

**Tuesday 20 October**  
**HSANZ Symposium: Acute Leukaemia/Acute Biology**

**0830-1000**  
**Hall C**  
**0830**

## **Transcription Factor C/EBP alpha Regulates Hematopoietic Stem Cell Proliferation and Maintenance**

**Daniel Tenen**

*Harvard Institute of Medicine, Boston, USA*

Hematopoietic stem cells (HSCs) undergo an abrupt change from an actively cycling state to largely quiescent in bone marrow 3 weeks after birth. However, little is known about how this switch is regulated. Here we report that levels of C/EBP alpha, a transcription factor that is frequently disrupted in human acute myeloid leukemia, regulate the proliferative states of HSCs. C/EBP alpha excision in adult mice results in a significant expansion of HSCs and elevated proliferation rates, indicating C/EBP alpha functions as a mitotic inhibitor in adult HSCs. Interestingly, HSCs show a rapid increase in C/EBP alpha expression 3 weeks after birth. Consistent with levels of its expression, loss of C/EBP alpha in 4-week old mice results in a large expansion of HSCs, while only a minor change is observed in C/EBP alpha deficient newborn mice. Furthermore, C/EBP alpha expression is diminished in adult cycling HSCs following cytotoxic cyclophosphamide treatment, suggesting that down-regulation of C/EBP alpha might contribute to the re-activation of quiescent adult HSCs. Gene profiling analysis of C/EBP alpha<sup>-/-</sup> HSCs shows up-regulation of Notch 3 and 4 and down-regulation of their inhibitors, indicating enhanced activation of Notch signaling, a signal pathway that has been implicated in promoting HSC expansion. Finally, C/EBP alpha deficiency also causes impaired adhesion and retention of HSCs, leading to massive egress of HSCs from BM to distal organs and a repopulating failure.

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## Insights from MRC Trials in AML

**Alan Burnett**

*School of Medicine, Cardiff University, UK*

There have been continuous MRC trials in AML since 1966. In 1994 the organisation came under the auspices of the newly formed National Cancer Research Institute (NCRI). Over the last 20 years annual recruitment has increased from 100 to >1200 with randomisations from 100 to >2500 and in that period over 10000 patients have contributed >25000 randomisations. Trials have focussed on studies in patients under 60 including children, on older patients who are fit for chemotherapy, and the elderly unfit population, and include patients with >10% marrow blasts.

In younger patients with intermediate and good risk disease, but not poor risk disease the longterm survival has improved, with around 80% achieving CR and 40-50% surviving. No more than a total of 4 treatment courses are required, and a retrospective study suggests that a total of 3 courses may be sufficient for good risk and intermediate risk patients which is a question being tested in the current AML17 trial. Of the several induction chemotherapy combinations tested none have proved to be superior to Daunrubicin/ Ara-C. The addition of Mylotarg to induction has provided significant benefit in CBF leukaemias (84% survival at 4 years) and a trend for benefit in intermediate risk but no benefit in poor risk patients. The traditional MRC MACE/MidAc consolidation is myelosuppressive and preliminary results from AML15 suggest that survival is similar with High dose Ara-C whether given at a dose level of 3g or 1.5 g. The additional contribution of stem cell transplantation to patients of intermediate risk is minimal, particularly if they have received mylotarg in induction, but adding mylotarg in consolidation produced no obvious additional effect.

Much has been learned about prognostic factors, and a new risk score can redefine a larger group of poor risk patients where we can for the first time see some benefit for transplantation. It is at the moment unclear how much additional information molecular characterisation provides with respect to who should be transplanted, and studies with FLT3 inhibition are ongoing.

In patients over 60 years who are given intensive chemotherapy the remission rate is 60%, but the relapse rate continues to be high, so in common with other collaborative groups virtually no improvement in overall survival has been seen in the last 30 years. MDR modulation with PSC-833 failed, as did an augmented dose of Ara-c, and there was no benefit in the addition of a 4<sup>th</sup> treatment course. The ongoing AML16 trial is testing the use of the novel nucleoside, clofarabine in combination with daunorubicin with or without mylotarg in induction and demethylation maintenance therapy. An important majority of older patients do not enter clinical trials and this maybe because the treatment options are unsuitable for less fit patients, who are a group of patients of current interest but difficult to precisely define. In order to cater for this group we compared Low Dose Ara-c with best supportive care and showed some superiority due to the 18% of patients who entered CR, but this was uncommon in patients with poor risk cytogenetics, however this did give a platform for a novel strategy of testing new combinations in a "pick a winner" which is ongoing.

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ANZSBT Free Communications 1

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Hall B

**O063**

0830

**The Efficacy of Prothrombinex<sup>®</sup>-VF for Acute Reversal of a Prolonged INR With or Without Fresh Frozen Plasma. A Two Centre Prospective Audit**

**Louise Bobbitt**<sup>1</sup>, Jacqueline Raynes<sup>2</sup>, Sue Dainty<sup>1</sup>, Hilary Blacklock<sup>2</sup>, Ross Henderson<sup>1</sup> and Sanjeev Chunilal<sup>1</sup>

1. North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand

2. Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand

**Aim**

To determine whether Prothrombinex-VF (PTX) is effective for acute reversal of a prolonged INR with or without concomitant use of Fresh Frozen Plasma (FFP).

