Published in final edited form as:
*Transplant Proc*. 1989 February ; 21(1 Pt 2): 2197–2200.

# Liver Transplantation: An Unfinished Product

**Thomas E. Starzl**, **Saturo Todo**, **Andreas G. Tzakis**, **Robert D. Gordon**, **Leonard Makowka**, **A. Stieber**, **Luis Podesta**, **Katsuhiko Yanaga**, **Waldo Concepcion**, and **Shunzaburo Iwatsuki**
Department of Surgery, University of Pittsburgh Health Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

After the introduction of cyclosporine for immunosuppression[1] and its combination with steroids,[2] liver transplantation transformed the practice of hepatology worldwide.[3] In our own program (University of Colorado until 1980 and University of Pittsburgh thereafter), the yearly number of liver replacements rose to a new high of 30 in 1981, the second year of the so-called cyclosporine era. By 1987, the number was 396 and over the first six months of 1988, the number was 250, projecting to a total in 1988 alone of about 500 (Figure 1).

## SURVIVAL

The improved survival in the cyclosporine era explains the avalanche of clinical activity. Whereas only one in three patients in the precyclosporine era lived for as long as a year postoperatively, survival has more than doubled since then (Figure 2). The one- and five-year actuarial survival of our 1,179 patients treated with cyclosporine before the end of 1987 with a minimum follow-up of at least seven months is 73 and 64%, respectively.

There has been considerable stability of this patient population after one year (Figure 2). However, a gradual mortality has continued after one year and a disproportionate contribution to this late fall-off has been from two diseases that have a high rate of recurrence, namely cancer and B virus hepatitis (Figure 3).[4]

## PREVENTION OF RECURRENT B-VIRUS HEPATITIS

Prevention of the recurrent B-virus carrier state is one of the improvements that can be envisioned. A human monoclonal antibody directed against HBsAg has been produced (Sandoz Corporation, East Hanover, NJ) by fusing peripheral blood lymphocytes from an immune adult human male to a mouse × human myeloma cell.[5] The resulting human monoclonal HBIgG is 50,000 times more potent than commercially available HBIgG prepared from the blood of immune donors. Two patients have been treated with this monoclonal HBIgG beginning preoperatively or at the anhepatic phase of liver transplantation. Using only a few milligrams of the super HIBgG one recipient had reduction of the surface antigen titer from 1:30,000 to equivocally detectable (titers 0 to 1:8), and the other (Figure 4) has had clearing of the surface antigen. The half-life of the human monoclonal IgG has been more than three weeks, allowing maintenance of an antibody excess with widely spaced injections (Figure 4). Although past efforts to treat the carrier state before and after transplantation with commercial HBIgG or interferon have failed, the monoclonal preparation looks more promising.



Address reprint requests to Thomas E. Starzl, MD, Department of Surgery, 3601 Fifth Avenue, Falk Clinic, Pittsburgh, PA 15213, USA..

## TRANSPLANTATION AND CANCER: ORGAN CLUSTERS

New strategies may also improve the outlook after hepatic replacement for the indication of liver malignancies, using the liver as part of an organ cluster. The most extreme example has been a multivisceral transplantation of the liver, pancreas, stomach, small bowel, and colon. This operation was performed in dogs in I960[6] and again 27 years later in a 3½-year-old child with a short-gut syndrome and hepatic failure.[7] The recipient lived for more than six months, and achieved meaningful nutritional function of the hollow viscera. For long periods, the child was liberated nearly completely from parenteral hyperalimentation. She died from complications of Epstein-Barr virus associated lymphoproliferative tumors (B-cell lymphomas) in the liver that eventually caused biliary obstruction and lethal bacterial sepsis. There was no rejection in the graft. In addition, there was no evidence of graft-versus-host disease (GvHD), possibly because the multivisceral donor had been treated with a large dose of OKT3, with intense localization in donor lymphoid tissue of the mouse immunoglobulin.[7] Shaffer and Monaco, et al,[8] have shown in rat $F_1$ hybrid studies how donor pretreatment with antilymphocyte serum (ALS) can prevent GvHD and this objective may have been achieved in our human case.

