thereafter. For prophylaxis against cytomegalovirus, 5 mg of ganciclovir per kilogram was administered intravenously every 12 hours while the patient was hospitalized, followed by oral therapy (1000 mg three times daily) until three months after transplantation.

RESULTS

Graft Rejection

There were no complications during the intraoperative and immediate postoperative periods. Reha-

TABLE 1. REHABILITATION PROGRAM FOR A HAND-TRANSPLANT RECIPIENT.

WEEKS AFTER TRANSPLANTATION	THERAPY INITIATED
1	Use of dynamic crane extension outrigger and brace; protected active range of motion
2-3	Light electrical stimulation of wrist and finger flexor and extensor muscles; progressive tendon gliding and active-assisted exercises
3-4	Anticlaw splint and spring-loaded metacarpophalangeal control glove
5	Combination movement activities and exercises to increase strength and range of motion
5-8	Light-resistance activities
9	Muscle stretching and strengthening with the use of dynamic splinting
6-12	Exercises to improve forearm pronation, wrist and finger flexion, and pinch strength; increase in functional activities

bilitation therapy progressed rapidly; there was less edema than after reconnection of a severed hand. Mild perivascular lymphocytic infiltrates without visible signs of rejection were noted on histologic examination of skin-biopsy specimens at 21 and 30 days, but no treatment was judged to be necessary.

At six weeks, a maculopapular rash developed circumferentially over the wrist. Skin biopsy revealed moderate acute cellular rejection, characterized by moderate perivascular and dermal lymphocytic infiltration and mild epidermal degeneration (Fig. 2A).² Initial treatment consisted of intravenous methylprednisolone (total dose, 2 g over a period of three days) and topical application of tacrolimus daily for two weeks. After two weeks, a mild macular rash persisted, and topical clobetasol, a high-potency glucocorticoid, was substituted for topical tacrolimus. The rash completely resolved within a few days, and the findings on follow-up biopsy of the graft skin were normal (Fig. 2B).

Twenty weeks after transplantation, a rash again developed on the graft. Biopsy revealed the same histologic signs of moderate acute rejection as those seen at six weeks. The rash resolved in a week after treatment with intravenous methylprednisolone (total dose, 1 g over a period of three days) and daily topical clobetasol. The results of a follow-up biopsy were normal, as were those at six months. At 27 weeks, a rash was again noted, a biopsy was performed, and a confirmed episode of moderate rejection was treated with oral prednisone (2 mg per kilogram per day, tapered to 10 mg per day over a period of 21 days) and with topical tacrolimus and clobetasol. This episode also resolved completely, and the results of two subsequent biopsies at 32 and 52 weeks were normal.

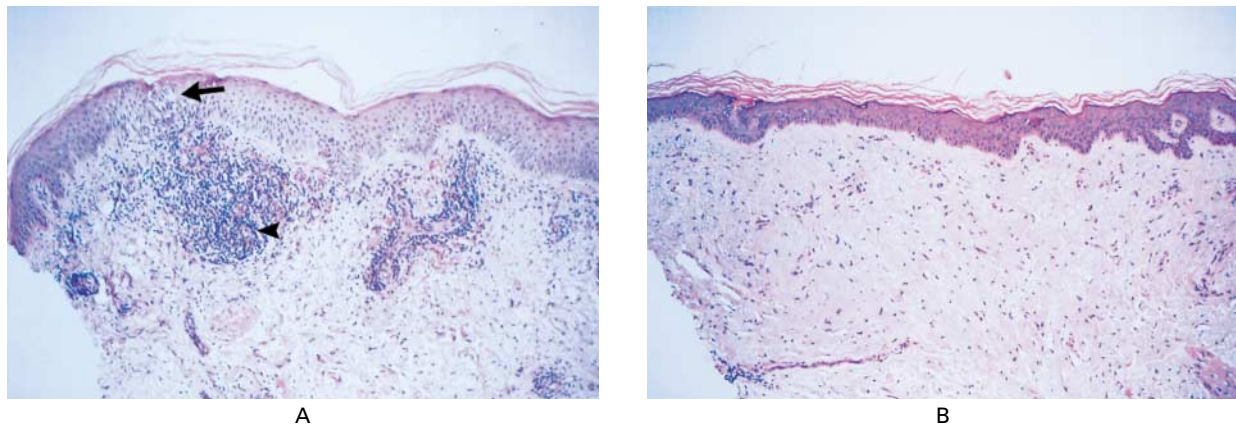


Figure 2. Photomicrographs of Skin-Biopsy Specimens from the Grafted Hand after Transplantation.

Panel A shows moderate acute cellular rejection during the patient's initial episode at six weeks, with moderate perivascular infiltration (arrowhead) and dermal lymphocytic infiltration and mild epidermal degeneration (arrow). Panel B shows complete resolution at the one-year follow-up, after combined local and systemic treatment. (Hematoxylin and eosin, $\times 40$.)