**Method**

A prospective audit of patients who received PTX between August 2008 and May 2009 at two Auckland Hospitals. Eligible patients were all those who received PTX with or without FFP for correction of a prolonged INR. The dose of PTX and vitamin K prescribed along with the decision whether to use FFP was made by a Clinical Haematologist on a case by case basis and based on the patients actual or estimated weight and relevant clinical history and co-morbidities.

**Results**

A total of 122 separate doses of PTX administered to 120 patients for acute reversal of a prolonged INR. Forty two percent of patients received FFP (average 2 units per person) with their PTX. Over 80% of patients in both groups received vitamin K with average doses of 4.8mg in the no FFP group and 5.3mg in the FFP group. The mean dose of PTX given was 1487IU (no FFP) versus 1670IU (with FFP). The mean INR before reversal was similar for both groups 4.9 (no FFP) and 5.0 (with FFP). On average the post reversal INR was collected at 10 hours after PTX administration and was 1.3 for both groups irrespective of vitamin K administration.

**Conclusion**

Prothrombinex-VF is effective in quickly reversing a prolonged INR and was achieved with relatively low doses (20IU/kg). The efficacy of reversal was independent of the administration of vitamin K or FFP.

*This research was supported by CSL. The company had no role in the design, data analysis or preparing the abstract.*

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ANZSBT Free Communications 1

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Hall B

**O064**

0845

## **Benchmarking Transfusion Across New Zealand**

**Richard Charlewood**

*New Zealand Blood Service, Auckland, New Zealand*

### **Aim**

By comparing transfusion rates between individuals or institutions, a relative indication of the individuals or institution's performance can be obtained. This exercise, often called benchmarking, has been applied to various aspects of health care.

New Zealand Health Information Services (NZHIS) stores medical procedure codes as part of the National Minimal Dataset (NMDS) provided by all DHBs. NZBS stores the transfusion history of all patients transfused with blood issued by all but the very smallest of blood banks. By extracting data from the NMDS and NZBS databases and linking the two datasets, the aim is to derive transfusion rates per procedure for each district health board (DHB).

### **Method**

NZHIS extracted a table of with, NHI, and date of procedure and procedure code for all patients from 1 January 2002 until 31 December 2007 undergoing abdominal hysterectomy, total hip replacement, CABG and trans-urethral prostatectomy. NZBS extracted a table of red cells transfused using the NHI and date of surgery. NZHIS provided a table of procedure codes and procedure names. Using the database, the numbers of procedures performed and numbers of units transfused per procedure performed were extracted for each DHB. The multi-region ethics committee gave ethics approval for this study prior to commencement. Opt-in was gained from 18 of 21 DHBs at the time of the first data extract.

### **Results**

A total of 69684 procedures were identified. The mean proportion of patients transfused was 13%, 32%, 52% and 5% for hysterectomy, hip replacement, CABG and TURP respectively. The (geometric) mean number of units transfused was 3.1, 2.3, 6.6, 2.3 for hysterectomy, hip replacement, CABG and TURP respectively. Analysis of means was used to identify outlying DHBs - both relative under and over-transfusers.

### **Conclusion**

The initial concept has been demonstrated on four procedures and some useful information about relative performance of DHBs shown.

*No conflict of interest to disclose*

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**O065**

0900

**Transfusion Practices in Massive Haemorrhage in Intensive Care**

**R Sinha**<sup>1</sup>, D Roxby<sup>2</sup>, R Seshadri<sup>2</sup>

<sup>1</sup> Flinders University, Adelaide, South Australia

<sup>2</sup> SA Pathology, Flinders Medical Centre, Adelaide, South Australia

**Background**

Primary resuscitation for massive haemorrhage often occurs in emergency departments or operating theatres with ongoing resuscitation in intensive care (ICU).

**Aim**

To retrospectively review transfusion practice in the pre-ICU phase and ICU for patients with massive haemorrhage and associated mortality risk factors.

**Methods**

During 1998 to 2006, we developed an electronically linked database of blood and blood product usage and laboratory data with clinical outcome. All surgical patients who received ten or more units of red cells and required ICU admission were included.

**Results**

Two hundred and sixty three surgical patients were identified from a total of 307 patients who received  $\geq 10$  units of red cells. Two hundred and twenty five surgical patients were treated in both pre-ICU and ICU settings. Pre-ICU patients received a median of 11 units of red cells, 4 of FFP and 2 of platelets in a RC:FFP ratio of 1:3 and RC:Platelet ratio of 1:10.

Following ICU admission, patients received a median of 4 units of red cells, 3 of FFP and 1 of platelets in a RC:FFP ratio of 1:1 and RC:Platelet ratio of 1:4. Patients on arrival in ICU had a median platelet count of  $109 \times 10^9/L$  (IQR 79-152), INR 1.6 (IQR 1.4-1.9), APTT 48.7 seconds (IQR 38.4-68.3) and base deficit of -7 mmol/L (IQR -11 to -2). Median INR decreased to 1.4 within 8 hours of ICU admission and remained constant. Median base deficit decreased to -8 mmol/L during the first 4 hours and returned to normal by 24 hours. The ICU mortality rate was 19% and was associated with acidosis and a significant base deficit ( $p = 0.005$ ).