Multivisceral transplantation is not an all-or-none procedure. Recently, we have provided two patients with pancreas-liver grafts which in one case included the duodenum and a segment of jejunum. The first patient had sclerosing cholangitis with cholangiocarcinoma of the distal common duct. The second had a spindle cell sarcoma of the duodenum which had metastasized to the liver, but not elsewhere (Figure 5). In these patients, most of the colon and all of the organs in the upper abdomen (liver, pancreas, stomach, duodenum, spleen, and proximal jejunum) were removed. Under veno-venous bypass from the superior mesenteric vein and from the vena caval bed, the hepatico-pancreatic grafts were placed and GI continuity was restored as shown in Figure 6. These recipients are well but still with a postoperative follow-up of only a few weeks.

The use of organ clusters that include the liver-pancreas axis will undoubtedly be used more frequently. A number of tumors which cannot be treated now will become susceptible to excisional therapy including those already mentioned as well as bile duct cell carcinomas and neuroendocrine tumors of the pancreas which metastasize to the liver.

## IMPROVEMENTS OF IMMUNOSUPPRESSION

Although cyclosporine has been central to the revolution of the last decade in transplantation, its principal side effect of nephrotoxicity puts a cap on the permissible dosage, and this has meant that not enough of the drug can be given to control all rejections. As an alternative, polypharmaceutical regimens have been developed based on cyclosporine and steroids[2] to which azathioprine or monoclonal ALGs can be added in what have been called double, triple, and quadruple regimens. By using smaller doses of individual drugs, their toxicity usually can be minimized. The other approach is to continue to add new and safer agents to our armamentarium.

A prime contender as a new agent is the immunosuppressive drug, FK506, which was first reported by Ochai, et al, at this meeting two years ago,[9] and described most optimistically by Todo, et al, of the University of Pittsburgh.[10] Much of Todo's work has been published, but we will mention some unpublished observations as well as follow-ups of seven previously reported dogs given orthotopic livers and then treated with FK506 on postoperative days four, five, and six.[10] In these dogs, no other therapy was given. A remarkable prolongation of survival was obtained with three of the animals living beyond a half year. Two beagle recipients are still alive in their eighth month with well tolerated livers from mongrel donors (Table 1). It has been difficult in the past to achieve this kind of tolerance induction (or quasi-tolerance)

in outbred large animals with short course treatment or single dose therapy, antilymphocyte serum (ALS) being the only previous agent that has made this possible.[11]

The most significant new (and unpublished) studies with FK506 have been with baboons, using the kidney (rather than the liver) model for testing. At first, Todo's results with baboons were disappointing, using doses per kg that were taken from rat and dog experiments (Groups I-III, Table 2). When the doses were increased by 5 to 10 times (Groups IV and V, Table 2), nearly universal success was achieved. The lack of effect of FK in doses that were extrapolated from rats and dogs was perplexing but eventually explainable by experiments of Dr Adriana Zeevi (of Pittsburgh) in which the allo-reactivity of baboon lymphocytes was quantitated in tissue culture after exposure to donor antigens. It required almost 10 times more FK506 in the tissue culture medium to switch off the mixed lymphocyte reactions than was necessary to suppress rat and dog lymphocyte reactions. Thus, there is a major species variability in sensitivity to FK506. This can be quantitated with Zeevi's clever in vitro technique instead of the trial and error approach of times past.

FK506 will undoubtedly be tried clinically within a short time. The drug is not toxic to baboons as was feared in some of the preliminary observations reported at an FK symposium in Gothenberg a little more than a year ago.[12]

## ORGAN PRESERVATION

Another reason to project an increased acceptance and wider application of liver transplantation is improved preservation. Until last autumn, human livers were transplanted with a sense of urgency, the outside margin of safety being pretty much set at 8 or 10 hours using Collin's solution[11] or plasma-like infusates.[14] This was drastically changed by Jamieson, Kalayoglu, Belzer, and their associates,[15] with the so-called University of Wisconsin (UW) solution. Using the UW solution for slush preservation, we have reported a lack of correlation between the time of preservation out to one day, and liver injury as reflected by the longest prothrombin time in the first postoperative week, highest SGOT, graft survival, or patient survival.[16]

When the UW solution was tried more widely, there were word-of-mouth reports by others of a syndrome of late hepatic failure three or four days after seemingly good primary function. This delayed syndrome has been said to be characterized by a secondary rise of bilirubin, or a failure of the bilirubin to fall to normal in the first place.