Fifteen weeks after transplantation, the patient presented with abdominal pain and diarrhea. The work-up, including colonoscopy and colon biopsy, revealed tissue-invasive cytomegalovirus disease. Intravenous ganciclovir treatment was restarted at 5 mg per kilogram twice daily for two weeks, followed by oral ganciclovir (1000 mg three times daily) for nine months, until the results of tests for cytomegalovirus DNA in serum were negative. The symptoms resolved within one week after ganciclovir therapy was reinstated. No other complications related to immunosuppression occurred.

Functional Recovery

Skin, wound, and bone healing proceeded normally. Nerve regeneration, as assessed by the presence of Tinel's sign, progressed more rapidly than had been anticipated from our experience with replantation.¹⁴ Tinel's sign was noted in the palm (15 cm from the anastomosis of the nerves) by three months and in the fingertips (30 cm from the anastomosis) by six months. By one year, return of function was documented as follows: temperature, pain, and pressure sensation was present in the hand and fingers; there was electromyographic evidence of innervation of the intrinsic muscles of the hand; and weak adduction of the thumb was possible. At one year, the patient also had a grip strength of 2.7 kg (6 lb), 3.6 kg (8 lb), and 5.0 kg (11 lb) at three hand positions, with a lateral pinch strength of 1.4 kg (3 lb), but digital motion was limited without wrist stabilization, possibly because of tenodesis (Fig. 1B and 1C).

The active range of motion at the forearm and wrist and the active-flexion range of motion of the fingers without the anticlave splint, with and without wrist stabilization, one year after transplantation are shown

in Tables 2 and 3. At this time, the patient could perform the following activities with his left hand, which he had not been able to perform with his prosthesis before surgery: throw a baseball, swing a lightweight bat, turn pages of a newspaper, write, pick up checkers or poker chips, and tie his shoelaces.

The patient was able to return to work three and a half months after the transplantation. At the one-year follow-up, his diabetes was well controlled (glycosylated hemoglobin value, 5.5 percent), although adjustments to the insulin dose were needed during the treatment of rejection episodes. The serum creatinine concentration was 1.5 mg per deciliter (133 μmol per liter); creatinine clearance was 90 ml per minute, and the results of liver-function tests and the complete blood count were normal. The patient remained psychologically well adjusted and had incorporated the graft into his self-image. He assessed his level of function with the graft as superior to that with the prosthesis he used before transplantation.

DISCUSSION

With the goal of direct clinical application, we studied the efficacy and toxicity of several immunosuppressive regimens in pigs after allografting of extremities.^{6,7} In 10 animals that received cyclosporine, 2 osteomyocutaneous flaps were lost to rejection, and there was persistent, mild-to-moderate acute rejection in 5. Three pigs had pneumonia (fatal in one), two had septic arthritis, and one had wound infection. In contrast, among nine pigs that received tacrolimus, there was no rejection in eight (one had persistent mild rejection at the time of death from gastric rupture), but five pigs had pneumonia (fatal in three), four had septic arthritis, three had toe abscesses, and five had diarrhea and decreased weight gain. In these

TABLE 2. ACTIVE RANGE OF MOTION AT THE FOREARM AND WRIST ONE YEAR AFTER HAND TRANSPLANTATION.

TYPE OF MOVEMENT	RANGE OF MOTION	
	VALUE FOR PATIENT	NORMAL VALUE
	degrees	
Forearm pronation	40	>80
Forearm supination	90	>70
Wrist dorsiflexion	40	>60
Wrist palmar flexion	45	>60
Wrist radial deviation	10	>20
Wrist ulnar deviation	10	>30

TABLE 3. ACTIVE DIGITAL-FLEXION RANGE OF MOTION WITHOUT ANTICLAW SPLINT AND WITH AND WITHOUT WRIST STABILIZATION ONE YEAR AFTER HAND TRANSPLANTATION.*

DIGIT AND JOINT	VALUES FOR PATIENT		NORMAL VALUES
	EXTENSION AND FLEXION WITH WRIST STABILIZATION	EXTENSION AND FLEXION WITHOUT WRIST STABILIZATION	
	degrees		
Index MP	7/50	35/50	20/90
Index PIP	40/77	43/77	0/100
Index DIP	15/45	20/45	0/70
Long MP	12/60	50/60	20/90
Long PIP	37/85	40/85	0/100
Long DIP	20/48	20/48	0/70
Ring MP	0/45	40/45	20/90
Ring PIP	35/90	55/90	0/100
Ring DIP	20/47	25/47	0/70
Small MP	0/35	35/35	20/90
Small PIP	45/80	52/80	0/100
Small DIP	30/25	30/68	0/70
Thumb MP	20/30	NA/NA	0/60
Thumb IP	0/30	NA/NA	10/90

*MP denotes metacarpophalangeal, PIP proximal interphalangeal, DIP distal interphalangeal, NA not applicable, and IP interphalangeal. The distance between fingertips and midpalm with flexion was 2.0 cm. Normal values were determined in the patient's other hand.

studies, however, drug doses were not adjusted according to the clinical progress of the animals, as would be done when humans are treated. Therefore, our decision to proceed with a tacrolimus-based regimen for immunosuppression after human hand transplantation was based on the hypothesis that efficacy

in preventing rejection and systemic toxicity could be balanced clinically. Indeed, the immunosuppressive regimen required to prevent and treat rejection in our patient and the initial success achieved were not at all predictable from data on primates but, rather, were more in line with our findings in pigs. The functional results have been good, and nerves have regenerated many years after amputation of the native hand.

