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vs. 8.7%, $P < 0.001$) displayed significantly higher frequencies among AA patients than among a general Japanese population. The percentage of patients displaying DR15 was significantly higher in the 128 patients ≥ 30 -years-old (77.3%) than in the 54 patients < 30 -years-old (37.0%, $P < 0.001$). When all patients were divided into PNH⁺ and PNH⁻ groups, comprising 95 patients with a minor population of PNH-type cells and 62 patients without PNH-type cells, respectively, the increased frequency of DRB1*1502 was observed in both PNH⁺ (23.9%) and PNH⁻ patients (20.7%), while the increased frequency of DRB1*1501 was only observed in PNH⁺ patients (21.2% vs. 6.7%). Both DRB1*1501 and the presence of PNH-type cells predicted response to monotherapy with cyclosporin A (CsA; odds ratios (ORs)=12.2 and 13.6, respectively), in addition to response to antithymocyte globulin (ATG) $\pm$ CsA therapy (OR=9.26 and 4.27, respectively). DRB1*1502 was not predictive of response to either therapy (OR=0.72 and 0.66, respectively). Multivariate analysis confirmed the predictive values of DRB1*1501 and the presence of PNH-type cells in both CsA therapy ($P=0.047$ and $P=0.023$, respectively) and ATG $\pm$ CsA therapy ($P=0.048$ and $P=0.034$, respectively). These data indicate that although both DRB1*1501 and DRB1*1502 contribute to the development of AA, their contributions may differ. Apparent age-dependent differences in HLA-DR15 frequency suggest that the pathophysiology of AA in adult patients may differ from that in pediatric patients. Furthermore, DRB1*1501 and the presence of a minor population of PNH-type cells represent independent factors favorably affecting response to IST in AA patients.

Abstract# 1855**Poster Board #-Session: 26-II**

Apoptosis and Proliferation of CD34 Positive Bone Marrow Cells of Polycythemia Vera Patients. Jie Bai*, Zonghong Shao, Hong Liu*, Jun Shi*, Guangsheng He*, Yanran Cao*, Meifeng Tu*, Yuhong Wu*, Liping Jing*, Tiejun Qin*, Hairong Jia*, Juan Sun*, Zhenzhu Cui*, Yanping Xue*, Huishu Chen*, Linsheng Qian*, Tanying Yang*, Chongli Yang*. *Institute of Hematology and Blood Disease Hospital, CAMS and PUMC, Tianjin, China.*

Objective To study the apoptosis and proliferation of CD34 positive (CD34⁺) bone marrow cells (BMC) of patients with polycythemia vera (PV). **Method** The expression of Annexin V and proliferation related protein Ki67 in the CD34⁺ BMC of 20 PV patients and control cases [10 primary thrombocythemia (ET), 12 normal persons] were assessed by Bicolor flow cytometry (FCM), then the correlation between apoptosis and clinical situation was analysed in PV patients. **Result** The expression of Annexin V were (15.96% $\pm$ 1.45%) in PV patients' CD34⁺ BMC (15.53% $\pm$ 1.76%) in ET patients' CD34⁺ BMC which were lower than the expression in normal persons' (23.61% $\pm$ 3.89%) ($P < 0.05$). The expression of Ki67 were (48.79% $\pm$ 11.68%) in PV patients' CD34⁺ BMC and (49.60% $\pm$ 9.98%) in ET patients' CD34⁺ BMC which were significantly higher than that of normal control's (33.87% $\pm$ 6.82%). The ratio of apoptosis/proliferation of PV patients was (0.33 $\pm$ 0.104) and that of ET patients (0.32 $\pm$ 0.02) which was significantly lower than that of normal control's. The apoptosis of CD34⁺ BMC was negatively correlated with the level of hemoglobin (Hb) ($r = -0.481$, $p = 0.037$), white blood cell (WBC) ($r = -0.538$, $p = 0.026$) and the numbers of endogenous erythroid colony (EEC) of PV patients. The ratio of apoptosis/proliferation of PV patients was negatively correlated with their Hb ($r = -0.537$, $p = 0.018$) and WBC ($r = -0.667$, $p = 0.003$). **Conclusion** There were lower apoptosis and higher proliferation in CD34⁺ BMC of PV patients. Lower apoptosis was correlated with the disease severity of PV.