To examine this question, we have now looked at an even larger total of 266 liver preservations of livers given to patients undergoing primary transplantation. The preservation time was for an average of 12.1 ± 6.6 (SD) hours (range 4 to 35) in the UW groups versus 6.0 ± 1.6 (SD) hours (range 4 to 9) in 142 comparable restrospective controls in which Euro-Collins solution was used. These studies have merely confirmed the revolutionary value of the UW solution. Clearly, preservation for a day, or possibly even longer, is safe. There was no evidence of a late injury pattern that made the recovery profile of the recipients differ from that in the past with Euro-Collins solution.

## SUMMARY

Liver transplantation has become an extraordinarily valuable and useful operation, but one that is not perfect and that has not been exploited to anything like its full potential. Better immunosuppression may become available soon as exemplified by developments with the Japanese drug, FK506. Improved preservation with the UW solution is already here. With these advantages, liver transplantation is certain to become far more widely used than at any time in the past. Examples were cited of innovative approaches using liver transplantation for the treatment of hepatic malignancies.

## Acknowledgments

Supported by Research Grants from the Veterans Administration; Project Grant No. AM29961 from the National Institutes of Health, Bethesda, Maryland, USA.

## REFERENCES

1. Calne RY, Rolles K, White DJG, et al. Lancet 1979;2:1033. [PubMed: 91781]
2. Starzl TE, Klintmalm GBG, Porter KA, et al. N Engl J Med 1981;303:266. [PubMed: 7017414]
3. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Hepatology 1982;2:614. [PubMed: 6749635]
4. Iwatsuki S, Starzl TE, Todo S, et al. Transplant Proc 1988;20:498. [PubMed: 3279643]
5. Ostbert L, Purseh E. Hybridoma 1983;2:361. [PubMed: 6678802]
6. Starzl TE, Kaupp HA Jr, Brock DR, et al. Am J Surg 1962;103:219. [PubMed: 13916395]
7. Starzl TE, Rowe M, Todo S, et al. JAMA. 1988 (In press).
8. Shaffer D, Maki T, DeMichele SJ, et al. Transplantation 1988;45:262. [PubMed: 3125634]
9. Ochiai T, Nakajima K, Nagata M, et al. Transplant Proc 1987;19:1284. [PubMed: 2484094]
10. Todo S, Ueda Y, Demetris JA, et al. Surgery 1988;104:239. 1988. [PubMed: 2456627]
11. Starzl TE, Marchioro TL, Porter KA, et al. Surg Gynecol Obstet 1967;124:301. [PubMed: 4163340]
12. Starzl TE, Makowka L, Todo S. 1987;19(suppl 6):4.
13. Benichou J, Halgrimson CG, Weil R III, et al. Transplantation 1977;24:407. [PubMed: 339435]
14. Wall WJ, Calne RY, Herbertson BM, et al. Transplantation 1977;23:210. [PubMed: 324041]
15. Jamieson NV, Sundberg R, Lindell S, et al. Transplant Proc 1988;20:945. [PubMed: 3291330]
16. Todo S, Tzakis A, Nery J, et al. JAMA. 1988 (In press).

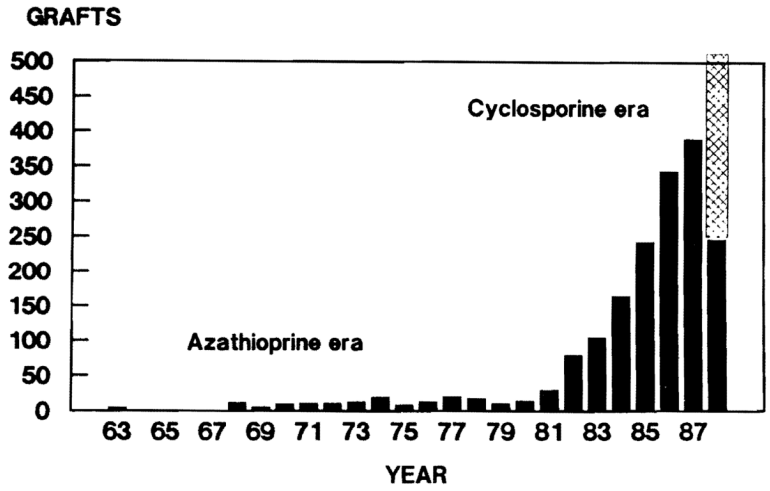


**Fig 1.**
Liver transplantation by year at the University of Colorado (through 1980) and the University of Pittsburgh (1981, onward).

