

Serum Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Organ Recovery From Delayed Graft Function After Kidney Transplantation From Donors After Cardiac Death

Mamoru Kusaka, Yoko Kuroyanagi, Terumi Mori, Kayuri Nagaoka, Hitomi Sasaki, Takahiro Maruyama, Kunihiro Hayakawa, Ryoichi Shiroki, Hiroki Kurahashi, and Kiyotaka Hoshinaga

Department of Urology, Division of Molecular Genetics, Institute for Comprehensive Medical Science and 21st Century COE Program, Development Center for Targeted and Minimally Invasive Diagnosis and Treatment, Fujita Health University School of Medicine, Aichi 470-1192, Japan

Because of a worldwide shortage of renal grafts, kidneys procured from donors after cardiac death (DCD) have recently become an important source of renal transplants. However, DCD kidneys often have complications with delayed graft function (DGF) and recipients require hemodialysis (HD) in the early period after kidney transplantation (KTx). This study evaluated serum NGAL as a potential specific parameter to predict early functional recovery of transplanted DCD kidneys. The average serum neutrophil gelatinase-associated lipocalin (NGAL) level in normal samples was 53 ± 30 ng/ml, while that in patients with chronic renal failure requiring HD was markedly raised at 963 ± 33 ng/ml. In patients undergoing a living-related KTx from a living donor ($n = 11$), serum NGAL level decreased rapidly after KTx, and only in two cases, with serum NGAL levels over 400 ng/ml on postoperative day 1 (POD1), was HD required due to DGF. In contrast, all patients undergoing a KTx from a DCD ($n = 5$) required HD due to DGF. Even in these cases, serum NGAL levels decreased rapidly several days after a KTx prior to the recovery of urine output and preceding the decrease in serum creatinine level. The pattern of decline in serum NGAL was biphasic, the decrease after the second peak indicating a functional recovery within the next several days. These data suggest that monitoring of serum NGAL levels may allow us to predict graft recovery and the need for HD after a KTx from a DCD.

Key words: Donation after cardiac death; Delayed graft function; Kidney transplantation; Neutrophil gelatinase-associated lipocalin (NGAL)

INTRODUCTION

Because of a critical worldwide shortage of renal grafts, kidneys procured from deceased donors providing a donation after cardiac death (DCD) have been recently recognized as an option in obtaining kidneys for transplantation (KTx) (20,28,29). However, in the early period after KTx, kidneys from DCD often require hemodialysis (HD); this is known as a delayed graft function (DGF). A small percentage of the kidneys never recover their function, and they are referred to as primary nonfunction (8,28). DGF is fundamentally a clinical manifestation of acute tubular necrosis (ATN), which is caused by warm ischemia of the graft after cardiac arrest in DCD. In addition to the common complications of KTx, such as acute rejection or calcineurin inhibitor nephrotoxicity, DGF is an important problem during the

early posttransplant period (8). DGF predisposes the graft to both acute and chronic rejection (1,7,9,14,22–25,30). Therefore, DGF is an independent risk factor for suboptimal graft function at 1 year posttransplant.

A variety of clinical parameters have been proposed for prediction of DGF based on preoperative risk factors (2,11), but no objective and reliable markers are currently available for the early diagnosis of DGF following a KTx from a DCD. Several clinical definitions of DGF that employ urine output, creatinine reduction ratios, or HD requirement have been reported in the literature (1,2,7,9,11,14,22–25,30). However, these clinical variables typically identify DGF only several days after a KTx. A graft biopsy during the early period to identify findings of ATN and/or rejection or calcineurin inhibitor nephrotoxicity is the only way to make a timely diagnosis of DGF in a KTx from a DCD. Novel specific bio-

Received February 5, 2007; accepted September 30, 2007.

Address correspondence to Mamoru Kusaka, M.D., Department of Urology, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192 Japan. Tel: +81-562-93-2181; Fax: +81-562-93-7863; E-mail: mkusaka@fujita-hu.ac.jp

markers to predict graft recovery of transplanted kidneys during the anuric period after a KTx from a DCD are highly desirable.