Abstract# 1856**Poster Board #-Session: 27-II**

Flow Cytometric Analysis of Medullary Hematopoiesis in Tumor Necrosis Factor- α (Tg197) Mice: A Potential Model of Anemia of Chronic Disease. Renold J. Capocasale*,¹ J. O'Brien*,¹ D. Makropoulos*,¹ P. Rafferty*,¹ J. Quinn*,² R. Achuthanandam*,³ M. Kam*,³ L. Hrebien*,³ P. Bugelski*,¹ (Intr. by Emmanuel C. Besa) ¹Experimental Pathology, Centocor, Malvern, PA, USA; ²School of Biomedical Engineering, Science, and Health Systems, Drexel University, Philadelphia, PA, USA; ³Dept of Electrical and Computer Engineering, Drexel University, Philadelphia, PA, USA.

Rheumatoid arthritis is a chronic inflammatory disease commonly associated with anemia of chronic disease (ACD). Heterozygous Tg197 transgenic mice expressing human tumor necrosis factor- α (TNF- α) develop a chronic progressive polyarthritis and weight loss and have been used as a model of rheumatoid arthritis (Shealy et al *Arth Res* 4:R7, 2002). As TNF- α is believed to play an important role in the pathogenesis of ACD, we used 4-color flow cytometry and routine hematology to evaluate the potential of Tg197 mice to serve as a model of ACD. Groups of 8 heterozygous Tg197 were euthanized at 5 or 10 weeks of age after 24 hr pulse labeling with BrdU. Age matched CBF1 mice served as controls. Hind limbs were collected and fixed in 10% formalin for paraffin sections. Blood and femoral bone marrow were collected for hematology and flow cytometry, respectively. Antibody to Sca-1 was used to evaluate hematopoietic stem cells, Ter-119/CD71 erythroid progenitors, Gr-1/CD11b granulocyte and monocyte progenitors and IL-7R- α , lymphoid progenitors. Annexin V binding, BrdU and 7-AAD were used to evaluate apoptosis and cell cycle in these populations. Histologic evaluation revealed a progressive arthritis and hematology a mild progressive, microcytic hypochromic anemia with reticulocytosis and monocytosis. Preliminary analysis of the flow cytometric data revealed increased numbers of dead and apoptotic erythroid precursors. The results of in-depth analysis will be presented. Taken together, our data suggest that Tg197 mice may be a useful model of ACD.

Abstract# 1857**Poster Board #-Session: 28-II**

Relationship between Serum Erythropoietin and Hemoglobin Concentration in Community-Dwelling Older Women: The Women's Health and Aging Studies I and II. Paulo H. M. Chaves*, Qian-Li Xue*, Linda P. Fried*. (Intr. by Richard C. Woodman) *Johns Hopkins Center on Aging and Health, Baltimore, MD, USA.*

BACKGROUND. Anemia in older women is typically defined as Hb < 12 g/dL. The current criteria used to define anemia were mainly derived from statistical distribution considerations. There is, however, limited physiologic data supporting or refuting these criteria. The objective of this study was to investigate the relationship between the continuous distributions of serum erythropoietin (EPO) – a surrogate marker for tissue oxygenation – and hemoglobin concentration (Hb) in older adults, focusing on the characterization of potential threshold effects. Specifically, we tested the assumption that within the Hb range defined as normal for older women by the World Health Organization (WHO); i.e., 12–16 g/dL, serum EPO is constant and lowest.

METHODS. This cross-sectional analysis used data from the Women's Health and Aging Studies (WHAS) I and II, two complementary population-based studies investigating the epidemiology of disability progression in 1002 women ≥ 65 yrs (WHAS-I, 1992-95), and disability onset in 436 high functioning women 70-80 yrs (WHAS-II, 1994-96). For this analysis, baseline WHAS I and WHAS II data from women 70-80 yrs were pooled ($n=865$). EPO was measured in sera samples stored at -70°C by enzyme immunoassay. Within- and between-assays coefficients of variability for EPO were 13.3% and 11.6%, indicating acceptable reproducibility. Hb was measured by spectrophotometry using the traditional cyanmethemoglobin method. Baseline EPO and Hb were available for 662 subjects. To minimize the impact of outliers, we restricted this analysis to subjects with Hb between 10–16 g/dL, and excluded 3 subjects with EPO values above the 99th percentile level (≥ 63 mU/mL). This study final sample size was 641. A generalized linear model with a log-link and gamma distribution was used to estimate the mean serum EPO per Hb concentrations, and EPO differences between different Hb concentrations with corresponding 95% confidence intervals (CI).

