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Figure legends

Fig. 1. Study design. In the Bone marrow cell (BMC) group, Dark Agouti (DA) rats, which served as the liver transplant donors, underwent total body irradiation (TBI) followed by intravenous injection of BMCs isolated from LacZ-transgenic Lewis (LacZ-Tg LEW) rats. Six days later, these rat livers were excised and transplanted orthotopically into LEW rats. In the control (CTR) group, liver transplant donors were not treated prior to liver transplantation. We monitored the survival of five recipient rats after LT in each group. We also sacrificed the recipient rats at 7 days after LT and conducted the serological and histopathological analyses (n=5, each group).

Fig. 2. Dark Agouti (DA) rats were irradiated with 10 Gy and received bone marrow cell (BMC) transplants from LacZ-transgenic Lewis (LacZ-Tg LEW) rats. Six days later, liver grafts were excised and transplanted to LEW rats (BMC group). To abrogate the function of Kupffer cells in the liver graft, gadolinium chloride ($GdCl_3$) were injected to the DA rats one day before liver transplantation (BMC + $GdCl_3$ group). In the control (CTR) group, liver

transplant donors were not treated prior to liver transplantation. Kaplan-Meier curves were constructed and the survival after liver transplantation was compared using log rank test. (A) BMC transplantation prolonged survival of the BMC group ($P = 0.0027$, compared with the CTR group) after LT. (B) Treating rats with $GdCl_3$ abrogated prolonged survival ($P = 0.2416$, compared with the CTR group).

Fig. 3. Dark Agouti (DA) rats were irradiated with 10 Gy and received bone marrow cell (BMC) transplants from LacZ-transgenic Lewis (LacZ-Tg LEW) rats. Six days later, liver grafts were excised and transplanted to LEW rats. In the control (CTR) group, liver transplant donors were not treated prior to liver transplantation. The liver transplant recipients were sacrificed 7 days after LT, and liver tissues and blood were obtained. (A–F) Liver sections were examined by hematoxylin-eosin staining (A–C, CTR group; D–F, BMC group). Severe mononuclear cell infiltration was observed in the livers of the CTR group (A, original magnification: ×100), and the infiltration into bile ducts was severe (B, original magnification: ×400, indicated by the arrows). In the BMC groups, the extent of infiltration was significantly alleviated (D, original magnification: ×100; E, original magnification:

×400). In both groups, hepatocyte injury was not severe, and ballooning or vacuolation was rarely observed (C and F, original magnification: ×400). Scale bars represent 100 μm. (b) Liver graft damages were evaluated using two scoring systems. (G) Rejection Activity Index of the CTR and BMC groups. (H) Graft damage scores of the CTR and BMC groups. Serum concentrations of (I) aspartate aminotransferase (AST); (J) alanine aminotransferase (ALT); (K) total bilirubin (T-Bil); and (L) hyaluronic acid (HA) in the BMC and CTR groups were examined. Values are means ± standard deviation. n=5 in each group. $*P < 0.05$ compared with CTR group. (■) CTR; (□) BMC.