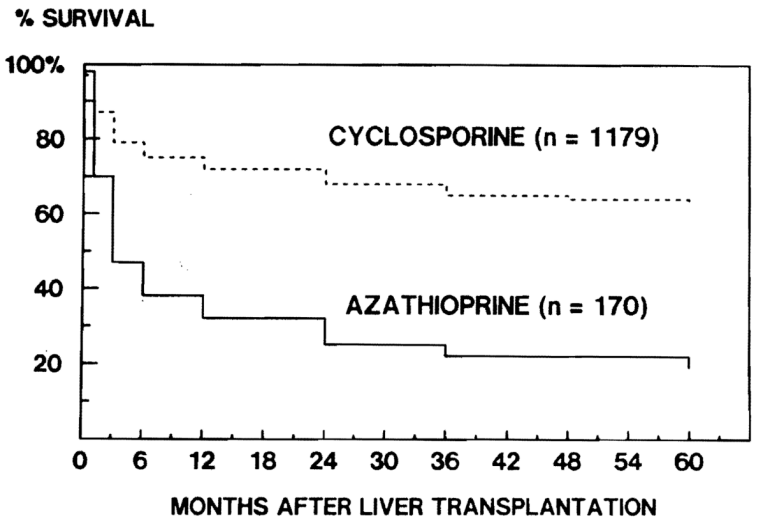


**Fig 2.**

Actuarial survival of orthotopic liver recipients in the precyclosporine era (1963-1979) and after the introduction of cyclosporlne-steroid therapy In early 1980 (1980-1987).

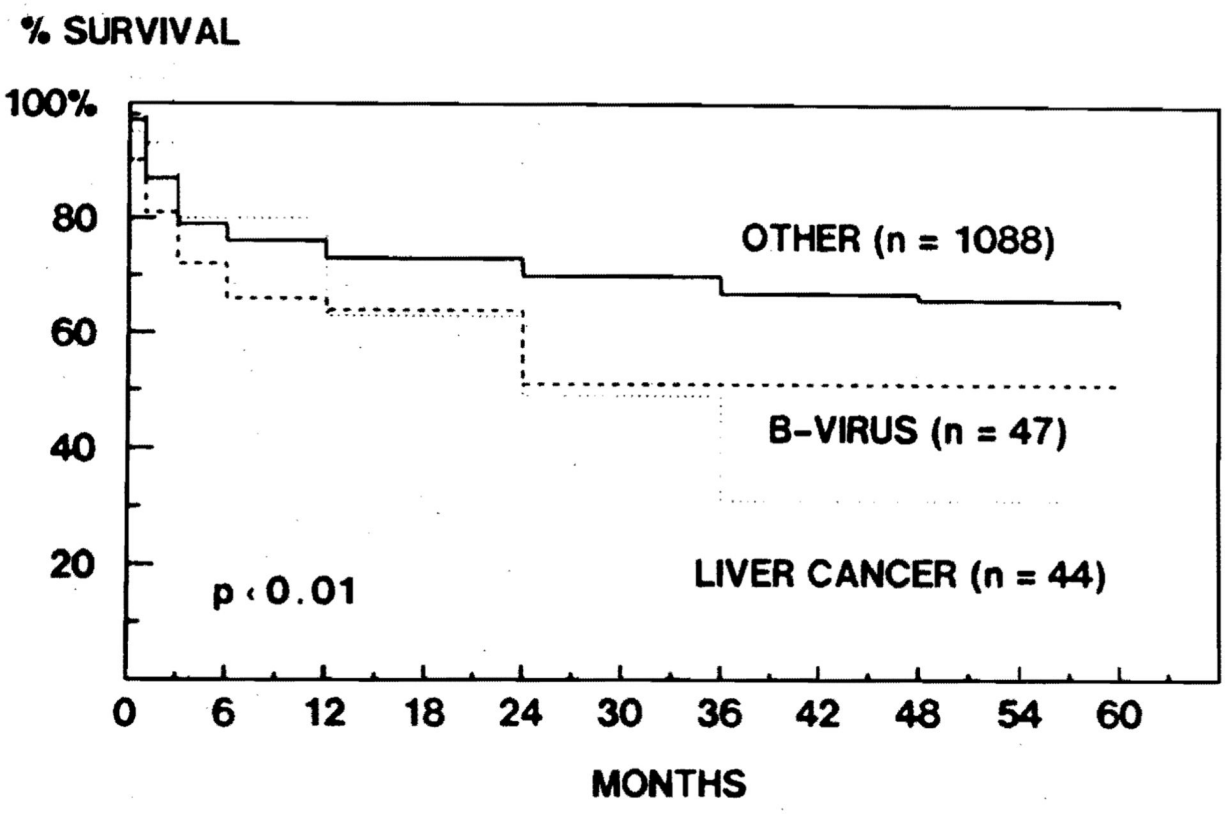


**Fig 3.**
Survival curves of patients who were B-virus carriers, or whose reasons for transplantation was hepatic malignancy.