RESULTS. Median EPO was 7.1 mU/mL (25th – 75th percentiles: 3.1 – 13.6). Mean Hb was 13.2 $\pm$ 1.1 g/dL. Mean age of study group was 74.3 $\pm$ 2.9. The observed relationship between Hb and EPO was best described by a curvilinear, quadratic curve. EPO was highest at the lowest Hb, and monotonically decreased with increasing Hb up to 14.2 g/dL (95% CI: 13.1, 15.3), the tangent to the curve. As compared to EPO at a Hb of 12 g/dL (11.3 mU/mL), mean EPO linked to a Hb of 10 g/dL (23.7 mU/mL) and 11 g/dL (15.4 mU/mL) were significantly higher; i.e., EPO was 2.1 (95%CI 1.4, 3.1) and 1.4 (95%CI 1.2, 1.6) times higher, respectively. Even within the normal Hb range, there was a substantial EPO gradient. For example, EPO at a Hb of 14.2 g/dL was .75 (95%CI .65, .88) times lower than at the low-normal Hb of 12 g/dL. Adjustment for age, race, and calculated creatinine clearance did not change these estimates.

CONCLUSION. We found a meaningful relationship between decreasing EPO and increasing Hb up to levels currently perceived as mid-normal Hb. These results support the hypothesis that mid-normal Hb concentrations might offer a clinical advantage over mild anemia (10-12g/dL) and possibly low-normal Hb (12-13 g/L). In addition, our findings are in accordance with recently published epidemiologic studies suggesting that a Hb of 12 g/dL might be a suboptimal criterion to define anemia in older women.

ERYTHROPOIESIS II

Abstract# 1858**Poster Board #-Session: 29-II**

Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over a Prolonged Period of Therapy. Peter Hillmen,¹ Claire Hall*,¹ Judith Marsh*,² Dupe Elebute*,² Stephen Richards,¹ Scott A. Rollins*,³ Christopher F. Mojcik*,³ Russell P. Rother*,³ ¹H.M.D.S., Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; ²Haematology, St. George's Hospital Medical School, London, United Kingdom; ³Alexion Pharmaceuticals, Inc., Cheshire, CT, USA.

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Deficiency of the terminal complement inhibitor CD59 from PNH red cells is the principle cause of the complement-mediated hemolysis. Eculizumab is a humanized monoclonal antibody that binds to C5 inhibiting terminal complement activation. We previously reported that eculizumab was very effective at acutely controlling intravascular hemolysis in a 3-month Pilot study of transfusion-dependent PNH patients. We now report that all 11 patients from the initial study entered an extension trial of 900mg eculizumab by i.v. infusion over 30 minutes every other week for one year. To date all patients remain on eculizumab, completing between 11 to 15 months of therapy. Results presented below represent cumulative data through 6 months. Eculizumab continues to be well tolerated with no dose limiting toxicity. The adverse events in the extension study are similar to those in the pilot study. The dramatic improvement in the biochemical parameters of hemolysis occurring in all patients within a week of starting therapy persists. Mean LDH decreased from 3111 $\pm$ 598 U/L over the 12 months prior to treatment to 670 $\pm$ 69 U/L over 6 months following treatment ($p=0.003$). Hemoglobinuria (daily urine color scale) decreased from 3.0 to 0.2 paroxysms/patient-month since starting eculizumab therapy with a significant improvement in quality of life measures related to hemolysis. In addition, PNH type III red cells progressively increased during the treatment period from a mean of 37% to 57% at 6 months ($p=0.009$). There was also a continued reduction in transfusion requirement from a median 1.8 units/patient/month in the 12 months prior to treatment to 0.4 units/patient/month over the last 6 months ($p=0.001$), and 5 of the 11 patients remain completely transfusion independent after a year of therapy. Patients with purely hemolytic disease (macroscopic hemoglobinuria with a normal platelet count; $n=6$) had the best response