There is accumulating evidence that neutrophil gelatinase-associated lipocalin (NGAL) is as a sensitive marker for the detection of kidney dysfunction. NGAL is one of the most remarkably upregulated genes in the kidney after ischemia (5,18,26). In addition, NGAL is one of the genes rapidly induced in rat kidney isografts from brain-dead donors (12). The expression of NGAL is induced in the proximal tubular epithelial cells during the regeneration process after kidney injury (17,18). Importantly, NGAL is a highly predictive biomarker both for acute and chronic kidney injury (3,15,19,27). It has also been suggested that urine NGAL level or immunostaining intensity of NGAL may serve as early biomarkers for renal injury after KTx (16,21). This study evaluates the usefulness of serum NGAL as a predictor of graft recovery after KTx from DCD.

MATERIALS AND METHODS

Study Design

This investigation was approved by the Institutional Review Boards of our centers. Written informed consent was obtained from each patient or legal guardian before enrollment. Consecutive patients undergoing either a living-related ($n = 11$) or DCD KTx ($n = 5$) at this center were prospectively enrolled. The immunosuppressive regimen was similar in all patients, consisting of basiliximab, tacrolimus, or cyclosporine with prednisone and mycophenolate mofetil.

The clinical characteristics of patients undergoing KTx from DCD are shown in Table 1. All donors after cardiac death from this hospital were classified as type IV in this study. The cause of donor death was cerebrovascular disease in all cases. Although all cases required HD (5–22 days) after KTx because of DGF, the function of all of the transplanted kidneys eventually recovered. There were no cases of rejection or calcineurin inhibitor nephrotoxicity, which were confirmed by a biopsy during DGF.

Serum samples were collected before and following KTx and stored in aliquots at -80°C . The primary outcome variable was the development of DGF, defined as the need for HD within the first few weeks after transplantation. The decision to initiate HD was taken by the primary transplant nephrologists and transplant surgeons, without any involvement from the study investigators. Other variables collected included age, gender, original kidney disease, warm and total ischemic time, urine output, and serial serum creatinine.

ELISA for NGAL Quantification

The ELISA for serum NGAL was performed as previously described (15). Briefly, microtiter plates were pre-coated with a mouse monoclonal antibody raised against human NGAL (HYB211-05, AntibodyShop, Gentofte, Denmark) and blocked with buffer containing 1% BSA. The wells were then coated with 100 μl of serum samples or standards (NGAL concentrations ranging from 1 to 1000 ng/ml), and incubated with a biotinylated monoclonal antibody against human NGAL (HYB211-01B, AntibodyShop) followed by avidin-conjugated HRP (Dako, Carpinteria, CA, USA). TMB substrate (BD Biosciences, San Jose, CA, USA) was added for color development, which was read after 30 min at 450 nm with a microplate reader (Benchmark Plus, BioRad, Hercules, CA, USA). All measurements were made in triplicate. The inter- and intra-assay coefficient variations were 5–10% for batched samples analyzed on the same day. The laboratory investigators were blinded to the sample sources and clinical outcomes until the end of the study.

Statistical Analyses

The results are expressed as the mean \pm SEM. Statistical comparison between groups was performed by Student's t -test, and differences were considered to be significant at $p < 0.05$.

RESULTS

Using this ELISA system, the average serum NGAL level in samples from healthy donors was 63 ng/ml (range

Table 1. Patient Characteristics: Donation After Cardiac Death (DCD)

Patient ID	Donor Age (Year)	Cause of Donor Death	Recipient Age (Year)	Gender (M/F)	WIT (min)	TIT (min)	Dialysis Post-Tx (Days)	Duration of HD (Months)	Immunosuppressive Regimen
DCD 98	22	CVA	39	F	3	463	10	157	Basiliximab, FK, MMF, steroid
DCD 99	62	CVA	30	F	1	473	22	175	Basiliximab, CsA, MMF, steroid
DCD 100	63	CVA	37	M	1	1502	14	176	Basiliximab, CsA, MMF, steroid
DCD 101	58	CVA	56	M	1	972	6	124	Basiliximab, FK, MMF, steroid
DCD 102	52	CVA	60	M	5	359	17	160	Basiliximab, FK, MMF, steroid

WIT: warm ischemic time, TIT: total ischemic time, Tx: transplantation, HD: hemodialysis, CVA: cerebrovascular attacks, FK: tacrolimus; CsA: cyclosporine, MMF: mycophenolate mofetil.