**Conclusions**

This study indicated that patients in ICU received more aggressive use of FFP and platelets to correct coagulopathy compared to the pre-ICU phase. A similar approach in pre-ICU settings may be effective in decreasing overall red cell requirements and improving mortality.

*No conflict of interest to disclose*

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Hall B

**O066**

**0915**

## **Understanding Transfusion Outcomes Through Clinical Registries: Validation of a Linkage Technique**

**Louise Phillips**<sup>1</sup>, Nikita Schembri<sup>1</sup>, Zoe McQuilten<sup>2</sup>, Mark Polizzotto<sup>2</sup>, Christine Akers<sup>3</sup>, Melissa Wills<sup>4</sup>, Susan Whitehead<sup>3</sup>, Erica Wood<sup>2</sup>, John McNeil<sup>1</sup>, Merrole Cole-Sinclair<sup>4</sup>

<sup>1</sup>*Transfusion Outcomes Research Collaborative, Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Victoria, Australia.* <sup>2</sup>*Transfusion Medicine Services, Australian Red Cross Blood Service, Melbourne, Victoria, Australia.*

<sup>3</sup>*Haematology Unit, Alfred Pathology Service, Alfred Hospital, Melbourne, Victoria, Australia*

<sup>4</sup>*Diagnostic Haematology, St Vincent's Hospital, Melbourne, Victoria, Australia*

### **Background**

It is unclear how variation in transfusion practice affects patient outcomes. Several registries gather clinical outcomes data without transfusion information. Hospitals are required to retain information regarding blood components transfused. An opportunity exists to use these two sources to explore effects of transfusion on clinical outcomes.

### **Methods**

Prospective validation of LIS data against individual patient records was undertaken at two major Victorian hospitals. Data regarding all transfusion episodes were compared over seven 24 hour periods. All clinical areas, fresh component types, and days of the week were included.

### **Results**

Data regarding 596 units were captured; 218 centre 1 (37%), 378 centre 2 (63%), comprising 399 red cells, 95 platelets, 72 plasma and 30 cryoprecipitate units. They were issued to: inpatient 221 (37%), intensive care 109 (18%), outpatient 95 (16%), operating theatre 45 (7.5%), emergency department 27 (4.5%) and unrecorded 99 (17%).

All products recorded issued by the LIS were transfused to intended patients. Median time from component issue to transfusion initiation could be calculated for 482 (81%) components: red cells 18 minutes (95% CI 16-20; IQR 10-33), platelets 20 (95% CI 16-24; IQR 11-38), FFP 60 (95% CI 17-96; IQR 13-163) and cryoprecipitate 44 (95% CI 3-179; IQR 7-194). Transfusion commenced within recommended timeframe for 73% of red cells, 69% platelets, 50% plasma and 68% cryoprecipitate.

### **Conclusions**

Across a range of blood component types and destinations comparison of LIS data with clinical records demonstrated concordance. The difference between LIS timing data and patient clinical records reflects the expected time to transport, check and prepare transfusion but does not affect the validity of linkage for most research purposes. Linkage of clinical registries with LIS data can therefore provide robust information regarding individual patient transfusion. This enables analysis of joint data sets to determine the impact of transfusion on clinical outcomes.

*There are no conflicts of interest to declare*

**A132**

**Tuesday 20 October**  
**ANZSBT Free Communications 1**

**0830-1000**  
**Hall B**

**O067**

**0930**

## **Appropriateness of Red Cell Usage within 7 major New Zealand Hospitals**

Richard Charlewood, Suzie Rishworth & **Christopher Corkery**  
*New Zealand Blood Service, Auckland, New Zealand*

### **Aim**

There was little published information about the appropriateness of red cell usage in New Zealand, therefore a prospective audit involving three common surgical procedures (CABG, THR, TAH) at seven major NZ hospitals was undertaken to assess appropriateness of this component following surgery and to assess what alternatives to blood transfusion were employed.

### **Method**

Transfusion nurse specialists prospectively collected data from a minimum of fifty operations at each of seven hospitals in New Zealand. Transfusion data was collected from the time of admission until the patient was discharged, reached day seven, underwent repeat surgery or died. Each transfusion was assessed by two Transfusion Medicine Specialists.

### **Results**

416 operations involving 415 patients were identified over the 10 month period. A total of 327 red cell units were transfused to 29% (n=119) of the patients. Transfusion rates showed significant differences between hospitals and surgical procedures. 84% patients had an appropriate indication for transfusion. 62% of patients were assessed as having been over-transfused. 69% of all units transfused were assessed as appropriate. 15% of all patients had low haemoglobin levels pre-operatively, but only a third of anaemic patients had been investigated with 14% of these treated preoperatively. Use of autologous blood collected in theatre or post-surgery was almost exclusively limited to cardiac surgery. Indication for transfusion was recorded in 46% of transfusions.

### **Comment**

The present audit is the first such audit to look at red cell usage within New Zealand Hospitals on a national basis. This audit identified several areas that could be responsive to education including: a) red cell dosage to avoid over transfusion, b) discourage routine two red cell unit prescribing c) investigate barriers to blood sparing techniques, d) identification and treatment of anaemic patients before surgery, e) documentation and indication for transfusion can be improved.