with cessation of hemolysis, an increase in type III red cells from 39% to 67% and a decrease in transfusions from a median of 2.0 units/patient-month to 0 units/patient-month. Four patients who did not become transfusion independent have been treated with subcutaneous erythropoietin in addition to eculizumab with some improvement in hemoglobin and transfusion requirement. Interestingly, in most patients LDH levels remain just above the upper limit, the bilirubin remains slightly to moderately elevated (under 50 $\mu\text{mol/L}$), the haptoglobins remain undetectable and the reticulocytosis persists indicating a low level of well-compensated, presumably extravascular, hemolysis. Two patients experienced transient breakthroughs in complement activity associated with increased LDH, hemoglobinuria and mild symptoms; these resolved immediately upon next dose of eculizumab and further breakthroughs were prevented by a slight decrease in the dosing interval. These data support the role of terminal complement activation in hemolysis of PNH red cells and the mechanism of action of eculizumab in the control of hemolysis and symptoms in PNH. In summary, this study demonstrates that eculizumab is well tolerated, dramatically decreases hemolysis and transfusion requirement as well as improving the symptoms of PNH. The effectiveness of eculizumab has been maintained for a median of 12 months of therapy and is ongoing in all patients.

Abstract# 1859**Poster Board #-Session: 30-II**

A Novel GATA-Specific Inhibitor (GSI) Rescues Anemia of Chronic Disease by Oral Administration. Shigehiko Imagawa,¹ Yoko Nakano*,¹ Naoshi Obara*,¹ Norio Suzuki*,² Toshiro Nagasawa*,¹ Masayuki Yamamoto.² ¹Division of Hematology, Institution of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan; ²TARA center, University of Tsukuba, Tsukuba, Ibaraki, Japan.

The disorders associated with anemia of chronic disease (ACD) are characterized by the production of interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), which increase the binding activity of GATA-2 and NF- κ B and inhibit production of erythropoietin (Epo). Because Epo promoter activity is negatively regulated by GATA binding, GATA-2 may be responsible for impaired Epo synthesis in inflammatory disease *in vivo*. On the other hand, we found that N^G-monomethyl L-arginine (L-NMMA), which is increased in patients with chronic renal failure, inhibits NO and cGMP production, increases the binding activity of GATA and mRNA expression, and inhibits Epo promoter activity. Therefore, one common pathogenesis of ACD and anemia of renal disease appears to be via the stimulation of GATA binding activity. We have shown that intraperitoneal injection of K-7174, a GATA-specific inhibitor, improves Epo production which had been inhibited by IL-1 β and TNF- α . In this study, a novel GSI, which has a 100-fold higher affinity than K-7174, was examined to further improve Epo production that had been inhibited by IL-1 β and TNF- α . The addition of 100 nM GSI rescued the inhibition of Epo protein production and promoter activity induced by IL-1 β and TNF- α , respectively. Electrophoretic mobility shift assays revealed that the addition of GSI decreased GATA binding activity, which was increased with the addition of IL-1 β and TNF- α . Furthermore, intraperitoneal injection of mice with IL-1 β or TNF- α decreased Epo levels, reticulocyte counts, hematocrits (Hts), hemoglobins (Hbs), the numbers of CFU-E from spleen and bone marrow, and the number of CD71+Ter119+ cells from the spleen. However, oral administration of GSI reversed these effects. These results raise the possibility of using GSI as a novel drug for treating ACD by oral administration.

Effects of GSI on Hbs, Hts, reticulocyte counts, Epo levels, the number of CFU-E and CD71+Ter119+ cells from ICR mice induced by IL-1 β or TNF- α					
	Control	+IL-1 β	+TNF- α	+IL-1 β + 3 mg/kg GSI	+TNF- α + 3 mg/kg GSI
Hb (g/dL)	14.8 $\pm$ 0.8 (15)	13.5 $\pm$ 0.5 (13)*	13.4 $\pm$ 0.6 (11)*	14.0 $\pm$ 0.8 (14)***	13.8 $\pm$ 0.5 (12)****
Ht (%)	46.4 $\pm$ 2.8 (16)	41.6 $\pm$ 2.2 (13)*	42.7 $\pm$ 2.0 (12)*	43.4 $\pm$ 2.7 (14)***	43.2 $\pm$ 2.1 (12)****
Reticulocyte (%)	163 $\pm$ 29 (10)	122 $\pm$ 19 (8)*	92 $\pm$ 32 (12)*	304 $\pm$ 38 (8)***	253 $\pm$ 55 (12)****
Epo (mU/mL)	24.8 $\pm$ 31.9 (9)	3.0 $\pm$ 4.6 (7)*	3.3 $\pm$ 5.6 (8)*	17.1 $\pm$ 24.1 (7)***	49.4 $\pm$ 45.8 (9)****
CFU-E (spleen)	10.0 $\pm$ 8.9 (8)	4.7 $\pm$ 3.6 (6)*	7.5 $\pm$ 4.7 (8)**	30.4 $\pm$ 19.8 (8)***	67.8 $\pm$ 7.9 (8)****
CD71+Ter119+	19.6 $\pm$ 6.9 (4)	16.8 $\pm$ 6.9 (3)	ND	41.8 $\pm$ 11.6 (3)***	54.3 $\pm$ 1.2 (2)***

