Acknowledgments: The authors thank Kevin Silverstein, PhD, Bioinformatics Research Scientist at the Masonic Cancer Center, University of Minnesota, for help with the analysis of microarray results.

This research was supported by grants from the National Institutes of Health (R01-CA087053 to J.H.K., and K08-CA122191 to A.R.K.), the Leukemia Research Fund (A.R.K.), and by the Children's Cancer Research Fund (J.H.K. and A.R.K.).

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Ashish R. Kumar, Division of BMT and Immune Deficiency, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45236; e-mail: ashish.kumar@cchmc.org.

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To the editor:

Bone marrow as a site for pancreatic islet transplantation

We read with great interest the study by Cantarelli et al in which the authors definitively demonstrated the ability to cure streptozotocin-induced diabetes in mice by transplanting islet isografts into the bone marrow (BM) cavity of the femur.[1] We agree with the authors that this site has many potential technical advantages over the traditional intraportal site.[2] However, we have 2 queries for the authors. First, the full justification for use of this site is not articulated, and we would ask the authors to elaborate on their theoretical rationale for this implantation site. Our own work in this area was explicitly designed to investigate the BM as a potential site for grafts of nonhematopoietic tissue[2] and was based upon an immunologic theory proposing that the BM maintains a proportion of suppressive clones to facilitate the avoidance of autoimmunity.[3,4] Indeed, our results suggest that the BM does impart some degree of immunologic privilege as a transplantation site, based upon histologic demonstration of intact insulin- and glucagon-positive islet allografts within the marrow cavity of the rat 3 weeks after transplantation without evidence of islet allograft rejection and without immunosuppression.[2] Using similar protocols, rat islet allografts transplanted at other sites (portal vein, kidney capsule) are uniformly rejected, functionally and histologically, in less than a week.[5,6] Second, we would ask the authors to elaborate further on their methods used for the implantation process. Their method is identical to that described in our previous work, except for the use of the marrow cavity of the mouse femur in their work versus the rat tibia as we described.[2] In our studies, there was a concern regarding leakage of part of the islet "plug" from the marrow cavity, which can prevent the achievement of an adequate graft volume. For this reason, we chose to use histology to demonstrate proof of principle that islets could be successfully transplanted and engraft within the bone marrow site. Did the authors add any measures beyond the methods from our original paper to prevent leakage of the implanted cells? It is likely that drilling upward from the knee into the distal femur of a mouse would result in some leakage, as did drilling downward from the knee into the proximal tibia of a rat. Regardless, we have found that the procedure is technically much easier in larger animals with a larger bone and marrow cavity, and we have used this technique to successfully transplant neonatal pig islet cells into the intramedullary bone marrow of the pig tibia. The findings of both Cantarelli et al and ourselves support further work examining the utility of the BM as a site for transplantation, with an enormous potential for further research and clinical application.

Anastasio Salazar-Bañuelos
Department of Surgery, Division of Transplantation, University of Calgary, Calgary, AB

Luis Benitez-Bribiesca
Oncological Research Unit, National Medical Center, Instituto Mexicano del Seguro Social, Mexico City, Mexico

David L. Sigalet
Department of Surgery, Alberta Children's Hospital, University of Calgary, Calgary, AB

Greg Korbutt
Department of Surgery, University of Alberta, Edmonton, AB

James R. Wright Jr
Department of Pathology & Laboratory Medicine, Alberta Children's Hospital, University of Calgary and Calgary Laboratory Services, Calgary, AB

Contribution: All authors contributed equally.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Anastasio Salazar-Bañuelos, Department of Surgery, Division of Transplantation, Foothills Medical Centre, 1403-29th St NW, Calgary, AB Canada T2N 2T9; e-mail: anastasio.salazar@albertahealthservices.ca.

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To the editor:

No influence of gene polymorphism of LCT (C13910T) on transplantation outcomes in acute myeloid leukemia patients who received transplantations from HLA-identical sibling donors

Recently, Hauser and coworkers reported that a single nucleotide polymorphism (SNP) of the lactase persistence gene (LCT) at position 13910 of the donor influenced patient outcome after allogeneic hematopoietic stem cell transplantation.[1] They reported in a study of 111 recipients/donor pairs that median overall survival (OS), death in remission, and relapse rate were significantly improved when recipients received transplantations from donors homozygous for CC at 13910 in the LCT gene. They argued that lactose malabsorption changes the composition of colonic microflora, which could be caused by genetic polymorphisms leading to nonpersistence of lactase phlorizin hydrolase, a β-galactosidase, expressed exclusively in the small intestine.[1] Changes in the composition of colonic microflora and in the gut-associated immune system might influence the outcome of transplantation as reported for genetic variants of NOD2/CARD15 genes, which are associated with an increase in incidence and severity of acute graft-versus-host disease (GVHD) after transplantation.[2,3]

We studied the influence of the gene variant of LCT-13910 on transplantation in HLA-identical sibling donors of a homogeneous group of 123 patients, all diagnosed with acute myeloid leukemia and all receiving transplantations of non-T cell–depleted grafts after myeloablative conditioning.