*No conflict of interest to disclose*

Tuesday 20 October  
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Hall B

**O068**

0945

## **Snapshot of Current Platelet Transfusion Practice in Five South Australian Hospitals**

Romi Sinha<sup>1,2</sup>, Russell Hunt<sup>1</sup>, Karen Olsen<sup>1</sup>, Barbara Parker<sup>1</sup>, Beverleigh Quedsted<sup>1,2</sup>, Tracey Roffey<sup>1</sup>, Trudi Verrall<sup>1</sup>, **Kathryn Robinson**<sup>1,2</sup>.

1. *BloodSafe Program, Adelaide, South Australia, Australia*

2. *Australian Red Cross Blood Service, Adelaide, South Australia, Australia*

### **Aim**

To examine the appropriateness of platelet transfusion practice across five metropolitan teaching hospitals in Adelaide, South Australia.

### **Method**

Retrospective case note audits of consecutive platelet transfusion from the last quarter of 2008 were performed by five Transfusion Nurse Consultants. The data was entered into an auditMaker™ database customised to include relevant clinical information (such as patient demographics, clinical diagnosis, and indication for transfusion, consent and documentation of the process). The data was assessed by a haematologist for appropriateness against NHMRC/ABST guidelines.

### **Results**

One hundred and thirteen platelet transfusion episodes (129 units) in 74 patients were audited. The main indications for platelet use were prophylaxis for bone marrow failure, prophylaxis for surgery/invasive procedure, abnormal microvascular bleeding and documented platelet disorders. Fifteen percent of platelet transfusions were found to be outside NHMRC guidelines based on available documentation. Forty percent of the platelet transfusions were used for prophylaxis for bone marrow failure. The reason for transfusion was documented in 90% of cases and consent in 61%.

### **Conclusion**

While overall 15% of platelet transfusion episodes were outside of guidelines based on available documentation, around half of these were prophylactic platelet transfusions in patients with bone marrow failure in the outpatient setting with platelet counts approaching 10. Transfusion in this setting, to avoid a return visit the following day, may have been reasonable. Many of these patients were children. The remainder of transfusions outside guidelines (based on documentation) were for varying reasons including pre-emptive platelet transfusion for critical bleeding, and maybe in line with local protocols.

*No conflict of interest to disclose*

**A134**

**Tuesday 20 October**  
**ASTH Symposium: Topics in Venous Thrombosis**

**0830-1000**  
**Hall D**  
**0830**

## **Diagnosis of Venous Thrombosis**

**Paul A Kyrle**

*Medical University of Vienna, Austria*

In patients with suspected deep-vein thrombosis or pulmonary embolism, accurate diagnosis is of utmost importance: an untreated thrombus can result in fatal pulmonary embolism, whereas anticoagulation in the absence of thrombosis is irresponsible. Since only approximately a quarter of patients with suspected venous thromboembolism actually have the disease, the optimal therapeutic strategy is to safely rule out thromboembolism by non-invasive, rapid, and cost-effective methods. To achieve this goal, clinical assessment, laboratory studies, and imaging techniques are combined.

With regard to clinical assessment, several standardized prediction rules for assessing pretest probability of acute deep-vein thrombosis or pulmonary embolism are available and can be accurately applied in inpatients and outpatients by medical staff of various degrees of training and simplified models have been successfully validated in emergency departments.

Regarding laboratory assays, measurement of d-dimer has gained a prominent role as a simple and inexpensive test for ruling out acute venous thromboembolism in patients with a low pretest probability.

Contrast venography is the most sensitive and accurate imaging test for diagnosis of deep-vein thrombosis, but is invasive and has potential contraindication. It should thus be reserved either for patients with negative non-invasive tests and a high clinical probability, or for those in whom non-invasive test are equivocal or non-feasible. Compared with venography, compression ultrasonography has a sensitivity of 97 – 100% and a specificity of around 99%. In one study, the rate of venous thromboembolism in patients with a negative ultrasound was 0.7% during a 6-month follow-up, indicating that few thromboses were missed and that anticoagulation can be safely withheld in these patients. In patients with suspected pulmonary embolism, computed tomographic pulmonary angiography (CTPA) has become the preferred imaging technique, in particular when using a multi-row-detector (MD). Ventilation-perfusion lung scanning is less attractive because of the large number of non-diagnostic readings and compression ultrasound has been shown to be unnecessary in patients with a negative MD-CTPA

Tuesday 20 October  
ASTH Symposium: Topics in Venous Thrombosis

0830-1000  
Hall D  
0910

## Cerebral Venous Sinus Thrombosis: An Update

**Andrew Lee**

*Affiliations: Flinders Comprehensive Stroke Centre, Flinders University and Medical Centre, Bedford Park, South Australia*

Cerebral venous sinus thrombosis is caused by a thrombus obstructing the draining veins of the brain and is an uncommon but important cause of stroke. In this presentation, the author will review key areas of the pathophysiology, diagnosis and treatment of this disease.