(experimental numbers) * Significance compared with control, P<0.005; **Significance compared with control, P<0.025; Significance compared with +IL-1 β , P<0.005; ***Significance compared with +IL-1 β , P<0.025; ****Significance compared with +TNF- α , P<0.005; #+TNF- α + 1 mg/kg GSI; ND: not done

Abstract# 1860**Poster Board #-Session: 31-II**

Stress Erythropoiesis Is Not Efficiently Supported by a Minimal Epo Receptor Phosphotyrosine-Null Allele. Don M. Wojchowski,^{PSU} Vinit G. Karur*,^{PSU} Madhu P. Menon*,^{PSU} Ke Li,^{PSU} Jamie Crater*,^{PSU} ¹Department of Veterinary Sciences, The Pennsylvania State University, State College, PA, USA; ²Pathobiology program, Department of Veterinary Sciences, The Pennsylvania State University, State College, PA, USA; ³Molecular Medicine, Huck Institute of Life Sciences, The Pennsylvania State University, State College, PA, USA; ⁴Department of Veterinary Sciences, The Pennsylvania State University, State College, PA, USA; ⁵Department of Veterinary Sciences, The Pennsylvania State University, State College, PA, USA.

Anemia intensifies signals for red cell production and activates stress erythropoiesis mechanisms. This can involve accelerated medullary erythropoiesis, enhanced cytokine action, stimulation of latent progenitor cell populations and extra-medullary erythropoiesis. To investigate ways in which subsets of Epo receptor linked factors might regulate this process, mice with a knocked-in truncated and phosphotyrosine-null EpoR allele (EpoR-HM) were challenged with phenylhydrazine. In these EpoR-HM mice, stress erythropoiesis was discovered to falter in several ways: 1) Hemoglobin levels, hematocrits and RBC numbers failed to efficiently rebound; 2) Interestingly, reticulocyte levels nonetheless approximated those in wt-EpoR controls; 3) In response to this hemolytic anemia, spleens of EpoR-HM

mice essentially failed to enlarge; 4) Immunohistochemical analyses revealed decreased red pulp expansion in spleens of EpoR-HM mice; 5) Analyses of constituent erythroid progenitor cells revealed an apparent developmental deficiency in EpoR-HM mice at a late CD71-high, Ter119(+) stage; 6) In splenocyte preparations, proliferative responsiveness to Epo was several-fold lower for EpoR-HM mice, and markedly lower in the absence of serum; 7) Affymetrix profiling of purified Ter119(+) erythroid progenitor cells from spleen revealed elevated expression of several genes in EpoR-HM mice including an interesting set of GTP-regulated factors. These findings in general reveal that important roles are exerted by distal EpoR PY-encoding domains during stress erythropoiesis (as illustrated, for example, by defective red cell production and splenic enlargement). In addition, insight into stress erythropoietic mechanisms also is advanced. This includes first a sustained deficit in mature red cells vs an efficient production of reticulocytes observed in EpoR-HM mice; this suggests that EpoR PY signaling normally may impact on reticulocyte half-life and/or maturation. Second, Epo-dependent stress erythropoiesis also may be significantly assisted in EpoR-HM mice by an accessory serum growth factor. Finally, profiling outcomes suggest that erythroid progenitor cell-intrinsic mechanisms also are activated in response to deleted Epo-PY coupled events, and in part this may involve a selective engagement of GTP-protein linked pathways. Such novel stress erythropoietic mechanisms may have significant clinical relevance.