The median age of our patients was 47 years (range, 16-68 years) and that of donors was 46 years (range, 15-72 years). Conditioning regimens included total body irradiation (68%) or chemotherapy alone (32%). The GVHD prophylaxis in 119 patients (96%) was cyclosporine A (CsA) and methotrexate (MTX) and in 5 patients (4%) CsA and mycophenolate mofetil. Forty-nine percent of the patients received a transplantation in first complete remission and 51% of the patients in more advanced disease.

We preformed genotyping of LCT-13910 by real-time polymerase chain reaction and melting curve analysis as published earlier.[4,5] The detected allele frequencies were found in Hardy Weinberg equilibrium ($P > .05$). We detected the homozygous C allele in 36 of 123 donors (29.3%), whereas 87 donors (70.7%) had CT or TT genotype, which is comparable to frequencies published in the study by Hauser et al. Although we included more patients than Hauser et al we did not find a statistically significant longer median OS rate in patients who received transplantations from donors with CC gene variant of LCT-13910 as shown in Figure 1. The estimated rate of death in remission was slightly better with 33% versus 15.9% but failed to achieve statistical significance. Furthermore, we found no difference in the estimated relapse rate at 5 years after transplantation. The different results reported by Hauser et al might be

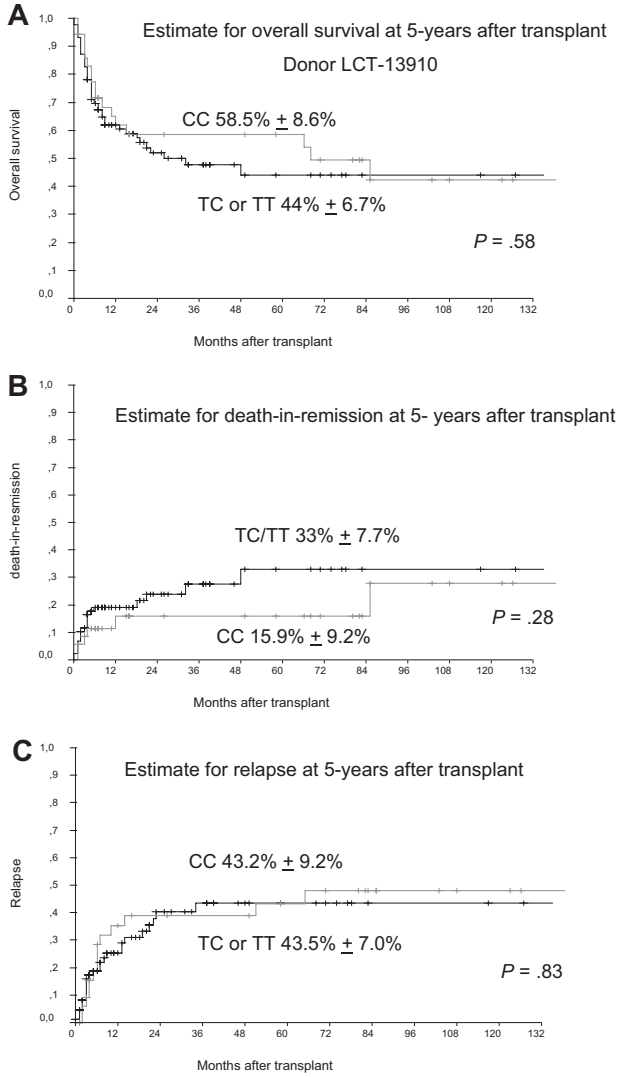

Figure 1. Donors with gene variant of LCT-13910. (A) Estimate for overall survival (OS) in patients receiving transplantations from donors with gene variants of LCT 13910. Patients receiving transplantations from donors with the homozygous CC gene variant of LCT at amino acid position 13910 compared with TC/TT gene variants showed no significantly different 5-year OS. (B) Estimate for death in remission (TRM) at 5 years after transplant. Patients receiving transplantations from donors with the homozygous CC gene variant of LCT at amino acid position 13910 compared with TC/TT gene variants had a slightly improved 5-year TRM (not significant). (C) Estimate for relapse 5 years after transplant, which shows no differences for patients receiving transplantations from donors with the homozygous CC gene variant of LCT at position 13910 compared with donors with TC or TT gene variants.