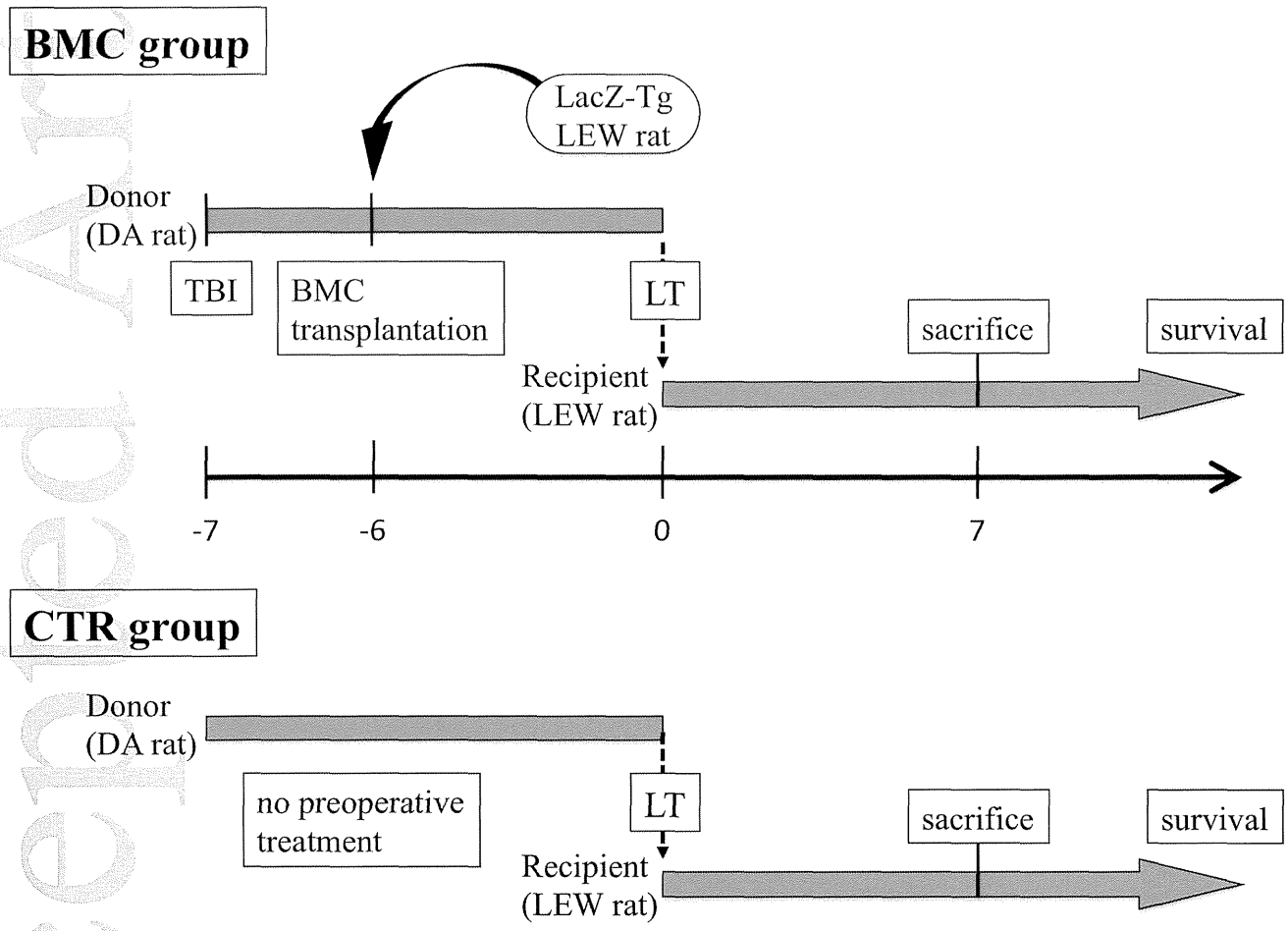
Fig. 4. Dark Agouti (DA) rats were irradiated with 10 Gy and received bone marrow cell (BMC) transplants from LacZ-transgenic Lewis (LacZ-Tg LEW) rats. Six days later, liver grafts were excised and transplanted to LEW rats. In the control (CTR) group, liver transplant donors were not treated prior to liver transplantation. The liver transplant recipients were sacrificed 7 days after LT, and liver tissues were obtained. Messenger RNA (mRNA) expressions of interleukin-2 (IL-2), interleukin-10 (IL-10), interferon-γ (IFN-γ), and transforming growth factor-β (TGF-β) in liver grafts were analyzed. Values are means ±

standard deviation. n=5 in each group. *$P < 0.05$ compared with CTR group. (■) CTR; (□) BMC.