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**ASTH Symposium: Topics in Venous Thrombosis**

**0830-1000**  
**Hall D**  
**0935**

## **Post-thrombotic Syndrome: Diagnosis, Prevention and Management**

### **Kurosh Parsi**

*Sydney Children's Hospital, St. Vincent's Hospital, Sydney & UNSW, Sydney, NSW & Australasian College of Phlebology*

Post-thrombotic syndrome (PTS) presents with non-specific clinical signs and symptoms of chronic venous hypertension. The diagnostic criteria for PTS are non-specific and the recent ISTH initiative has not been helpful due to its adaptation of Villalta criteria, a collection of clinical signs that are also commonly found with chronic venous insufficiency secondary to varicose veins. Others have defined PTS based on the presence of reflux, a definition that lacks validity because reflux is not a measure of venous insufficiency but venous incompetence. The clinical signs of PTS should be correlated with the site and extent of the previous DVT and the presence of significant post-thrombotic deep vein incompetence (DVI) in a relevant anatomical distribution.

Adequate anticoagulation, as against the duration of anticoagulation, has been associated with a decreased incidence of PTS. This is presumably because adequate anticoagulation would prevent further extension of the thrombus and further damage to the venous wall. Post-thrombotic ultrasound examination should not simply look for evidence of 'residual vein thrombosis', another inaccurate term, but for the presence of sequelae of the previous thrombus which include wall thickening, septae, webbing, and double lumens. Spectral, Colour and Power Doppler examination should be performed to establish the degree and the pathway of DVI. Venous function tests including air or photo plethysmography are helpful in establishing the function of the venous system and should be incorporated into the assessment of PTS. Treatment, apart from conservative measures and compression stockings should include oblitative measures to treat any superficial venous incompetence which can be readily treated. Treatment of the superficial system can help to improve the overall venous hypertension. Modern techniques to achieve this include endovenous laser ablation and ultrasound guided sclerotherapy. In selective cases, the same techniques can be used to target and selectively occlude incompetent deep veins.

Tuesday 20 October

Nurses Symposium: Recovery, Survivorship, and Adolescents Symposium

0830-1000

Hall A

0830

## Exercise and Recovery from Cancer: From Research to Clinical Practice

**Morgan Atkinson**

*Centre for Physical Activity in Ageing, Hampstead Rehabilitation Centre, Hampstead, SA, Australia*

Treatment for Blood related disorders, including bone marrow transplantation has been associated with treatment related toxicity which can compromise recovery. Functional impairments such as muscular atrophy leading to reduced muscular strength and functional capacity, impaired pulmonary and cardiac function, reduced bone mineral density, impaired glucose tolerance and dyslipidaemia, and cancer related fatigue have been extensively documented in the literature.

Currently cancer rehabilitation is progressing towards standard practice as the evidence base increases. Studies have consistently reported that structured exercise programs for cancer patients increase muscular strength and endurance, cardiorespiratory fitness, flexibility and overall quality of life. Furthermore, studies support the use of exercise participation in reducing feelings of anxiety, depression, pain and nausea, the duration of neutropenia, thrombocytopenia, period of hospitalisation and feelings of fatigue and weakness.

Late and long term side effects and lifestyle diseases such as diabetes, cardiac disease, obesity and osteopenia are commonly reported in cancer survivors. Physical activity is an accepted treatment modality in the management and prevention of such diseases and may have implications in long term health following cancer treatment.

So with the body of evidence growing why isn't exercise an accepted treatment modality, and what should be considered as best practice in exercise rehabilitation?

**Tuesday 20 October**

**Nurses Symposium: Recovery, Survivorship, and Adolescents Symposium**

**0830-1000**

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**0900**

**Adolescent and Young Adult Issues for Cancer Care**

**Sharon Bowering**

Abstract not received at time of going to print

Tuesday 20 October  
Nurses Symposium: Recovery, Survivorship, and Adolescents Symposium

0830-1000  
Hall A  
0930

## A Survivorship Programme in South Australia

Alison Keenan<sup>1</sup>, Uwe Hahn<sup>1</sup>, Margaret Colbeck<sup>2</sup>

*Department of Haematology and Oncology<sup>1</sup>, South Australian Cancer Registry<sup>2</sup>, The Queen Elizabeth Hospital, Adelaide, South Australia*

### Background

Global evidence demonstrates that whilst the cure rate for adult-onset Hodgkin's Lymphoma (HL) is significantly higher in recent years, survivors are also at an increased risk for 'Late Effects' (LE) as a consequence of their curative treatment. Psychosocial and physical LE range from anxiety through to second malignancies and can occur many years later.

### Objective

The aim was to develop a Survivorship Programme at the Queen Elizabeth Hospital in Adelaide. Through screening, early detection of risk factors and the initiation of preventative measures, its purpose was to improve the long term outcome for survivors of adult-onset HL.

### Methods

Survivors of HL were identified from the South Australian Cancer Registry for the North Western Area Health Service. Survivors diagnosed after 1975, aged over 17 and disease-free for a minimum of five years were eligible for invitation to participate. 74 were invited: 38 accepted, 9 returned to sender and 27 did not reply.

### Results

35 survivors have been assessed; 24 females, 11 males. 3 of the female survivors had been diagnosed with breast cancer (a ratio of 1 in 8). All three had received 40Gy of upper mantle radiotherapy at a pre-menopausal age and developed breast cancer 16-21 years post treatment. For the general population the risk is 1 in 12 up to 75 years. Many patients were unaware of the risk of breast cancer and not enrolled in regular screening programs using mammography.

