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Dancers at Bazaar del Mundo, Old Town, San Diego, California. Photo courtesy of Getty Images.

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emerged that some genes such as HOXB4 and BMI-1, function for the proliferation and maintenance of stem cells. In this study, we examined expression levels of HOXB4 and BMI-1 in CD34 positive cells by quantitative PCR in 10 patients with AA and 13 with idiopathic thrombocytopenic purpura (ITP). Between these two factors, the expression level of HOXB4 was markedly decreased in AA compared with in ITP, whereas that of BMI-1 was not. Moreover, the expression level of GATA-2 in these populations was significantly correlated to HOXB4 gene expression (Spearman's rank correlation, $r=0.6573$ $p<0.01$) compared to that of BMI-1 ($r=0.4107$, $p>0.05$). As they function as a transcription factor, these results raise the possibility that GATA-2 and HOXB4 regulate each other. To explore this possibility, first, we cloned HOXB4 5' flanking region by PCR and performed promoter analysis. Since the previous report showed that the region from -164 to -116 was important for promoter activity of HOXB4 gene, we focused on a GATA element located at -160. When this element was deleted, the reporter activity was decreased to 60% of wild-type in K562 cells. Furthermore, co-transfection of GATA-2 expression vector significantly activates the reporter gene in a dose dependent manner. EMSA revealed that GATA-2 binds specifically to this element. On the other hand, the active region both of exon 1S and 1G promoter of GATA-2 gene, which was identified by the promoter analysis, did not contain the consensus sequence recognized by HOXB4. These findings suggest that in stem cells in AA, the decreased expression of GATA-2 gene lead to the reduced HOXB4 gene expression, which may be responsible for the development of the disease.

Abstract# 2822 Poster Board #-Session: 92-III

A Pilot Application of SELDI Serum Proteomics in Bone Marrow Failure Syndromes. Sujith Rao Kalmadi,¹ Ron Wu*,¹ Magdalena Plasilova*,¹ Elaine Sloan,² Naomi Galili*,³ Azra Raza*,³ Jaroslav P. Maciejewski*,¹ ¹Experimental Hematology and Hematopoiesis, R 40, Cleveland Clinic Foundation, Cleveland, OH, USA; ²Hematology Branch, NHLBI, NIH, Bethesda, MD, USA; ³Myeloid diseases and MDS center, Rush University Medical Center, Chicago, IL, USA.

Clinically, bone marrow failure syndromes show significant overlap. Newer analytic approaches may lead to improved diagnosis and better understanding of underlying pathophysiology. In contrast to traditional biomarker diagnostic principles, proteomic technologies such as surface-enhanced laser desorption/ionization (SELDI) method enable screening of protein patterns without knowledge of the identity of targets. The recent refinement of SELDI mass spectrometry has allowed for the early diagnosis of occult solid tumors. We explored the potential application of SELDI proteomics to the study of bone marrow failure states. An extensive sample library included 28 Aplastic anemia, 129 Myelodysplastic syndrome (MDS), 28 Paroxysmal Nocturnal Hemoglobinuria (PNH) patients and 36 control specimens. Within the MDS cohort, subgroups with RA (N=77), RARS (N=15) and RAEB/t (N=37) were studied. Analyses were also performed for patients with specific cytogenetic abnormalities, including those with 5q-syndrome (N=21), trisomy-8 (N=15), aberrations of chromosome 7 (N=15) and compared to MDS patients with normal cytogenetics (N=57). In preliminary experiments, H4 chips were selected for further study: spectra with >80 peaks were considered as informative. Initially, our analysis included learning sets in which 20 randomly selected samples from individual categories were compared to each other in order to identify specific peptide peaks. Subsequently, the results obtained in the learning set were confirmed using separate validation sample sets. A scoring system was applied for analysis in which signal/noise ratio was a sole criterion for peak recognition and assignment of non-parametric scores. Reproducibility was assured by repeating measurements of standard plasma sample and multiple determinations.