Fig. 5. Dark Agouti (DA) rats were irradiated with 10 Gy and received bone marrow cell (BMC) transplants from LacZ-transgenic Lewis (LacZ-Tg LEW) rats. Six days later, liver grafts were excised and transplanted to LEW rats. The liver transplant recipients were sacrificed 7 days after liver transplantation, and β-galactosidase activity in the liver grafts was evaluated using X-gal staining. X-gal generates blue staining and Contrast Red stains nuclei red (A, original magnification: ×100; B, original magnification: ×200). The β-galactosidase-positive cells are present in the sinusoidal space of the liver allograft. Scale bars represent 100 μm. (C-H) Dual immunofluorescence study of the liver allografts were performed. Liver graft sections were incubated with (C) X-gal (blue, original magnification: ×100), (D) antibody to CD31 (green, original magnification: ×100), (E) antibody to CD68 (red, original magnification: ×100), and (F) antibodies to CD31 and CD68 (original magnification: ×100). (G, H) Magnified images of the circled areas of (C) and (D), respectively. Cells expressing β-galactosidase (transplanted BMC-derived cells) were $CD31^{-}CD68^{+}$. (I-L) Dual

immunofluorescence study of the liver allografts were performed. Liver graft sections were incubated with (I) X-gal (blue, original magnification: ×200), (J) antibody to CD31 (green, original magnification: ×200), (K) antibody to CD163 (red, original magnification: ×200). (L) Merged image of the Fig. I-K. Cells expressing β-galactosidase were $CD163^+$. These results indicate that the transplanted BMDCs differentiated into KCs.

Supplementary Fig. To confirm bone marrow cell (BMC) engraftment, BMCs were isolated from Green fluorescence protein-transgenic Lewis (GFP-Tg LEW) rats and transplanted to Dark Agouti (DA) rats. Six days after BMC transplantation, using flow cytometry, GFP expression by transplanted BMCs was assayed in the peripheral blood of irradiated DA rats.



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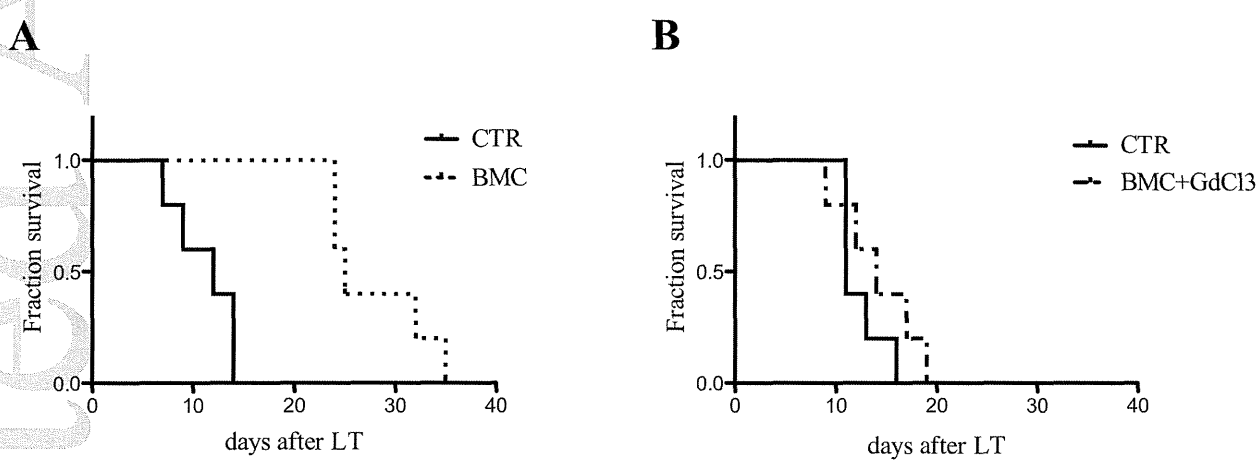