### Implications

Whilst the focus in this abstract is on breast cancer, the Programme identified many more Late Effects in this small cohort. It would therefore be reasonable to suggest that further studies of survivors of Hodgkin's Lymphoma are needed to increase our knowledge and consequently provide more efficacious care for this group of individuals.

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Hall C

**O069**

1030

**Invariant Natural Killer T Cells in Chronic Lymphocytic Leukaemia**

**Robert Weinkove**<sup>1,2</sup>, John Carter<sup>2</sup>, Ian Hermans<sup>1</sup>, Franca Ronchese<sup>1</sup>

<sup>1</sup> *Malaghan Institute of Medical Research, Wellington, New Zealand*

<sup>2</sup> *Blood and Cancer Centre, Wellington Hospital, Wellington, New Zealand*

**Aim**

Invariant natural killer T (iNKT) cells release proinflammatory cytokines and induce dendritic cell maturation in response to glycolipid antigens such as  $\alpha$ -galactosylceramide ( $\alpha$ GalCer) presented on the CD1d molecule.  $\alpha$ GalCer can powerfully augment anti-tumour immunity in preclinical models of cancer. We evaluated iNKT cell number, phenotype and function, and expression of CD1d on normal and leukaemic cells in patients with chronic lymphocytic leukaemia (CLL), with a view to using iNKT cells in CLL immunotherapy.

**Method**

Peripheral blood mononuclear cells were obtained from patients with untreated CLL (n=29) and healthy age-matched controls (n=29). iNKT cell number and phenotype, and CD1d expression of normal and leukaemic cells, was assessed by flow cytometry. Following immunomagnetic B cell depletion,  $\alpha$ GalCer-induced cytokine production and in vitro iNKT cell proliferation were evaluated.

**Result**

iNKT cell number was similar in patients (median 115/mL blood, range 0 – 2273) and controls (median 96/mL, range 0 – 3279). iNKT cell CD4 and CD25 status was unchanged, but CD8+ iNKT cells were significantly reduced in patients. CD1d was expressed on CLL cells in all patients, at a similar level to that of normal B cells. CD1d expression on myeloid dendritic cells and monocytes was normal.  $\alpha$ GalCer-induced production of interferon gamma, IL-4, IL-13 and IL-17 was not impaired. Although in vitro iNKT cell proliferation was modestly reduced, patient-derived iNKT cell lines were successfully generated from four of ten patients with CLL.

**Conclusion**

Patients with untreated CLL have a similar number and phenotype of iNKT cells to healthy controls, and  $\alpha$ GalCer-induced cytokine production is not impaired. CLL cells themselves express CD1d, and CD1d expression on antigen presenting cells is normal in patients with CLL. iNKT cell lines can be derived from patients with CLL. Novel immunotherapy strategies exploiting the iNKT/CD1d axis may be feasible in CLL.

*No conflict of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 5

1030-1130  
Hall C

O070

1045

## Mutation Screening of *TP53* Exons 2-11 in Chronic Lymphocytic Leukaemia Using High Resolution Melting Analysis

**Chelsee Hewitt**, Giada Zapparoli, Dennis Carney, John Seymour, David Westerman, Alexander Dobrovic  
*Peter MacCallum Cancer Centre, East Melbourne, VIC Australia.*

### Aims

Loss of 17p13 is a prognostic marker for poor survival and chemorefractoriness to alkylating agents and purine analogues in patients with chronic lymphocytic leukaemia (CLL). The target of the 17p13 deletion is thought to be the tumour suppressor gene *TP53*. It has been recently demonstrated that *TP53* mutations are an independent predictor of poor survival and chemorefractoriness in CLL. Consequently *TP53* mutation analysis is likely to become an important tool in the stratification of CLL patients for appropriate treatment. *TP53* mutations are spread throughout the gene but are thought to cluster within the DNA binding region, which stretches from the middle of exon 4 to the beginning of exon 9. However, to some extent the distribution may reflect the fact that the majority of studies limit their mutation detection to exons 5-8.

### Methods

We developed high resolution melting (HRM) assays to allow efficient high throughput screening of mutations throughout the entire coding region of *TP53* (exons 2 to 11). In a pilot study we screened 25 CLL patients using these HRM assays followed by sequencing of amplicons with aberrant melting patterns.

### Results

We identified *TP53* mutations in 40% (10/25) of the CLL patients. Eight mutations were situated within exons 5-8 (1 nonsense, 6 missense and 1 insertion). A previously reported nonsense mutation was revealed in exon 9 outside the DNA binding domain. One patient harboured 2 alterations in exon 4, a nonsense mutation within the DNA binding domain and a synonymous change outside the DNA binding domain.

### Conclusions

1. *TP53* mutations in CLL can occur outside the DNA binding domain, therefore limiting mutation screens to exon 5-8 may underestimate their prevalence.
2. HRM is a cost-effective methodology for the rapid detection of mutations, especially where the probability of a mutation in an individual exon is low.