37–106 ng/ml). The normal control samples showed 21.4, 37.5, and 102.2 ng/ml (53 ± 30 ng/ml), which were within the reported normal range. In contrast, the average serum NGAL level of the patients with chronic renal failure requiring HD was 963 ± 33 ng/ml ($n = 138$).

First, serum NGAL levels of 11 patients who received a KT_x from living donors were examined serially before and after the KT_x. Before the KT_x, the serum NGAL concentration of the 11 cases ranged as high as 750–1300 ng/ml. However, the serum NGAL concentration decreased dramatically in all cases as early as post-operative day 1 (POD1) after the KT_x (Fig. 1). Two out of 11 cases manifested DGF and required additional HD for 5 days after the KT_x. One of these two DGF cases had a graft biopsy and the histological findings indicated typical ATN. In these two cases, the serum NGAL level at POD1 was significantly higher than that in the other nine cases (459 ± 27 vs. 213 ± 29 ng/ml, $p < 0.01$). In all cases, the serum NGAL reached a high normal level at POD2 and was stable thereafter.

Similarly, the serum NGAL levels of the five cases that underwent a KT_x from DCD were analyzed serially before and after the KT_x. All the five cases that had DGF underwent graft biopsies, and the histological findings indicated typical ATN. Serum NGAL levels at POD1 were significantly higher than those from patients with a KT_x from a living donor (Fig. 1). Although the function of the transplanted kidneys finally recovered in all these cases, they had a period of anuria after the KT_x due to DGF and required HD (5–22 days). The serum

creatinine level gradually decreased during this period, which correlated reciprocally with a gradual increase in urine output (Fig. 2). In contrast, the decrease of serum NGAL level in each patient generally followed a biphasic pattern. The high level of NGAL prior to the KT_x rapidly decreased within 5 days after the KT_x, preceding the decrease in creatinine. Thereafter, the NGAL levels demonstrated another increase during the DGF period between 7 and 10 days after the KT_x. A decrease from the second peak started several days before the increase in urine output. The serum NGAL level at the last day of HD was below 500 ng/ml (mean 330 ng/ml) and then reached similar levels as those of who received a KT_x from a living donor at 9 days after cessation of HD (Fig. 2).

NGAL was retrospectively considered to be an indicator of recovery of graft function, providing a guide for the withdrawal of HD. In three cases (DCD 99, DCD 101, and DCD 102), the serum NGAL levels decreased below 400 ng/ml several days before the final HD, but not in the remaining two cases (DCD 98 and DCD 100), who also recovered from DGF (Fig. 2). Therefore, the serum concentration of NGAL alone was insufficient as an indicator of prognosis. On the other hand, the second peak of the biphasic decline of serum NGAL might be a good indicator of the functional recovery of grafts, because all cases except for DCD 101 showed a rapid increase in urine output and loss of the requirement for HD several days after the decrease from the second peak of serum NGAL (Fig. 2).

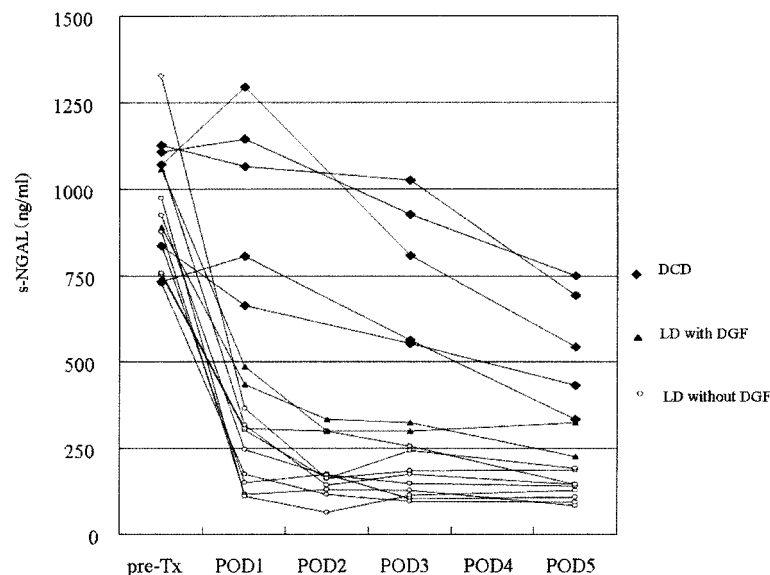


Figure 1. Serum NGAL concentrations following a KT_x from a living donor or a DCD. The time course of serum NGAL levels is shown for patients treated with a KT_x from a living donor with (triangles) or without (circles) DGF. Diamonds indicate the time course of serum NGAL levels from a DCD KT_x. Serum NGAL levels from a DCD KT_x at POD1 were significantly higher than those from living-related KT_x.