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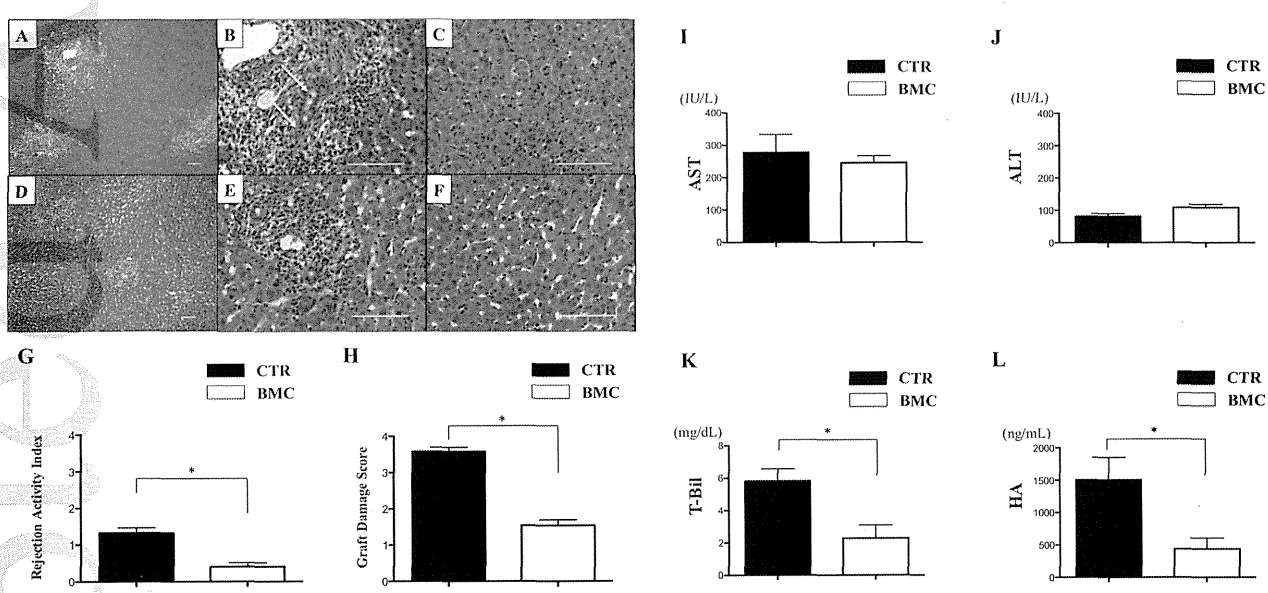

