results in VHL-deficient erythrocytes.[6] Although the tumor origin of hemangioblastoma-associated stromal cells, reactive blood vessels, and intratumoral erythrocytes has been established, the origin of the abundant intratumoral mast cells is not known.

Normally associated with the allergic response in peripheral tissues, mast cells are not usually observed in the CNS, although they can be found there under certain inflammatory conditions.[7] However, inflammatory cellular infiltrate is not a feature of hemangioblastomas, leading to speculation about the origin of intratumoral mast cells in this setting. We hypothesized that these mast cells arise from VHL-deficient tumor cells in a manner analogous to the VHL-deficient erythrocytes identified in areas of intratumoral extramedullary hematopoiesis.[6] To determine whether mast cells in hemangioblastomas are derived from VHL-deficient tumor cells, we performed LOH analysis on microdissected intratumoral mast cells. We analyzed 4 confirmed hemangioblastomas (3 from the cerebellum and 1 from the spinal cord) resected from 4 VHL patients and procured according to National Institutes of Health guidelines.

Mast cell distribution occurred randomly throughout the tumors as single cells or in clusters (Figure 1A-B). No mast cell perivascular cuffing was observed around the tumor vasculature, as occurs with inflammatory infiltration. Mast cells also stained for KIT, the SCF receptor that is required for mast cell development.[8] Microdissection (Figure 1C-F) was performed on frozen sections that were immunostained for the mast cell marker tryptase (Figure 1C-D) or the stromal cell marker inhibin-A (Figure 1E-F). The distinct morphology and staining patterns of the mast and stromal cells allowed for clear identification of the cell populations under study. For each patient, LOH analysis in the *VHL* alleles was performed for tumor stromal cells, mast cells, and peripheral blood lymphocytes. Because hemangioblastomas are resected without removal of adjacent normal tissue, we were unable to microdissect mast cells from nontumor tissue as a control. Consistent with a tumor cell origin, mast cell samples from all 4 patients exhibited LOH in the *VHL* alleles compared with the peripheral blood lymphocytes (Figure 1G-H).

VHL-deficient tumor cells in hemangioblastomas are pluripotent.[5] Endothelial, erythrocyte, granulocyte, and now mast cell (this report) progeny can arise from VHL-deficient cells. Erythrocytes, granulocytes, and mast cells all derive from a common myeloid progenitor. KIT, a key receptor in mast cell development[8] and erythropoiesis,[9] has been observed in hemangioblastomas.[5] The Kit signaling pathway may contribute to the ability of some of the VHL-deficient pluripotent neoplastic cells to develop into more differentiated progeny, including mast cells and erythrocytes.

Marsha J. Merrill
Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

Nancy A. Edwards
Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

Russell R. Lonser
Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

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Contribution: M.J.M. designed the study, interpreted the data, and wrote the manuscript; N.A.E. designed and performed the experiments and analyzed the data; and R.R.L. supervised the study, reviewed the data, and revised the manuscript for intellectual content.

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Correspondence: Marsha J. Merrill, PhD, Surgical Neurology Branch, NINDS, 10 Center Dr, Rm 3D-20, National Institutes of Health, Bethesda, MD 20892-1414; e-mail: merrillm@ninds.nih.gov.

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To the editor:

Comparison of the efficacy of rabbit and horse antithymocyte globulin for the treatment of severe aplastic anemia in children

Immunosuppressive therapy (IST) with horse antithymocyte globulin (h-ATG) and cyclosporine (CSA) is an effective therapy for aplastic anemia (AA), resulting in a response rate of 60%-70% and an excellent survival for responders. However, lymphoglobulin (h-ATG; Genzyme) was withdrawn from the market in 2007. Because of the unavailability of h-ATG in most countries, the evaluation of rabbit ATG (r-ATG) as first-line therapy was stimulated. Marsh et al recently showed a low response to IST at 6 months (37%) in 35 patients who were given r-ATG (thymoglobulin; Genzyme).[1] The overall survival at 2 years was significantly