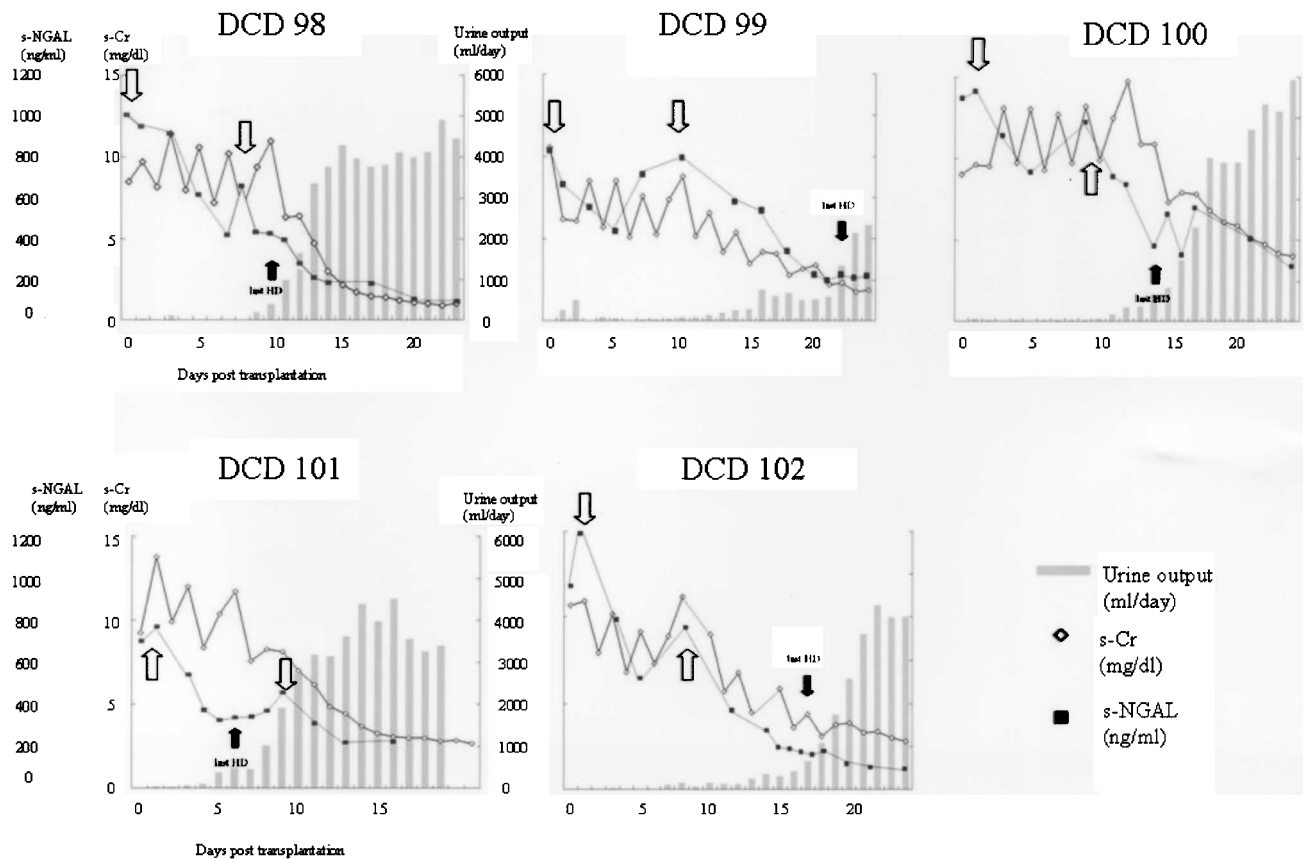


Figure 2. The clinical course of patients after a KTx from a DCD. The daily urine volume is indicated by bars, the serum creatinine level by open circles and NGAL by filled circles. The decrease in the serum NGAL level in each patient generally follows a biphasic course (as indicated by open arrows). The closed arrow indicates the day of HD cessation.