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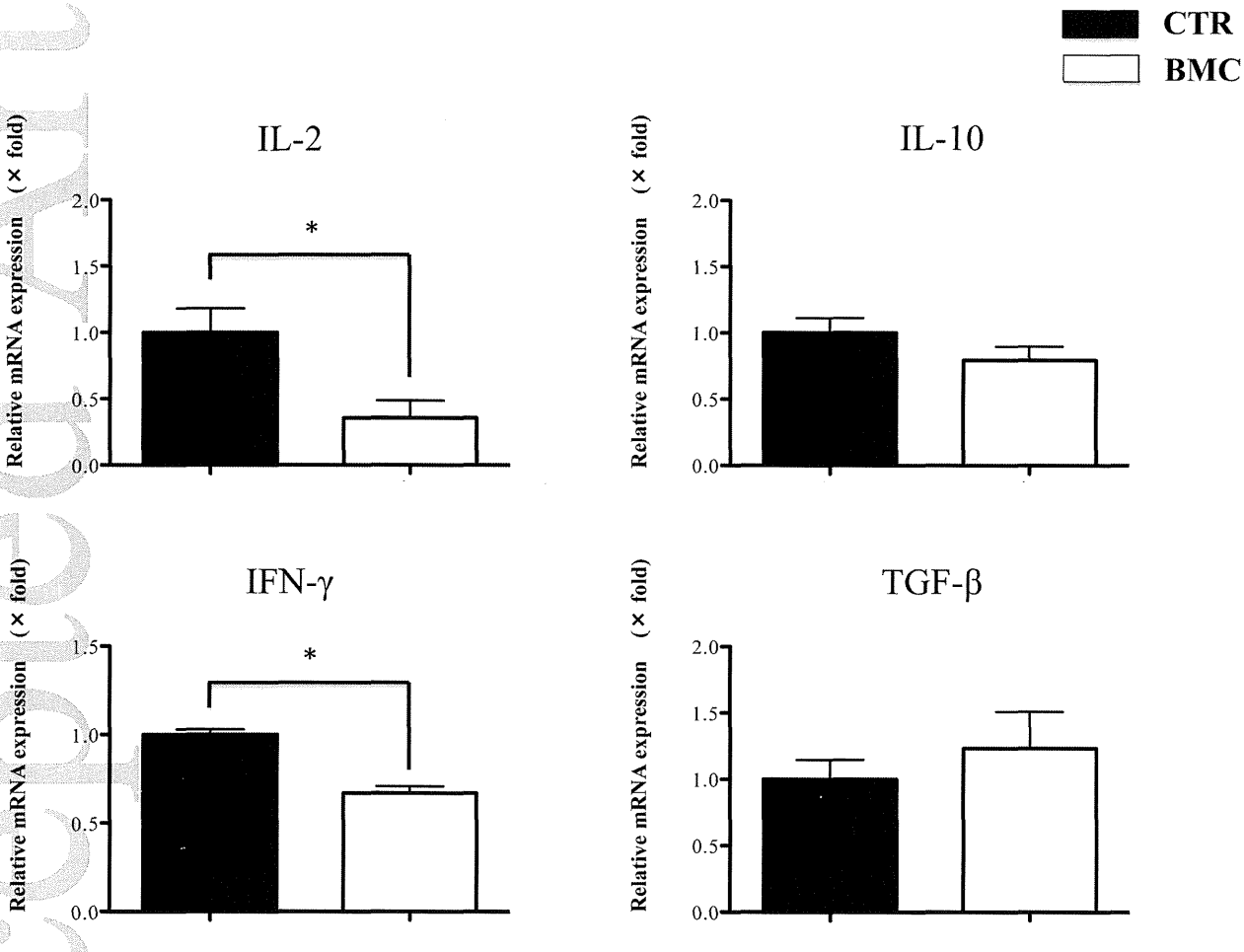

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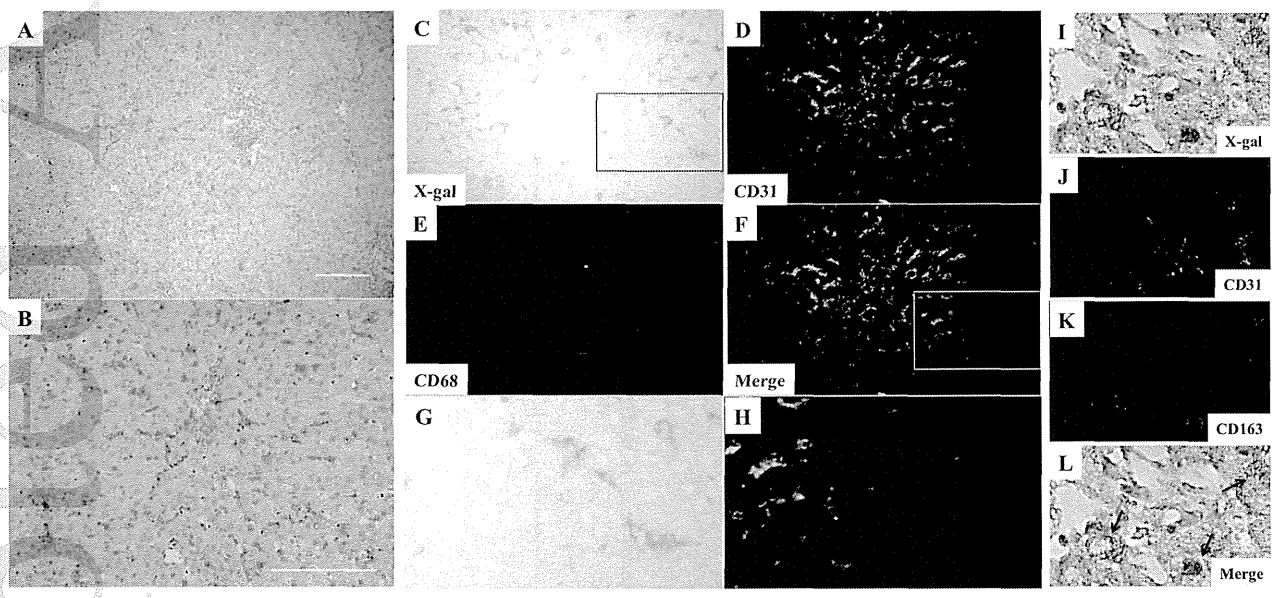