When AA spectra were compared to controls, AA could be distinguished with 87% sensitivity and 85% specificity based on the presence of a single peak at M/Z value of 3.095kDa. When compared to RA, AA was discriminated with 95% specificity and 80% sensitivity (1.02kDa). Globally, we devised a decision tree (using 3 different peaks in 6 steps of separation) that allows for the plasma-based discrimination of MDS and controls. Within MDS group, RA could be further differentiated from a more advanced MDS with 95% specificity and 90% sensitivity. A single peak at M/Z value of 3.88kDa distinguished RA from RAEB/t. Similar learning data sets performed for RARS patient can be obtained. Not overlapping sample sets are used for validation of obtained results. Finally, samples with atypical spectra can be investigated for features that may prompt diagnostic reassignment; e.g., in patients with hypocellular MDS to AA, and PNH to AA/PNH syndrome. Most intriguing is the possibility that specific cytogenetic defects may result in proteomic patterns that may provide important clinical clues. A large sample collection allows for subanalyses based on karyotype: for example, data and result sets exist for patients with 5q-, trisomy-8 and other more common chromosomal changes.

Our ongoing study demonstrates the feasibility of SELDI technology in detecting diagnostic protein signatures for individual bone marrow failure states. In the future, proteomic biomarker pattern-based analysis may allow for more precise definition and supplement the traditional diagnostic approaches.

Abstract# 2823 Poster Board #-Session: 93-III

Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy. Anita Hill*,¹ Dupe Elebute*,² Judith C. Marsh*,² Stephen J. Richards,¹ Bruce McNutt*,³ Beth E. Petro*,³ Russell P. Rother*,³ Peter Hillmen.¹ 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 results in complement-mediated hemolysis. Eculizumab, a humanized monoclonal antibody that inhibits terminal complement by binding to C5, is effective at

controlling intravascular hemolysis in PNH. We now report that 10 of the 11 patients from an initial 3 month study have continued to receive 900mg eculizumab every other week for 2 years. The remaining patient stopped eculizumab after 23 months despite effective control of intravascular hemolysis, as the patient continued to be transfused even after erythropoietin therapy. This patient had the most severe hypoplasia at the start of eculizumab therapy with a platelet count below $30 \times 10^9/L$, suggesting that the ongoing transfusions were due to the bone marrow failure and not continuing hemolysis. Eculizumab was safe and well tolerated with two reported SAEs in the last year, neither of which were attributed to the drug. The dramatic improvement in various parameters of hemolysis persisted during the 2 year treatment period for all patients. Mean LDH levels decreased from 3111 ± 598 U/L over the 12 months prior to treatment to 634 ± 34 U/L up to 24 months following treatment ($p=0.002$). PNH red cells with a complete deficiency of GPI-linked proteins (Type III red cells) progressively increased during the treatment period from a mean of 36.7% to 58.9% ($p=0.001$) while partially deficient PNH red cells (Type II) increased from 5.3% to 8.7% ($p=0.01$). There has been no change in the proportion of PNH neutrophils in any of the patients during eculizumab therapy indicating that the increase in the proportion of PNH red cells is due to a reduction in hemolysis and transfusions rather than a change in the PNH clone(s) itself. The mean and median transfusion rates decreased from 2.1 and 1.8 units/patient/month to 0.4 and 0.3 units/patient/month respectively ($p<0.001$). Three patients remained transfusion independent during the whole 2 year treatment period and the other 7 patients remaining on eculizumab all had at least a three-fold reduction in transfusion requirements. No patients have had a thrombosis during the study period, including 5 patients who were not on warfarin therapy. Prior to eculizumab, some patients suffered with abdominal pain, dysphagia and erectile dysfunction. Following the first dose of eculizumab there has been complete and sustained resolution of these symptoms. In addition, other symptoms related to hemolysis, such as lethargy, have shown a sustained marked improvement. These classical PNH symptoms have been attributed, at least in part, to the release of free hemoglobin (Hb) during intravascular hemolysis which overwhelms the protective Hb scavenging mechanisms. Free Hb efficiently absorbs and depletes nitric oxide (NO) which is a critical regulator of smooth muscle contraction, vascular tone and platelet activation. The potential role of NO in the symptomologies of PNH are currently under investigation. In summary, we report that eculizumab is well tolerated and has persisting efficacy as demonstrated by decreased hemolysis and transfusions, as well as improvement in the symptoms of PNH, for over 2 years of therapy.