DISCUSSION

In addition to the critical shortage of renal allografts, legal and ethical problems preclude brain-dead organ donation in Japan. Therefore, most of the cadaveric kidneys used over the past 3 decades in Japan have been derived from DCDs. Since April 1979, 477 kidneys were retrieved from DCDs at this center alone, thus representing approximately 10% of all kidneys procured in Japan. These kidneys were then often transplanted under suboptimal conditions. Approximately 40% of kidney grafts were derived from expanded criteria donors (10, 13). The DCDs from this hospital were classified mainly as type IV category donors, but mostly from the recently categorized “uncontrolled” DCD (4,6). Further, these patients had been waiting for a KTx for many years. All recipients who received a KTx from a DCD in this study had required HD for at least 10 years. Under these conditions for both donors and recipients, there was a high incidence of DGF and a prolonged period of ATN. Although an in situ regional cooling technique allows ex-

cellent renal function and good long-term graft survival, the mean duration of posttransplant HD at our center was still about 2 weeks (10,13). This situation, particular to Japan, prompted the need for highly sensitive prognostic marker for DGF in KTx from DCDs.

This study evaluated the usefulness of serum NGAL as a predictor of graft recovery after a KTx, particularly a KTx from DCD. The results strongly suggest that the serum NGAL level at POD1 predicts graft dysfunction in patients who received a KTx from a living donor. In patients receiving a KTx from a DCD, the decrease in the serum NGAL manifested a biphasic curve. This suggests that the decrease from the second peak may predict the recovery of organ function and the optimal timing for weaning of HD within the next several days. In comparison to the changes in serum NGAL level, the changes in serum creatinine level appeared to display lower correlation with graft recovery in each patient. The serum or urine NGAL levels have previously been reported to have an advantage over the serum creatinine level in predicting acute renal injury because of its rapid re-

sponse to changes in the kidney function (15,27). The present data lend support to this argument.

The immunostaining of NGAL has been reported to be a potential biomarker for recovery of kidney function after a KTx (16). A 1-h biopsy, the only established diagnostic tool, allows the sampling of kidney tissue by a routine biopsy after a KTx. However, repeated biopsy would be an invasive and stressful procedure for patients. Urine may be a useful alternative and noninvasive source for diagnostic samples. The urine NGAL has been recently reported to be a predictive biomarker for DGF (21). However, because prognostic biomarkers are required for patients in the anuric period of DGF that is often observed after a KTx from a DCD, urine NGAL is of limited usefulness as an early biomarker of graft recovery. Peripheral blood, which can be repeatedly obtained and noninvasively from patients who requires HD during the anuric period, may be a better source of diagnostic samples.

The kinetics of high serum NGAL levels in HD patients is still unclear. The high level of serum NGAL in acute or chronic kidney disease is due to (i) increased NGAL production from injured kidneys, and (ii) low clearance from the kidney because of the reduced glomerular filtration rate. All of the patients requiring HD manifested high serum NGAL levels. In the KTx cases from living donors, the serum NGAL decreased dramatically immediately after the KTx, but persisted at high normal levels. This may be because although NGAL clearance has been improved by the KTx, the remaining diseased kidney continues to produce NGAL. However, in two cases a high serum NGAL level at POD1 represented DGF. This was possibly because (i) clearance from the kidney was poor due to DGF, or (ii) the transplanted kidney newly synthesized NGAL due to DGF.

In comparison to the immediate decrease of serum NGAL in patients who received a KTx from living donor, the decrease in the serum NGAL level in cases undergoing a KTx from a DCD was generally delayed. It is possible that this was because (i) recovery of urine output was delayed compared with those that received a KTx from living donors, or (ii) the DGF was severe in cases undergoing a KTx from a DCD and the kidney graft produced much more NGAL. The serum NGAL concentration itself is unlikely to be a useful indicator of DGF, because it appears difficult to distinguish the reasons for the high levels of NGAL. However, this study indicates that the pattern of decline of serum NGAL appears to be biphasic. The later peak possibly arises from newly synthesized NGAL from the kidney injured by DGF, accelerated by the recovery of the renal blood flow. On this basis, it is reasonable to assume that the second peak should reflect the prognosis, clinical course, and graft recovery in each case. After these

NGAL changes, the urine output began to increase and all grafts recovered. It is still unclear as to why the serum NGAL level decreased prior to the recovery of the urine volume. Is NGAL a rapid turnover protein that is not affected by clearance from the kidney? Or does the switch of blood flow from the native kidney to the graft affect the NGAL level? The kinetics of NGAL in kidneys undergoing KTx deserve further investigation.

