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of FLVCR was also increased in cell lines that are used to study heme transport (e.g., intestinal (Caco-2, 13696 copies/ng, MFI 35), and hepatic cells (HepG2, 504 copies/ng, MFI 56)), or have increased heme utilization (e.g., cancer cell lines (n=5, mRNA range 502-1845 copies/ng; MFI 28-54)).

This is the first description of a mammalian heme transporter. FLVCR exports heme to protect CFU-E from heme toxicity. Our expression studies suggest that hFLVCR may also be important for heme transport in other tissues, e.g., the small intestine, where heme serves as the predominant source of human dietary iron.

Abstract# 153

Imatinib Mesylate Reduces Phlebotomy Requirements in Polycythemia Vera. Richard T. Silver. *Hematology/Oncology, New York-Presbyterian Hospital Weill Cornell Medical University, New York, NY, USA.*

Erythrocytosis is the clinical feature that separates polycythemia vera (PV) phenotypically from the other chronic myeloproliferative diseases and is the cause of many of its most serious complications. The mechanism for autonomous erythropoiesis in PV remains unknown, but a number of growth factors other than erythropoietin including stem cell factor (SCF) are also essential for erythroid progenitor cell proliferation and differentiation. SCF signals by inducing tyrosine phosphorylation of its receptor, c-kit, and cross-talk may also exist between c-kit and the erythropoietin receptor. We therefore sought to determine if the tyrosine kinase inhibitor, imatinib mesylate (IM), which is known to block SCF signaling through c-kit could inhibit the autonomous erythropoiesis of PV. Seven patients, four women and three men, with PV as established by the diagnostic criteria of the Polycythemia Vera Study Group, were studied. All had an increased red blood cell mass by direct measurement, and all causes of secondary erythrocytosis were excluded. Their ages ranged from 32 to 76 yrs, (median 55 yrs). Before IM therapy, disease duration ranged from two months to 2.5 yrs (median 1.5 yrs, mean 1.4 yrs) and the number of phlebotomies per patient ranged from 2 to 36 (mean 11.6, median 6). Four patients had been treated with phlebotomy alone, and three others additionally with either hydroxyurea (HU), interferon or anagrelide. Two of the seven patients had palpable splenomegaly (10cm below the LCM size). All patients were initially phlebotomized to a Hct less than 42%. The starting dose of IM was 400mg daily with a dose escalation of 100mg daily each week to a maximum of 800mg if the platelet count was above 600,000/ μ l at two weeks. All seven patients had suppression of erythropoiesis. One patient with palpable splenomegaly had a reduction in spleen size by 50% and one had complete regression after only one month of IM therapy. All patients had cessation of phlebotomy requirements within the first 2 months of IM therapy except for one who required one additional phlebotomy. The median duration on IM has been 87 days (mean 84). To date, three of the seven patients have had a reduction in platelet count below 600,000/ μ l. There was no significant change in the leukocyte count. Two patients developed dry scaly skin; in one, it was sufficiently severe to require discontinuation of IM. In summary, IM therapy suppressed erythropoiesis in seven PV patients, reduced spleen size in two of two and lowered platelet counts in three of seven. A longer duration of treatment may be necessary to influence thrombopoiesis and normalize spleen size. However, the present results suggest that IM by blocking c-kit (and/or PDGFR) may be a useful agent in the management of PV and warrants a more extensive clinical trial.