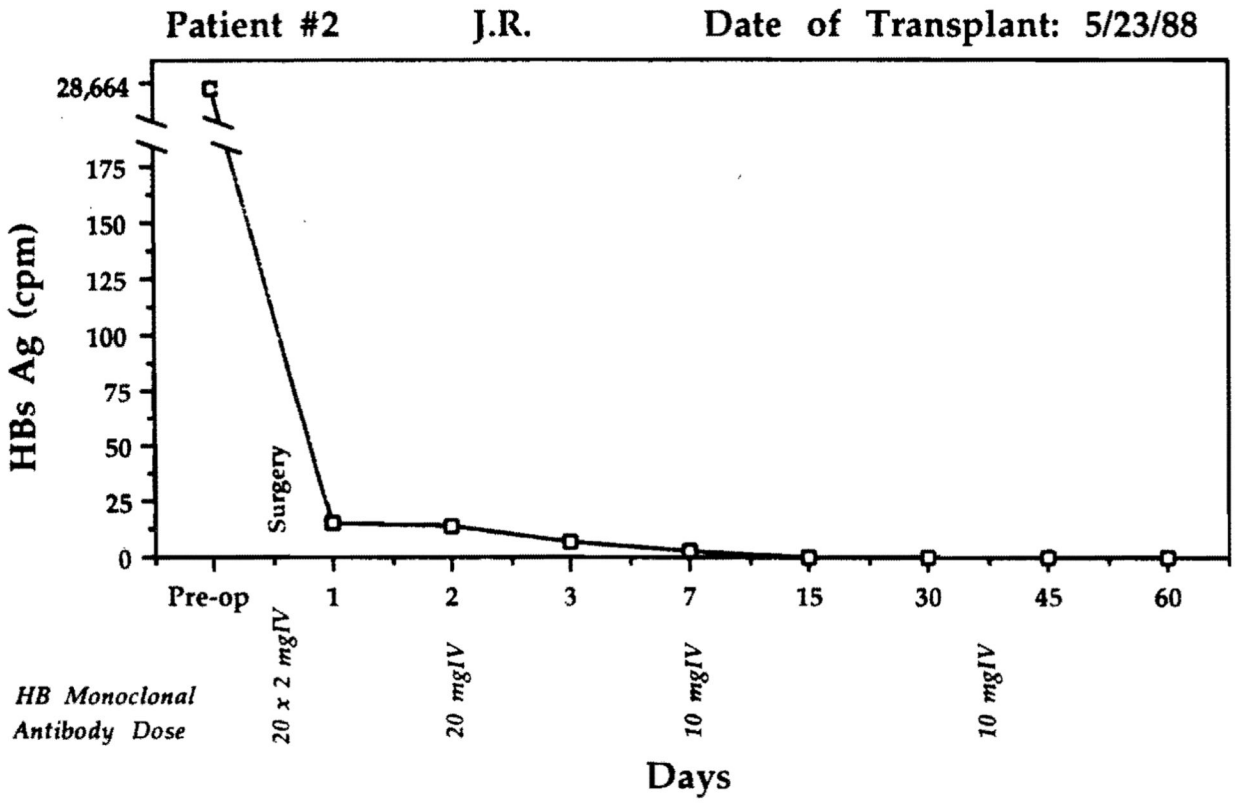


**Fig 4.**

Results of treatment of a B-virus carrier with human monoclonal HBIgG before and after orthotopic liver transplantation. The surface antigen titers were measured with a sandwich technique, using a gamma counter. Hepatitis B antigen was eliminated from the blood after administration of monoclonal antibody.