In summary, although the number of patients in this study was small, the present findings identified the serum NGAL levels to be a prime candidate for predicting organ recovery after a KTx, especially for a KTx from a DCD.

REFERENCES

1. Boom, H.; Mallat, M. J.; de Fijter, J. W.; Zwinderman, A. H.; Paul, L. C. Delayed graft function influences renal function, but not survival. *Kidney Int.* 58:859–866; 2000.
2. Brier, M. E.; Ray, P. C.; Klein, J. B. Prediction of delayed renal allograft function using an artificial neural network. *Nephrol. Dial. Transplant.* 18:2655–2659; 2003.
3. Brunner, H. I.; Mueller, M.; Rutherford, C.; Passo, M. H.; Witte, D.; Grom, A.; Mishra, J.; Devarajan, P. Urinary neutrophil gelatinase-associated lipocalin as a biomarker of nephritis in childhood-onset systemic lupus erythematosus. *Arthritis Rheum.* 54:2577–2584; 2006.
4. Daemen, J. W.; Kootstra, G.; Wijnen, R. M.; Yin, M.; Heineman, E. Nonheart-beating donors: The Maastricht experience. *Clin. Transpl.* 8:303–316; 1994.
5. Devarajan, P.; Mishra, J.; Supavekin, S.; Patterson, L. T.; Potter, S. S. Gene expression in early ischemic renal injury: Clues towards pathogenesis, biomarker discovery and novel therapeutics. *Mol. Genet. Metab.* 80:365–376; 2003.
6. Gagandeep, S.; Matsuoka, L.; Mateo, R.; Cho, Y. W.; Genyk, Y.; Sher, L.; Ciciarelli, J.; Aswad, S.; Jabbour, N.; Selby, R. Expanding the donor kidney pool: Utility of renal allografts procured in a setting of uncontrolled cardiac death. *Am. J. Transplant.* 6:1682–1688; 2006.
7. Giral-Classe, M.; Hourmant, M.; Cantarovich, D.; Dantal, J.; Blanco, G.; Daguin, P.; Ancelet, D.; Souillou, J. P. Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys. *Kidney Int.* 54:972–978; 1998.
8. Gok, M. A.; Asher, J. F.; Shenton, B. K.; Rix, D.; Soomro, N. A.; Jaques, B. C.; Manas, D. M.; Talbot, D. Graft function after kidney transplantation from non-heartbeating donors according to maastricht category. *J. Urol.* 172:2331–2334; 2004.
9. Halloran, P. F.; Hunsicker, L. G. Delayed graft function: State of the art, Nov 10–11; 2000. Summit Meeting, Scottsdale, Arizona, USA. *Am. J. Transplant.* 1:115–120; 2001.
10. Hoshinaga, K.; Shiroki, R.; Fujita, T.; Kanno, T.; Naide, Y. The fate of 359 renal allografts harvested from non-heart beating cadaver donors at a single center. *Clin. Transpl.* 12:213–220; 1998.
11. Irish, W. D.; McCollum, D. A.; Tesi, R. J.; Owen, A. B.; Brennan, D. C.; Bailly, J. E.; Schnitzler, M. A. Nomogram for predicting the likelihood of delayed graft function in adult cadaveric renal transplant recipients. *J. Am. Soc. Nephrol.* 14:2967–2974; 2003.

