demonstrates how such critical biologic information on tumors can be acquired by examining the putative cell of origin.

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Supported in part by the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) P50 CA97274.

K.L.G. performed research, analyzed data, and wrote the paper; A.D.A. performed research and analyzed data; W.R.M. performed research and analyzed data; E.D.R. performed research and analyzed data; P.J.K. designed research and analyzed data; and A.D. designed research, analyzed data, and wrote the paper.

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To the editor:

Interferon γ (IFN-γ) polymorphism in posttransplantation lymphoproliferative disease

Injecting severe combined immunodeficient (SCID) mice with peripheral blood mononuclear cells (PBMCs) from Epstein-Barr virus (EBV)–positive donors regularly produces EBV-positive B-lymphoproliferative disease, which closely resembles posttransplantation lymphoproliferative disease (PTLD) in humans.[1] In a recent paper in *Blood,* Dierksheide et al[2] presented interesting data showing that tumor development in SCID mice correlates with an adenosine (A)/thymidine (T) polymorphism at position +874 in the *IFNG* gene. Their data suggest that an A/A phenotype in the PBMC donor significantly associates with rapid, high-incidence tumor development.

As a consequence of these results, the authors speculate that the A/A *IFNG* gene phenotype confers a predisposition to PTLD. They report finding a significantly higher proportion (58%) of 12 PTLD patients exhibiting the A/A phenotype than non-PTLD transplant controls (27%).[2,3]

We have analyzed the identical *IFNG* polymorphism in blood samples from 37 patients with PTLD and 109 controls (patients who had not developed PTLD 5 years after transplantation). Patients with PTLD had received transplants of the following: liver with or without small bowel (n = 17), hematopoietic stem cells (n = 1), lung (n = 1), kidney (n = 10), and heart (n = 8). PTLD was diagnosed by clinical, morphologic, and immunophenotypic criteria. EBV positivity was assessed by in situ hybridization for EBV-encoded small RNAs (EBERs) or immunocytochemical staining for EBV nuclear antigen (EBNA) and latent membrane protein 1 (LMP1). Thirty five (95%) of 37 tumors were EBV positive.

IFNG sequences were amplified from extracted DNA by polymerase chain reaction (PCR), and products visualized by ultraviolet light on agarose gels containing ethidium bromide, as described by Pravica et al.[4] Statistical analysis was performed using Fisher exact test.

We found no significant difference in the incidence of *IFNG* polymorphic types between our PTLD patients and controls (Table 1): A/A was present in 32% of patients and 31% of controls; A/T, in 46% of patients and 41% of controls; and T/T, in 22% of patients and 28% of controls. Additional analysis of "early" (diagnosed < 1 year after transplantation; 35%) and "late" (diagnosed > 1 year after transplantation; 65%) cases separately did not demonstrate an association. Furthermore, there was no difference between the patients or controls and 181 healthy controls (A/A in 33%, A/T in 47%, and T/T in 20%).

PTLD is a histologically diverse tumor with a multifactorial pathogenesis. Intense immunosuppression and EBV seronegativity are the major risk factors.[5] The A/A *IFNG* polymorphism is associated with low IFN-γ production,[4,6] and Dierksheide et al[2] and VanBuskirk et al[3] postulate that low IFN-γ levels increase susceptibility of EBV-specific cytotoxic T lymphocytes to immunosuppression, thereby predisposing an individual to PTLD.

Our results presented here contrast those of Dierksheide et al[2] and VanBuskirk et al[3] in failing to show a significant increase of the A/A *IFNG* polymorphism in PTLD. This may, in part, be explained by the disparity in patient groups; their patients were all renal transplant recipients, whereas ours were more diverse (above). However, the discrepancy in results is most likely due to the small number of patients analyzed by Dierksheide et al[2] and VanBuskirk

Table 1. Incidence of interferon γ + 874 A/T polymorphism in PTLD patients and controls

	A/A polymorphism	No A/A polymorphism	Total
Patients with PTLD, no. (%)	12 (32)	25 (68)	37 (100)
Posttransplantation controls without PTLD, no. (%)	34 (31)	75 (69)	109 (100)
Healthy controls, no. (%)	60 (33)	121 (67)	181 (100)

et al.[3] In gene frequency studies such as this, a larger patient cohort yields a more robust statistical analysis.

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Response:

PTLD risk and *IFNG* polymorphisms

First, we would like to thank Thomas and colleagues for their interest in our work, their provision of additional data, and their commentary regarding genotyping studies and clinical posttransplantation lymphoproliferative disorder (PTLD). A central component of our prospective preclinical study using the human peripheral-blood leukocyte severe combined immunodeficient (hu PBL SCID) mouse model of Epstein-Barr virus (EBV) lymphoproliferative disease was the demonstration of a statistically significant association of the adenosine (A)/A interferon γ (*IFNG*) genotype with the spontaneous development of EBV lymphoproliferative disease. As part of our discussion, we mentioned that our prospective preclinical studies were in line with our retrospective clinical observation in a group of renal transplant patients showing that the same A/A IFN-γ genotype was statistically more prevalent in renal transplant patients who developed PTLD (n = 12) when compared with renal transplant patients who did not develop PTLD (n = 135, $P = .02$). This suggests that the A/A *IFNG* genotype may be a risk factor for the development of PTLD in renal transplant patients.

Thomas and colleagues did not observe an association of *IFNG* genotype with the development of PTLD in their transplant patients. However, as pointed out by Professor Thomas, our PTLD patients were all renal transplant recipients, while their cohort consisted of a heterogeneous group who had undergone renal, lung, heart, hematopoietic stem cell, and liver transplantations, the latter with or without small-bowel transplantations. Further, the control population in our retrospective analysis consisted entirely of renal-transplant patients who did not develop PTLD. It is unclear if the transplant-recipient controls in the Thomas et al study were matched for the organ transplanted, immunosuppression, race, or ethnicity. Assuming that the variables were not matched, the results from our analysis are not comparable with the data from Thomas et al. If the Thomas et al study was properly controlled and the results were as reported, it is conceivable that our hypothesis holds true for renal-transplant patients but not for other solid-organ transplant recipients who receive different regimens of immune suppression and have a different incidence of PTLD.

The hypothesis that an *IFNG* genotype is associated with the development of clinical PTLD is an active area of investigation. We do agree with Thomas and colleagues that a larger patient cohort is needed to properly assess this association in a statistically robust fashion. Most transplant centers have only a few PTLD patients each year, often of different organ types, making it difficult to perform well-controlled analyses. For this reason, we have joined with several medical centers to compare transplant patients with PTLD to transplant patients without PTLD that are matched for age, ethnicity, immune suppression, and for the transplanted organ. By our calculation, this analysis will require 65 PTLD organ transplant patients and 130 matched non-PTLD organ transplant patients to achieve 80% power. This study was recently funded by the US National Cancer Institute, and we would welcome the participation of other centers to assist us in determining if the *IFNG* genotype is a risk factor for the development of clinical PTLD.

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To the editor:

Dose-response relationship and pharmacogenetics of anti-RhD monoclonal antibodies

In their paper, Miescher et al[1] describe the effect of MonoRho, a recombinant anti–Rhesus D (RhD) human immunoglobulin G1 (IgG1)/kappa monoclonal antibody (mAb), on RhD^+ red blood cell (RBC) elimination, and the association between this elimination and both *FCGR2A* and *FCGR3A* gene polymorphisms. They conclude that (1) there is a correlation between dose and mAb serum concentrations and an absence of correlation between mAb dose and RBC elimination, and (2) *FCGR2A* and *FCGR3A* genotypes influence this elimination.