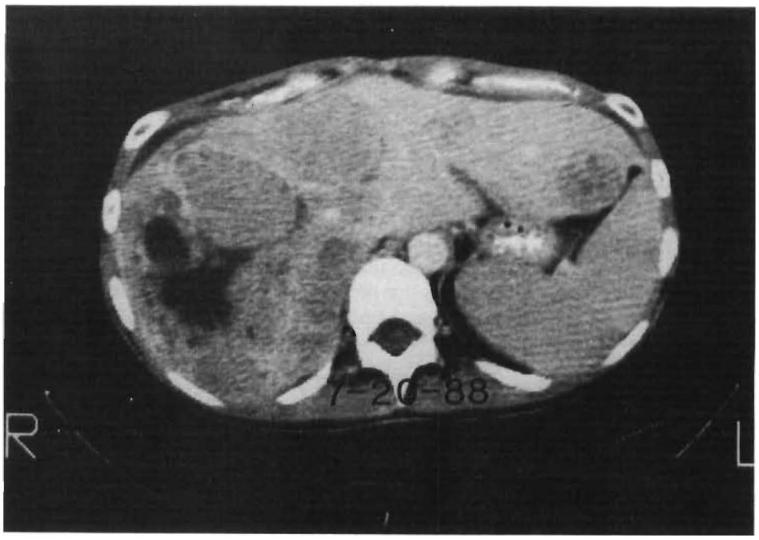


**Fig 5.**

CAT scan in a patient with a spindle cell sarcoma of the duodenum whose liver, pancreas, spleen, total stomach, ascending colon and transverse colon were removed en bloc. The replacement organs are shown in Figure 6. Note the Involvement by tumor metastases of all segments of the liver and cavitation of a dominant mass In the right lobe.

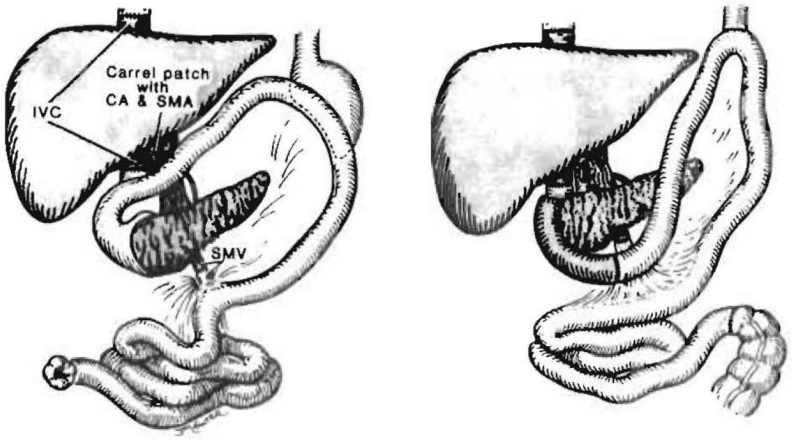


**Fig 6.**

Reconstruction after removal of upper abdominal organs en bloc including the liver, total pancreas, spleen, colon and all or part of the stomach. The homograft organ clusters are shaded. Left—The patient had sclerosing cholangitis and cholangiocarcinoma of the distal duct. Right—The patient had spindle cell sarcoma of duodenum with massive liver metastases (see Fig 5).

**Table 1**

"Tolerance" Induction by Acute High Dose Treatment with FK506

| Treatment Post Op | Canine OLTX Survival in Days | | | | | | |
|---|---|---|---|---|---|---|---|
| No Treatment | 6 (B/B) | 6 (M/B) | 7 (B/B) | 7 (M/B) | 7 (M/B) | 19 (B/B) | 35 (B/B) |
| One mg/kg FKi.m. on days 4, 5, 6 | 24 (M/B) | 28 (M/B) | 58 (B/B) | 72 (B/B) | 193 (B/B) | >232 (M/B) | >233 (M/B) |

(B/B)—Beagle donor to beagle recipient

(M/B)—Mongrel donor to beagle recipient

## Table 2

FK506 for Renal Transplantation in Unrelated Baboons

| | Dose (mg/kg/day) | | |
|---|---|---|---|
| **Groups** | **I.M.*** | **P.O.**** | **Survival Days** |
| I | 0 | 0 | 5, 7, 11, 14 |
| II | 0.5 | 2 | 14, 18 |
| III | 1.0 | 6 | 7, 23, 76 |
| IV | 2.0 | 12 | >22, >22, >25, >25, >27 |
| V | 2.0 | 18 | 23***, >76, >76, >77, >77 |

* I.M.: on days 1, 2, 3

** P.O.: from day 4, onward

*** Rejected.