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ELSEVIER

Evaluation of Liver Preservation Solutions by Using Rats Transgenic for Luciferase

J. Doi, T. Teratani, N. Kasahara, T. Kikuchi, Y. Fujimoto, S. Uemoto, and E. Kobayashi

ABSTRACT

Introduction. The solution in which graft tissue is stored (that is, preservation solution) is an important component of liver transplantation technology. Its protective effect is induced by substances in the solution, including radical scavengers, buffers, and energy-giving substances. New preservation solutions have proven to be effective in preventing organ damage during cold ischemia and in extending the time limits for storage.

Aim. This study determined the relationship between luminescence intensity and content of adenosine triphosphate (ATP) in liver tissue and proposes a new ex vivo screening system that uses Lewis rats transgenic for luciferase for evaluating the effectiveness of preservation solutions.

Methods. Samples (diameter, 2 mm) of liver were obtained from transgenic rats. The viability of these tissues after storage for as long as 6 hours in University of Wisconsin (UW) solution, extracellular trehalose solution of Kyoto, Euro-Collins (EC) solution, histidine–tryptophan–ketoflutarate solution, low potassium dextran solution, or normal saline was assessed by determining ATP content and luminescence intensity.

Results. Luminescence had a linear relationship ($R = 0.88$) with ATP levels. Regardless of the preservation solution used, the luminescence intensities of the liver tissue chips decreased linearly with time especially through a short span of time (0 to 2 hours; $R^2 = 0.58–1.0$). The luminescence of liver chip tissues maintained long term (2 to 6 hours) in UW solution tended to be higher than those of tissues stored in other solutions ($P < .05$; 6 hours). On the basis of luminescence intensity, EC might be preferable to the other solutions tested for ultra-short–term storage (0.5 to 2 hours).

Conclusion. Our model, which combines the use of the bioimaging system and Lewis rats transgenic for luciferase, effectively assessed the viability of liver tissue samples. We believe that this ex vivo screening system will be an effective tool for evaluating preservation solutions for liver grafts.

ORGAN transplantation has played some role in a wide variety of clinical situations. Over the course of the last century, many technical limitations of organ transplantation, including techniques for vascular anastomoses, management of immune responses, and organ preservation, have been overcome [1]. In particular, the field of liver transplantation has undergone dramatic advances during this time. Liver transplantation is now the treatment of choice for patients with end-stage liver diseases [2]. Some of the increased efficacy of liver transplantation is due to the development of effective solutions (that is, preservation solutions) in which to transport and store liver grafts. "Preservation injury" is the all-encompassing term used to describe the damage an organ or tissue graft sustains during the process of transplantation [3]. New preservation solutions have been developed that

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Eiiji Kobayashi is a chief scientific advisor to Otuska Pharmaceutical Factory. There are no products in development or marketed products to declare. Dr. Kobayashi's role does not alter the authors' adherence to all of *Transplantation Proceedings* policies on sharing data and materials. The other authors declare no competing financial interests.

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0041-1345/13/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.07.077

have proven effective in preventing organ damage during cold ischemia and in extending the limits for storage time [4]. This protective effect is induced by various substances in the solutions, including radical scavengers, buffers, and energy substrates [5].