Abstract# 1861**Poster Board #-Session: 32-II**

Complement-Mediated Hemolysis of Erythrocytes Is Blocked by RNA Aptamers to Complement Components C5 and C8. Jun-ichi Nishimura,¹ Shahid M. Nimjee*,² Haixiang Jiang*,³ George Pitoc*,² Thad A. Howard*,³ Christopher P. Rusconi*,² Mitsuhiro Omine*,⁴ Michael M. Frank*,³ Bruce A. Sullenger*,² Russell E. Ware.³ ¹Medical Oncology and Transplantation, Duke University Medical Center, Durham, NC, USA; ²Experimental Surgery, Duke University Medical Center, Durham, NC, USA; ³Pediatrics, Duke University Medical Center, Durham, NC, USA; ⁴Medicine, Showa University Fujigaoka Hospital, Kanagawa, Japan.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell disorder characterized by intravascular hemolysis, venous thrombosis, and bone marrow failure. The lack of GPI-anchored surface complement regulatory proteins, such as CD55 (DAF) but especially CD59, results in complement-mediated hemolysis and hemoglobinuria, which is a major clinical manifestation of PNH and an important cause of morbidity and mortality. Complement plays a critical role in the pathophysiology of hemolysis in PNH, and may also be important in the development of thrombosis. Accordingly, complement inhibition in PNH should control hemolysis and potentially reduce the risk of venous thrombosis. RNA aptamers that bind and functionally inhibit human complement protein C5 have been identified using a combinatorial RNA library and the systematic evolution of ligands by exponential enrichment (SELEX) *in vitro* selection method (Bieseker G. et al. : Immunopharmacology, 42:219, 1999). However, C5 is critical not only for complement activation, but also for proper regulation of inflammatory processes. Prolonged inhibition of C5 could, therefore, have undesired side effects that would limit its utility in patients with PNH. CD59 inhibits C9 from binding to the C5b8 complex, and is critically important in protecting erythrocytes from complement-mediated lysis. Individuals deficient in C9 are usually healthy, although inherited deficiencies in other complement proteins typically lead to various degrees of illness. Thus, complement proteins C8 or C9 may be the ideal targets to protect PNH erythrocytes from complement-mediated lysis without adverse side effects. We first synthesized one of the known C5-binding aptamers (UCUCAUGCGCCGAGUGAGUUUACCUUCGU) and confirmed inhibition of human serum hemolytic activity using an *in vitro* assay with sensitized sheep erythrocytes, C5-depleted serum, and purified C5. We have begun to identify RNA aptamers that inhibit complement components C8 or C9 by the SELEX procedure, to isolate high affinity, nuclease-resistant RNA ligands that bind specifically to C8 or C9. After only 4 rounds of the SELEX procedure, aptamers bound purified C8 with a K_d = 970 pM and also inhibited human serum hemolytic activity using an *in vitro* assay with sensitized sheep erythrocytes, C8-depleted serum, and purified C8. Complement-mediated lysis was inhibited at 50-100nM C8 aptamer concentrations, similar in potency to the published C5 aptamers. Additional rounds of the SELEX procedure should yield specific high-affinity C8-binding aptamers, and C9 aptamers are also being developed. Inhibition of complement activation is a new therapeutic goal for patients with PNH that could control hemolysis, reduce transfusion dependency, and potentially reduce the risk of thrombosis. The development of specific RNA aptamers by the SELEX procedure should provide new therapeutic options for patients with PNH in the near future.

Abstract# 1862**Poster Board #-Session: 33-II**

Increased Apoptosis of Erythroid Cells during Anemia Recovery in Prion Protein Deficient (Prnp^{0/0}) Mice. Jan H. Zivny*,^{1,2} Karel Holada*,² Jan Simak,¹ Jaroslav G. Vostal.¹ ¹Laboratory of Cellular Hematology, Center for Biologics Evaluation and Research, FDA, Bethesda, MD, USA; ²1st School of Medicine, Charles University, Prague, Czech Republic.

The cellular isoform of prion protein (PrP^c) is involved in the pathogenesis of prion diseases in both humans and animals but its normal function is not known. It has been proposed that PrP^c may protect cells against oxidative stress damage, promote survival and differentiation of neuronal cells and mediate copper transport. However, prion protein gene knock-out mice (Prnp^{0/0}) did not develop major phenotypic changes. PrP^c is expressed on many cell types including hematopoietic cells and red cells. We tested the role of PrP^c in erythropoiesis using a mouse erythroleukemia cell line (MEL) induced to erythroid differentiation by N,N'-hexamethylene bisacetamide (5mM) and a mouse model of accelerated erythropoiesis induced by acute anemia. Erythroid differentiation of MEL cells led to the induction of prion protein gene (Prnp) mRNA expression and up-regulation of cell surface