Even though our patient was seronegative for cytomegalovirus and therefore was at risk for primary cytomegalovirus disease after receiving a transplant from a seropositive donor, we, in accordance with standard practice in solid-organ transplantation in adults, did not restrict our donor pool to cytomegalovirus-negative donors. However, the risk of cytomegalovirus disease in our patient was unquestionably increased further by the administration of a potent immunosuppressive regimen containing mycophenolate mofetil and by treatment of an early episode of acute rejection with high doses of glucocorticoids. Cytomegalovirus disease developed in our patient 15 weeks after transplantation.

Our results and those of the first human hand transplantation, performed in France,¹⁰ show that early success in hand transplantation can be achieved with the use of currently available immunosuppressive drugs.

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APPENDIX

The other members of the Louisville Hand Transplant Team were D.K. Granger, D. Pidwell, M. Klapheke, G. Tobin, C. Marcell, C. Wimsatt, C. Wilson, B. Creamer, R. van Antwerp, A.W. Jevans, D. Rogers, S. Cheshier, C. Lewellyn, A. Hodges, L. Cendales, J. Kutz, T.M. Tsai, S. McCabe, A. Gupta, W. O'Neill, R. Shatford, M. Moskal, M. Favetto, H. Tien, J. Pederson, and M. Kim.

REFERENCES

1. Ren X, Shirbacheh MV, Üstuner ET, et al. Osteomyocutaneous flap as a preclinical composite tissue allograft: swine model. *Microsurgery* 2000; 20:143-9.
2. Zdichavsky M, Jones JW, Üstuner ET, et al. Scoring of skin rejection in a swine composite tissue allograft model. *J Surg Res* 1999;85:1-8.
3. Skanes SE, Samulack DD, Daniel RK. Tissue transplantation for reconstructive surgery. *Transplant Proc* 1986;18:898-900.
4. Stark GB, Swartz WM, Narayanan K, Moller AR. Hand transplantation in baboons. *Transplant Proc* 1987;19:3968-71.
5. Stevens HPJD, Hovius SER, Heeney JL, van Nierop PWM, Jonker M. Immunologic aspects and complications of composite tissue allografting for upper extremity reconstruction: a study in the rhesus monkey. *Transplant Proc* 1991;23:623-5.
6. Üstuner ET, Zdichavsky M, Ren X, et al. Long-term composite tissue allograft survival in a porcine model with cyclosporine/mycophenolate mofetil therapy. *Transplantation* 1998;66:1581-7.
7. Jones JW, Üstuner ET, Zdichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. *Surgery* 1999;126:384-8.
8. Barker JH, Jones J, Breidenbach WC, eds. Proceedings of the international symposium on composite tissue allotransplantation. *Transplant Proc* 1998;30:2687-787.
9. McCabe S, Rodocker G, Julliard K, et al. Using decision analysis to aid in the introduction of upper extremity transplantation. *Transplant Proc* 1998;30:2783-6.
10. Dubernard J-M, Owen E, Herzberg G, et al. Human hand allograft: report on first 6 months. *Lancet* 1999;353:1315-20.

- 11.** Scheker LR, Chesher SP, Netscher DT, Julliard KN, O'Neill WL. Functional results of dynamic splinting after transmetacarpal, wrist, and distal forearm replantation. *J Hand Surg [Br]* 1995;20:584-90.
- 12.** MacFarlane G, Scheller D, Ersfeld D, et al. A simplified whole blood enzyme-linked immunosorbent assay (ProTrac II) for tacrolimus (FK506) using proteolytic extraction in place of organic solvents. *Ther Drug Monit* 1996;18:698-705.
- 13.** Meiser BM, Pfeiffer M, Schmidt D, et al. Combination therapy with tacrolimus and mycophenolate mofetil following cardiac transplantation: importance of mycophenolic acid therapeutic drug monitoring. *J Heart Lung Transplant* 1999;18:143-9.
- 14.** Wang MS, Zeleny-Pooley M, Gold BG. Comparative dose-dependence study of FK506 and cyclosporin A on the rate of axonal regeneration in the rat sciatic nerve. *J Pharmacol Exp Ther* 1997;282:1084-93.