12. Kusaka, M.; Kuroynagi, Y.; Kowa, H.; Nagaoka, K.; Mori, T.; Yamada, K.; Shiroki, R.; Kurahashi, H.; Hoshinaga, K. Genome-wide expression profiles of rat model renal isografts from brain dead donors. *Transplantation* 83:62–70; 2007.
13. Kusaka, M.; Kubota, Y.; Sasaki, H.; Maruyama, T.; Hayakawa, K.; Shiroki, R.; Hoshinaga, K. Is pulsatile perfusion necessary for renal transplantation engrafting kidneys from cardiac death donors? *Transplant. Proc.* 38:3388–3389; 2006.
14. Lu, C. Y.; Penfield, J. G.; Kielar, M. L.; Vasquez, M. A.; Jeyarajah, D. R. Hypothesis: Is renal allograft rejection initiated by the response to injury sustained during the transplant process? *Kidney Int.* 55:2157–2168; 1999.
15. Mishra, J.; Dent, C.; Tarabishi, R.; Mitsnefes, M. M.; Ma, Q.; Kelly, C.; Ruff, S. M.; Zahedi, K.; Shao, M.; Bean, J.; Mori, K.; Barasch, J.; Devarajan, P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 365:1231–1238; 2005.
16. Mishra, J.; Ma, Q.; Kelly, C.; Mitsnefes, M.; Mori, K.; Barasch, J.; Devarajan, P. Kidney NGAL is a novel early marker of acute injury following transplantation. *Pediatr. Nephrol.* 21:856–863; 2006.
17. Mishra, J.; Ma, Q.; Prada, A.; Mitsnefes, M.; Zahedi, K.; Yang, J.; Barasch, J.; Devarajan, P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J. Am. Soc. Nephrol.* 14:2534–2543; 2003.
18. Mishra, J.; Mori, K.; Ma, Q.; Kelly, C.; Yang, J.; Mitsnefes, M.; Barasch, J.; Devarajan, P. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. *J. Am. Soc. Nephrol.* 15:3073–3082; 2004.
19. Mitsnefes, M. M.; Kathman, T. S.; Mishra, J.; Kartal, J.; Khoury, P. R.; Nickolas, T. L.; Barasch, J.; Devarajan, P. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. *Pediatr. Nephrol.* 22:101–108; 2007.
20. Nicholson, M. L.; Metcalfe, M. S.; White, S. A.; Waller, J. R.; Doughman, T. M.; Horsburgh, T.; Feehally, J.; Carr, S. J.; Veitch, P. S. A comparison of the results of renal transplantation from non-heart-beating, conventional cadaveric, and living donors. *Kidney Int.* 58:2585–2591; 2000.
21. Parikh, C. R.; Jani, A.; Mishra, J.; Ma, Q.; Kelly, C.; Barasch, J.; Edelstein, C. L.; Devarajan, P. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. *Am. J. Transplant.* 6:1639–1645; 2006.
22. Prommool, S.; Jhangri, G. S.; Cockfield, S. M.; Halloran, P. F. Time dependency of factors affecting renal allograft survival. *J. Am. Soc. Nephrol.* 11:565–573; 2000.
23. Salahudeen, A. K.; Haider, N.; May, W. Cold ischemia and the reduced long-term survival of cadaveric renal allografts. *Kidney Int.* 65:713–718; 2004.
24. Sayegh, M. H. Why do we reject a graft? Role of indirect allorecognition in graft rejection. *Kidney Int.* 65:1967–1979; 1999.
25. Shoskes, D. A.; Cecka, M. Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 66:1697–1701; 1998.
26. Supavekin, S.; Zhang, W.; Kucherlapati, R.; Kaskel, F. J.; Moore, L. C.; Devarajan, P. Differential gene expression following early renal ischemia-reperfusion. *Kidney Int.* 63:1714–1724; 2003.
27. Trachtman, H.; Christen, E.; Cnaan, A.; Patrick, J.; Mai, V.; Mishra, J.; Jain, A.; Bullington, N.; Devarajan, P. Investigators of the HUS-SYNSORB Pk Multicenter Clinical Trial. Urinary neutrophil gelatinase-associated lipocalin in D+HUS: A novel marker of renal injury. *Pediatr. Nephrol.* 21:989–994; 2006.
28. Weber, M.; Dindo, D.; Demartines, N.; Ambuhl, P. M.; Clavien, P. A. Kidney transplantation from donors without a heartbeat. *N. Engl. J. Med.* 347:248–255; 2002.
29. Wijnen, R. M.; Booster, M. H.; Stubenitsky, B. M.; de Boer, J.; Heineman, E.; Kootstra, G. Outcome of transplantation of non-heart-beating donor kidneys. *Lancet* 345:1067–1070; 1995.
30. Woo, Y. M.; Jardine, A. G.; Clark, A. F.; MacGregor, M. S.; Bowman, A. W.; Macpherson, S. G.; Briggs, J. D.; Junor, B. J.; McMillan, M. A.; Rodger, R. S. Early graft function and patient survival following cadaveric renal transplantation. *Kidney Int.* 55:692–699; 1999.