Abstract# 154

Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent. Peter Hillmen,¹ Claire Hall,¹ Judith Marsh,² Dupe Elebute,² Christopher F. Mojeik,³ Scott A. Rollins,³ Stephen Richards,¹ Russell P. Rother,³ ¹*Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom;* ²*Haematology, St. George's Hospital Medical School, London, United Kingdom;* ³*Alexion Pharmaceuticals, Inc., Cheshire, CT, USA.*

Paroxysmal nocturnal hemoglobinuria (PNH) is characterised by intravascular hemolysis, venous thrombosis and is associated with aplastic anemia. The complement-mediated hemolysis is due to the deficiency of complement-regulatory proteins on the surface of PNH red cells, particularly the terminal complement inhibitor CD59. The high risk of venous thrombosis results from PNH platelet activation by complement. Therefore complement inhibition in PNH should control the hemolysis and reduce the risk of venous thrombosis. Eculizumab is a humanized monoclonal antibody that binds to C5 and inhibits terminal complement activation. Ten transfusion-dependent PNH patients have been entered into an ongoing open label Pilot study of eculizumab and all patients will have completed the study by November 2002. Patients receive 600 mg eculizumab by intravenous infusion over 30 minutes weekly for 4 doses and then 900 mg every other week. To date, 4 patients have completed therapy and all have been entered into an extension study. Response data for at least 4 weeks of therapy is available for 6 of the 10 patients. Eculizumab has been well tolerated with no serious adverse events. No episodes of thrombosis have occurred although follow-up is short and 4 of 6 patients are on warfarin. The biochemical parameters of hemolysis dramatically improved or normalised for all patients within a week of starting therapy. Mean LDH decreased from 4494 $\pm$ 3380 U/L prior to treatment to 636 $\pm$ 166 U/L following treatment while mean AST decreased from 106 $\pm$ 66 U/L to 24 $\pm$ 9 U/L during the same interval. In addition, a progressive increase in the PNH type III red cells occurred during the treatment period. While hemoglobinuria was common in this patient group before treatment, no patient has had an episode of hemoglobinuria since commencing eculizumab therapy and patients report a marked improvement in symptoms related to hemolysis, such as dysphagia and lethargy. One patient began treatment during a severe acute hemolytic episode when she was passing nearly black urine and within 24 hours there was a complete resolution of her hemoglobinuria. Patients who had purely hemolytic disease (macroscopic hemoglobinuria with a normal platelet count; n=3) appeared to have the best response to eculizumab with cessation of hemolysis and an increase in mean hemoglobin from 9.4 $\pm$ 1.6 g/dL to 10.3 $\pm$ 0.6 g/dL at four weeks, obtained without transfusion. These hemolytic

patients without cytopenias also showed a more pronounced increase in the proportion of PNH red cells (mean increase equal to 62%) presumably due to a prolongation of PNH red cell survival. None of these patients have required transfusions to date. Cytopenic patients with laboratory evidence of hemolysis but minimal hemoglobinuria (n=3) had a marked improvement in hemolytic parameters but less effect on transfusion requirements. There was no change in the proportion of PNH neutrophils, monocytes or platelets in any of the patients whilst on eculizumab. In summary, the preliminary results from this pilot study demonstrate that eculizumab was well tolerated, decreased hemolysis and improved symptoms in PNH patients. This study suggests that blocking complement at C5 is an effective therapeutic strategy for hemolytic PNH resulting in control of hemolysis and a reduction in transfusion dependency.

Abstract# 155

TCR Sequencing: The Molecular Signature of Autoimmunity in Aplastic Anemia. Antonio M. Risitano*,¹ Spencer Green*,¹ Susan Sharpe*,¹ Christine O'Keefe*,² Weihua Zeng*,¹ Jaroslav P. Maciejewski*,² Neal S. Young.¹ ¹*Hematology Branch, NHLBI - NIH, Bethesda, MD, USA;* ²*Experimental Hematology and Hematopoiesis Division, Tuusig Cancer Center, Cleveland, OH, USA.*