*No conflict of interest to disclose*

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Hall C

**O071**

1100

**CCL2, CXCL2, IL-6 and IL-8 are Expressed in Primary Chronic Lymphocytic Leukaemia Cell Cultures and Enhance CLL Cell Long-Term Survival *in vitro***

**Melinda Burgess**<sup>1</sup>, Karunya Ravindranath<sup>1</sup>, Gunjeet Minhas<sup>1</sup>, Catherine Cheung<sup>2</sup>, Peter Mollee<sup>2</sup>, Nigel McMillan<sup>1</sup>, and Devinder Gill<sup>2</sup>

<sup>1</sup>Diamantina Institute for Cancer, Immunology and Metabolic Medicine, University of Queensland, Brisbane, Queensland, Australia and <sup>2</sup>Department of Oncology, Princess Alexandra Hospital, Brisbane, Queensland, Australia.

**Aim**

To investigate the role and clinical relevance of cytokines CCL2, CXCL2, IL-6 and IL-8 in the *in vitro* survival of CLL PBMC cultures.

**Methods**

PBMCs from CLL patients were purified and grown in culture at high density (10<sup>7</sup> cell/ml) for seven days before supernatants were collected and cytokines detected using the Human Cytokine Antibody Array III (Chemicon). Cultures were undertaken in the presences of these exogenous cytokines and with blocking antibodies and leukaemia cell survival was determined using trypan blue exclusion. The mRNA level of these cytokines was examined by real time PCR and results compared to age-matched normal PBMCs. In addition, expression of these cytokines receptors was also undertaken by FACS.

**Results**

The cytokines CCL2, CXCL2, IL-6 and IL-8 were found to be produced in CLL PBMC cultures. Addition of these cytokines improved *in vitro* survival of CLL cells; however, no further survival advantage resulted when these cytokines were used in various combinations. Additionally, blocking CCL2 and CXCL2 with specific antibodies resulted in the loss of this effect. Moreover, the expression of CCR2 and CXCR2 was found to decrease on CLL cells and increase on accessory cells over time in culture. Furthermore, the mRNA levels of these cytokines were elevated when compared to age-matched normal PBMCs.

**Conclusion**

The identification and increased expression of CCL2 and CXCL2 are novel in CLL culture systems and contribute to improved CLL cell survival *in vitro*. Through these chemokines, leukaemic cells and accessory cells may be able to create a supportive microenvironment for CLL.

*No conflict of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 6

1030-1130  
Meeting Rooms 1/2

**O073** **1030**  
**Temporal Differences in Mobilisation of Normal and Malignant Hematopoietic Cells by the CXCR4 Antagonist AMD3100**

**Robert Welschinger**, Florian Liedtke, Kenneth Bradstock and Linda Bendall  
*Westmead Institute for Cancer Research, Westmead Millennium Institute, NSW, Australia*

### **Introduction**

The chemokine CXCL12, and its receptor CXCR4, play a major role in the homing and engraftment of B lineage acute lymphoblastic leukemia (ALL) cells in the bone marrow (BM). Inhibition of the CXCL12/CXCR4 interaction results in ALL cell mobilisation into the blood. The separation of ALL cells from the protective BM microenvironment is likely to enhance the effectiveness of chemotherapy. However the CXCR4 antagonist, AMD3100, also mobilises normal hematopoietic stem cells (HSC) potentially increasing chemotherapy-related toxicity.

### **Aim**

To compare the temporal affects of AMD3100 on HSC and ALL cell mobilisation.

### **Methods**

The duration of AMD3100-induced mobilization of ALL cells was examined using a NOD/SCID mouse model of human ALL and compared to the kinetics of normal HSC mobilization in Balb/C mice. In NOD/SCID mice the ALL percentage and absolute cell number was measured, and in Balb/C mice Colony Forming Units (CFU) in the blood was assessed. Adhesion molecule and CXCR4 expression was determined by flow cytometry, and chemotaxis in transwell assays.

### **Results**

HSC and ALL cells showed peak mobilization between 1 and 3 hours post AMD3100 administration. However, while HSC had returned to the BM within 6 hours, in 6 of 7 ALL samples tested significant numbers of leukemic cells remained in the circulation. There was a direct correlation between the expression of CXCR4 and the mobilization of ALL cells. Comparison of the level of mobilisation following AMD3100 administration and the chemotaxis of ALL samples to CXCL12 was indicative of a positive relationship. Similarly, there was a weak negative association between VLA-5 expression and mobilization but no association between VLA-4 or CD44 expression could be detected.

### **Conclusion**

Prolonged mobilization of ALL cells by AMD3100 provides a window in which chemotherapy could be specifically targeted to circulating ALL cells after the HSC have safely returned to the BM.

*No conflict of interest to disclose*

**A144**

Tuesday 20 October  
HSANZ Free Communications 6

1030-1130  
Meeting Rooms 1 / 2

**O074**

**1045**

**Late Breaking Abstract:**

**Osteopontin expression levels are a prognostic indicator of overall patient survival in cytogenetically normal acute myeloid leukaemia**

**Jason A. Powell**<sup>1</sup>, Daniel Thomas<sup>1</sup>, Emma F. Barry<sup>1</sup>, Chung H. Kok<sup>2</sup>, Anna Brown<sup>2</sup>, Gregory J. Goodall<sup>4,5</sup>, Terence P. Speed<sup>6</sup>, Motomi Osato<sup>7</sup>, David N. Haylock<sup>8</sup>, Susan K. Nilsson<sup>8</sup>, Richard J. D'Andrea<sup>2</sup>, Angel F. Lopez<sup>3</sup> and Mark A. Guthridge<sup>1,5</sup>.