In the current study, we developed a method for comparing the effectiveness of these preservation solutions. We first assessed the relationship between the luminescence intensity of samples of liver tissue from rats transgenic for luciferase and the adenosine triphosphate (ATP) content of the samples. We then used this relationship to assess the viability of liver stored for various lengths of time in 6 currently available preservation solutions. We propose that the ex vivo screening system we used, which incorporates a luminescent transgenic rat model, is a valuable tool for evaluating the effectiveness of liver preservation solutions.

MATERIALS AND METHODS

Animals

Experiments were conducted using 14 male Lewis rats transgenic for the luciferase gene [6], weighing about 280 g on average. All experiments were conducted under the approval of the Jichi Medical University Guide for Laboratory Animals. Subjects were anesthetized with ether inhalation. Whole livers were excised without perfusion of any solutions.

Measurement of Luminescence and ATP

We used a hollow steel tube (diameter, 2 mm) to remove equal-sized portions of tissue ("chips") from the isolated rat livers. Liver chips were placed 1 per well immediately after harvest in 96-well tissue culture plates, and the luminescence emitted from each sample was measured using a bioimaging system. Afterward, each liver chip was added to chilled 0.5 N perchloric acid (5 mL), homogenized, and centrifuged. The supernatant was added to 0.5 N triethenolamine in 2.0 mol/L K_2CO_3 before being separated by centrifugation. For measurement of ATP, aliquots of 50 mL were applied to an high performance liquid chromatography (HPLC) system using a 15-cm Inertsil ODS-3 column (GL Science, Tokyo, Japan) at UV260 nm with a mobile phase containing 10 mmol/L KH_2PO_4 with methanol. These data are expressed as moles per microgram of protein.

We elucidated the relationship between the luminescence and ATP levels of liver chip tissues (n = 5).

Evaluation of Preservation Solutions on Measurement of Luminescence in Liver Tissue

Tissue chips of equal size (diameter, 2 mm) were obtained from liver harvested from luciferase transgenic rats as described previously. Each freshly isolated tissue chip was placed in a well of a 96-well tissue culture plate, each of which was immersed for 0.5 to 6 hours in a different preservation solution at 4°C. In the current study, we evaluated University of Wisconsin (UW) cold-storage solution, extracellular trehalose solution of Kyoto, Euro-Collins (EC) solution, histidine–tryptophan–ketoflutarate solution, low potassium–dextran solution, and normal saline. The previously described bioimaging system was used to predict the levels of ATP in each well (96-well plate) containing a tissue chip from liver. These measurements were performed at 0, 0.5, 1, 2, 3, 4, 5, and 6 hours after harvest. Just before image acquisition, D-luciferin (15 μg/each well) was added to wells containing organ pieces. Each 96-well plate was placed in the bioimaging system and imaged individually. After imaging, organ chips were transferred to fresh 96-well plates without D-luciferin.

The luminescence in organ pieces was calculated relative to that at the 0-hour time point, which was defined as 100%; we first established each relative percentage of each rat and then averaged those to obtain the overall average relative percentage at each subsequent time point (that is, 0.5, 1, 2, 3, 4, 5, and 6 hours after harvest). These data were compared between time points.

Statistical Analysis

The results are given as the mean ± standard deviation (SD). Statistical analysis was conducted using the Student t test for continuous data. A P value of $<.05$ was considered to be statistically significant.

RESULTS

Relationship Between Luminescence Intensity and ATP Content

A scatter plot of ATP levels against luminescence level (Fig 1) revealed a linear relationship ($R = 0.88$) between these parameters. Therefore, the luminescence of a sample of rat liver can be used to predict the amount of ATP in that sample.

Relative Luminescence Over Time

For all samples, luminescence decreased linearly over time ($R^2 = 0.58$–1.0) at the early time points (0.5 to 2 hours; Table 1). At the late time points (that is, 2 to 6 hours), the luminescence of liver chip tissues maintained in UW solution was approximately 30% to 40%, which was significantly greater than those in other solutions ($P < .05$). At the early time point of 0.5 to 1 hour, liver chip tissues stored in EC solution showed the highest levels of luminescence among the solutions evaluated, but not significantly.