Acquired aplastic anemia (AA) is a bone marrow failure syndrome characterized by immune-mediated destruction of hematopoietic progenitors. Because the specific, pathogenic antigens in AA are unknown, our research strategy has included analysis of the variable beta (V β)-chain to determine T-cell clonality and as a surrogate for an antigen-driven immune response. A major goal has been the molecular identification of disease-specific T-cell clones. In AA, the distribution of V β family usage is altered, with predominance or even expansion of particular V β subfamilies. Using flow cytometry, we have identified CD8+ V β -family expansions in 40 AA patients. As assessed by CDR3-length analysis, oligoclonally distributed V β families were selected, and their CDR3 cloned and sequenced in order to create a library of AA-specific clonotypes. As proof of principle, three frequently expanded V β families were initially selected (V β 2, V β 3 and V β 17) for further study, including inter-patient comparisons. RT-PCR was performed using a common constant beta (C β) primer and a V β -family specific oligonucleotide. Corresponding V β regions from healthy donors were cloned and sequenced to determine the normal level of CDR3 diversity. As anticipated from the enormous repertoire of TCR- β chains, in controls almost all individual colonies obtained from a single V β PCR product had different sequences. In contrast, PCR products from AA patients showed in all cases a high level of redundancy, with one or two CDR3 sequences accounting for more than 50% of the entire V β -specific repertoire, confirming the oligoclonal nature of the expansion. Major clones showed unique sequences for each patient; in some cases small subclones with limited amino acid substitutions from the major clonotype were also present. Perfect correspondence between CDR3 length analysis and sequence was observed. All clonotypic sequences were absent from normal controls, consistent with a putative pathogenic role for patient-specific V β expanded cells. In two patients, analysis of serial samples obtained in different stages showed good correlation between the quantity of the identified clonotypes and activity of disease, with the frequency much lower after successful immunosuppressive treatment. A PCR using clonotype-specific CDR3 primers was used to screen and compare a large cohort of patients sharing HLA-class I antigen or the same V β expansion (3 or 2). Cloning and sequencing of selected samples led to the identification of some new clonotypes; sequences with high homology to the original patient-specific clonotypes were also found in other cases but at a lower frequency. In conclusion, probably pathogenic T-cell clones are present in most AA patients, strong evidence for an underlying immune pathophysiology. Moreover, their frequency within the entire T-cell pool appears to correlate with disease activity. The significance of highly homologous CDR3 sequences among patients of similar HLA-class I antigen background deserves further investigation but is suggestive of common inciting antigens. Our data support a view of most acquired AA as marrow cell destruction due to antigen-driven oligoclonal T cell immune response, involving limited numbers of V β clonotypes, which may differ in antigen affinity, killing efficiency, and susceptibility to immunosuppressive therapy, but which likely share the same hematopoietic target.

HEMOGLOBINOPATHIES II

Abstract# 156

Anti-Inflammatory Therapy Ameliorates Endothelial Activation and Improves Microvascular Blood Flow in Transgenic Sickle Mice. Dhananjay K. Kaul,¹ Xiao-du Liu*,¹ Chris Bryant*,² John D. Belcher*,² Gregory M. Vercellotti,² Robert P. Hebbel.² ¹*Medicine, Albert Einstein College of Medicine, Bronx, NY, USA;* ²*Medicine, University of Minnesota, Minneapolis, MN, USA.*

In transgenic sickle (β^S) mice, but not normal mice, hypoxia followed by reoxygenation (H/R) causes a distinct inflammatory response characterized by endothelial oxidant generation, leukocyte recruitment and microvascular flow abnormalities (Kaul and Hebbel. J Clin Invest 106, 2000), indicating that hypoxia-induced sickling is etiologic in this response. This is consistent with our hypothesis that endothelial activation and leukocyte recruitment secondary to reperfusion injury would play an important role in the pathophysiology of sickle cell disease. The leukocyte recruitment is secondary to up-regulation of specific adhesion molecules on vascular endothelium. Previous studies have shown that sulfasalazine, a powerful inhibitor of nuclear factor (NF)- κ B, a transcription factor, causes a significant decrease in endothelial adhesion molecules, i.e., vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin in both sickle cell anemia patients and β^S mice (Solovoy et al. Blood 97, 2001). However, the consequences of NF- κ B inhibition on inflammatory response (i.e., leukocyte recruitment) to hypoxia/reoxygenation (H/R) have not been ascertained under in vivo microcirculatory