Abstract# 2824 Poster Board #-Session: 94-III

Blocking Complement-Mediated Hemolysis of PNH Erythrocytes by RNA Aptamers to C8 and C9. Jun-ichi Nishimura,¹ Shahid Nimjee*,² Haixiang Jiang*,³ Tatsuya Kawaguchi,⁴ Hideki Nakakuma,⁵ Mitsuhiro Omine*,⁶ Michael M. Frank*,³ Russell E. Ware,⁷ Bruce A. Sullenger*,² ¹Medicine, Duke University Medical Center; ²Surgery, Duke University Medical Center; ³Pediatrics, Duke University Medical Center, Durham, NC, USA; ⁴Internal Medicine II, Kumamoto University School of Medicine, Kumamoto, Japan; ⁵Hematology/Oncology, Wakayama Medical University, Wakayama, Japan; ⁶Medicine, Showa University Fujigaoka Hospital, Kanagawa, Japan; ⁷Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA.

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 complement regulatory proteins, such as CD55 (DAF) but especially CD59 (MIRL), results in complement-mediated hemolysis and hemoglobinuria, which are major clinical manifestations of PNH and an important cause of morbidity and mortality. Recent results from a pilot study in patients with PNH, using a humanized monoclonal antibody (eculizumab) that binds to human complement C5 and inhibits terminal complement activation, suggested that blocking complement activation is a new potential therapeutic option for PNH that could control hemolysis, reduce transfusion dependency, and possibly reduce the risk of thrombosis (N Engl J Med, 350:552, 2004). RNA aptamer inhibitors of human complement protein C5 have already been identified using a combinatorial RNA library and an in vitro selection method (SELEX) (Immunopharmacology, 42:219, 1999). We previously synthesized a known C5-binding aptamer (TCTCATGCGCCGAGTGTGAGTTTACCTTCGT) and found that it inhibited human serum hemolytic activity (Blood, 102:510a, 2003). However, since C5 is critical not only for complement activation, but also for proper regulation of inflammatory processes, prolonged C5 inhibition could have undesired side effects that would limit its utility in PNH. Terminal complement proteins C8 and C9 represent potentially better targets, since CD59 inhibits C9 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, C8 or C9 may be the ideal targets to protect PNH erythrocytes from complement-mediated lysis without adverse side effects. Using the SELEX procedure against purified C8 and C9 proteins, high affinity, nuclease-resistant RNA ligands were identified that bind specifically to C8 or C9. After 6 rounds of SELEX, C8 aptamers bound C8 with a Kd of 1 nM and a Bmax of 83%, and inhibited human serum hemolytic activity similar to or greater than C5 aptamers. After 16 rounds of SELEX, C9 aptamers bound C9 with a Kd of 12 nM and a Bmax of 58%, and also inhibited human serum hemolytic activity similar to or greater than C5 aptamers. C8 aptamers after 6 rounds, and C9 aptamers after 16 rounds, of SELEX have been cloned, sequenced, and categorized. All ten C8 aptamer clones had a similar sequence, while nine C9 aptamer clones had two families of similar sequences (n=5 and n=3, respectively). These clones are currently being synthesized for testing in both the binding and hemolytic inhibition assays. Selected high-affinity and high inhibitory aptamers will be modified in preparation for future in vivo studies in PNH. The development of blocking RNA aptamers, using the SELEX procedure against terminal complement proteins C8 and C9, represents a novel potential therapeutic option for patients with PNH.