DISCUSSION

Correlation between hepatocyte viability and intracellular ATP levels has been suggested previously but not evaluated [7]. In the current study, we used the in vivo imaging system (IVIS) to show that the luminescence of liver tissue chips

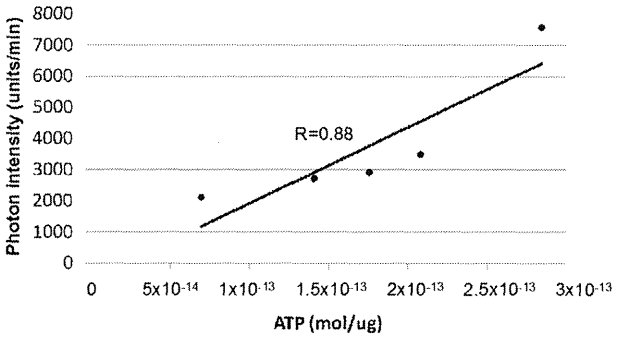

Fig 1. The photon intensity (that is, luminescence) of rat liver chips was plotted against their ATP contents; luminescence had a direct linear relationship with ATP levels ($R = 0.88$).

Table 1. Liver Viability Assessment, Relative Luminescence (%; Mean ± SEM) of Rat Liver Chips (n = 9) at Various Times After Harvest

	Time After Harvest (h)							
Solution	0	0.5	1	2	3	4	5	6
UW	100 ± 0	74.2 ± 2.15	61.2 ± 1.84	46.44 ± 1.61	38.09 ± 1.23	35.54 ± 1.16	32.22 ± 1.63	27.62 ± 1.48
ET-K	100 ± 0	79.67 ± 2.11	59.74 ± 0.87	40.28 ± 1.06	30.72 ± 1.13	19.59 ± 0.75	13.49 ± 0.6	8.21 ± 0.45
EC	100 ± 0	82.88 ± 2.03	67.41 ± 2.88	31.68 ± 1.55	21.29 ± 1.28	12.96 ± 0.74	9.13 ± 0.57	6.13 ± 0.43
HTK	100 ± 0	38.79 ± 1.40	17.56 ± 0.49	11.65 ± 0.6	6.37 ± 0.33	4.71 ± 0.43	2.37 ± 0.13	2.35 ± 0.14
LPDS	100 ± 0	22.67 ± 1.47	6.9 ± 0.62	2.14 ± 0.21	1.26 ± 0.11	0.77 ± 0.07	0.47 ± 0.03	0.39 ± 0.02
Saline	100 ± 0	15.69 ± 1.00	6.45 ± 0.33	2.08 ± 0.16	0.93 ± 0.06	0.56 ± 0.03	0.43 ± 0.02	0.37 ± 0.02

Note: The luminescence relative intensity of liver chip tissues preserved in each preservation solution at each time point (n = 9), given that each luminance value at the time point of 0 h in each plate was set to 100%. For each solution, the mean luminescence at 0 h was set as 100%.

Abbreviations: ET-K, extracellular trehalose solution of Kyoto; HTK, histidine-tryptophan-ketoflutarate; LPDS, low potassium dextran solution; saline, normal saline solution.

from Lewis transgenic rats was directly related to the ATP content of those samples. This finding indicates that luminescence intensity can be used to estimate the ATP content in, and therefore the viability of, rat hepatocytes. We then used this relationship to show that, among the 6 solutions tested, UW solution best maintained the viability of rat liver chips through 6 hours of cold ischemia. Our current data regarding this feature of UW solution support previous findings regarding this solution [8]. We therefore propose that our model that combines the use of Lewis rats transgenic for luciferase and the IVIS will be a valuable ex vivo screening system for comparing and improving preservation solutions for the storage and transport of hepatic grafts.

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