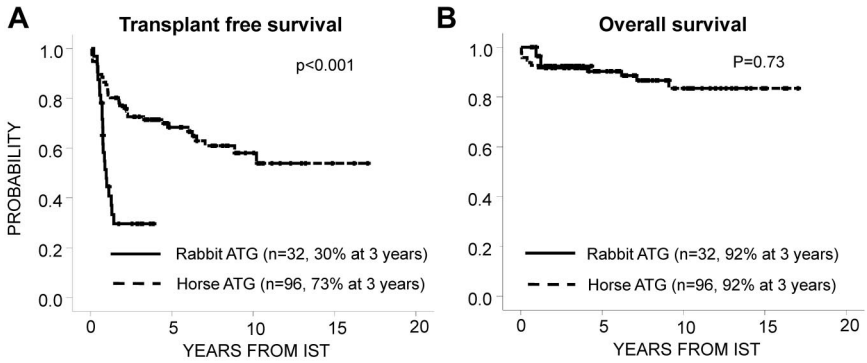

Figure 1. Transplantation-free and overall survival. Transplantation-free survival (A) and overall survival (B) after IST with r-ATG and CSA compared with h-ATG and CSA. Second-line HSCT was considered as an event in the analysis of transplantation-free survival. HSCT was performed in 20 patients at a median of 258 days (range, 57-504) after IST in the r-ATG group and in 29 patients with a median of 625 days (range, 27-3718) after IST in the h-ATG group.

lower (68%) compared with age- and disease-matched patients given h-ATG (n = 105, 86% $P = .009$). Furthermore, in a randomized controlled trial, Scheinberg et al showed an inferior response (37% vs 68% at 6 months, $P < .001$) and a decreased survival (76% vs 96%, 2 years, $P = .04$) after r-ATG (thymoglobulin) compared with h-ATG (ATGAM; Pfizer).[2] In none of the published series r-ATG was found to be superior to h-ATG.[3,4] However, these series did not focus on outcome of children, so we compared both ATGs in children with AA.

Children (< 18 years of age) with severe AA diagnosed in Germany, Austria, and Switzerland and registered in the SAA-94 study between November 1993 and August 2011 received IST if no matched sibling donor was available.[5] IST initially included h-ATG (lymphoglobulin 15 mg/kg/d for 8 days) and CSA as described previously.[5] G-CSF was given if the neutrophil count was $< 0.5 \times 10^9$/L. Because of the unavailability of h-ATG, 32 patients received r-ATG (thymoglobulin 3.75 mg/kg/d for 5 days) since 2007. Approval for the study was obtained from the institutional review board of the Ludwig-Maximilians University of Munich. Written informed consent was provided by the parents of each patient.

Patients receiving r-ATG (n = 32) were matched for age (categorized as < 10 or ≥ 10 years) and disease severity (very severe or severe) with patients receiving h-ATG (n = 96). The median age of patients in the r-ATG group was 9.7 years; 10 patients had severe disease and 22 patients had very severe disease. The median follow-up times were 2.1 years (r-ATG) and 6.9 years (h-ATG; $P < .001$). Response was defined as described previously.[5] The response rate at 6 months was 34% for r-ATG and 65% for h-ATG ($P = .003$). Although Marsh et al observed several late responses after r-ATG resulting in similar best response rates for r-ATG and h-ATG,[1] we observed only 2 late responses after r-ATG and a lower transplantation-free survival rate after IST with r-ATG compared with h-ATG (Figure 1A).[1] However, in contrast to previous studies, because of successful second-line hematopoietic stem cell transplantation (HSCT), the overall survival for both r-ATG and h-ATG was excellent (Figure 1B). The increased risk of death from infection after r-ATG that was observed by Marsh et al was not confirmed in our study.[1] These results demonstrate that in children with AA, IST with r-ATG is less effective than h-ATG. However, the majority of nonresponders could be rescued by HSCT. We conclude that, whenever possible, IST for treatment of children with AA should include h-ATG (ATGAM) and that, in the light of the improved results of unrelated HSCT, this procedure should be offered to all nonresponders at 6 months.[6,7] Even earlier HSCT should be considered in patients with prolonged severe neutropenia (0.2×10^9/L) to avoid fatal infections.

Ayami Yoshimi
Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany

Charlotte M. Niemeyer
Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany

Monika M. Führer
Dr von Haunersches Kinderspital, Children Hospital of the Ludwig-Maximilians-University of Munich, Munich, Germany

Brigitte Strahm
Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany

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Correspondence: Ayami Yoshimi, MD, PhD, Division of Paediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Mathildenstrasse 1, 79106 Freiburg, Germany; e-mail: ayami.yoshimi@uniklinik-freiburg.de.

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