*Cell Growth and Differentiation Laboratory*<sup>1</sup>, *Cytokine Receptor Laboratory*<sup>3</sup> and *Cytokine Signaling Laboratory*<sup>4</sup>, *Centre for Cancer Biology, Division of Human Immunology, Frome Rd. Adelaide, SA, Australia.* *Department of Haematology*<sup>2</sup>, *Centre for Cancer Biology, Adelaide, SA, Australia.* *Department of Medicine*<sup>5</sup>, *University of Adelaide Frome Rd. Adelaide, SA, Australia.* *Division of Bioinformatics*<sup>6</sup>, *The Walter & Eliza Hall Institute of Medical Research, Parkville, VIC, Australia.* *Cancer Science Institute of Singapore, National University of Singapore, Singapore*<sup>7</sup>. *Australian Stem Cell Centre, Monash University, Clayton, VIC, Australia.*<sup>8</sup>.

Acute myeloid leukemia (AML) remains a devastating haematological disease with overall 5 year survival rates in adults of <40%. Cytogenetic analysis remains an important tool for assigning treatment selection and for assessing patient prognosis. However, normal karyotype AML constitutes the largest subset of AML with patients demonstrating diverse responses to therapy and few prognostic indicators. Furthermore, the mechanisms by which normal karyotype patients fail to respond to chemotherapy may not solely reside within blasts themselves but depend on an interaction between the leukaemia stem/progenitor cells and stromal factors in the microenvironment. To discover new functional prognostic markers in AML we performed a global expression screen for cytokine-regulated hemopoietic cell survival genes. This screen examined a specific cell survival pathway emanating from Ser585 of the  $\beta$ c subunit of the IL-3/GM-CSF receptor<sup>1</sup>. Importantly, we have shown that while this Ser585 survival pathway is tightly regulated in normal primary myeloid cells, it is constitutively activated in AML<sup>2</sup>. We show that gene targets of this Ser585 survival pathway were over-expressed in AML. Importantly, we validated osteopontin (*OPN*) as a *bone fide* target of the Ser585 survival pathway and siRNA-mediated knockdown of *OPN* expression induces cell death in both primary AML blasts as well as in CD34<sup>+</sup>CD38<sup>+</sup>CD123<sup>+</sup> leukemic stem/progenitor cells<sup>3</sup>. We quantified *OPN* mRNA expression in a multicentre cohort of 60 normal karyotype AML samples from patients that received standard induction chemotherapy to test the effect of *OPN* expression on patient outcome. Multivariate analysis indicated that patients with high *OPN* expression had a significantly shorter overall survival (median 384 days) compared to patients with low *OPN* expression (median 1017 days)(n=60, p=0.01, HR=2.22, 95%CI 1.23-4.02). These results identify *OPN* as a new prognostic indicator with therapeutic potential in normal karyotype AML and suggests *OPN* may contribute to leukemic stem/progenitor cell survival and resistance to chemotherapy.

1 Guthridge MA, Stomski FC, Barry EF, et al. Site-specific serine phosphorylation of the IL-3 receptor is required for hemopoietic cell survival. *Mol. Cell.* 2000;6(1):99-108.

2. [Guthridge MA, Powell JA, Barry EF](#), et al. (2006) Growth factor pleiotropy is controlled by a receptor Tyr/Ser motif that acts as a binary switch. *EMBO J.* 2006;25(3):479-85.

3. Powell JA, Thomas D, Barry EF, et al. Expression profiling of a hemopoietic cell survival transcriptome implicates osteopontin as a functional prognostic factor in AML. *Blood.* 2009; In press.

*I have no conflicts of interest to declare*

Tuesday 20 October  
HSANZ Free Communications 6

1030-1130  
Meeting Rooms 1 / 2

O075

1100

## The GM-CSF Receptor Utilises $\beta$ -catenin and TCF4 to Specify Macrophage Lineage Differentiation

Anna Brown<sup>1,2,3</sup>, Diana Salerno<sup>1,2</sup>, Chris Wilkinson<sup>2,3</sup>, Teresa Sadras<sup>1,3</sup>, Chung Kok<sup>3,4</sup>, Michelle Perugini<sup>1,2</sup>, Gregory Goodall<sup>1</sup>, Thomas Gonda<sup>5</sup> and Richard D'Andrea<sup>1,2,3,4</sup>

<sup>1</sup> Centre for Cancer Biology, SA Pathology, Adelaide, South Australia, Australia.

<sup>2</sup> Women's and Children's Health Research Institute, Adelaide, South Australia, Australia

<sup>3</sup> University of Adelaide, Adelaide, South Australia, Australia

<sup>4</sup> Queen Elizabeth Hospital, Adelaide, South Australia, Australia.

<sup>5</sup> Diamantina Institute, University of Queensland, Brisbane, Australia.

### Background

Over the past several years we have used a factor-dependent murine bi-potential cell line, FDB1, in combination with activated mutants of the GM-CSF receptor common beta subunit (h $\beta$ c) to dissect signalling and gene expression changes that can contribute to differences in myeloid cell differentiation and growth.

### Aim

To determine the mechanisms through which signalling from a single receptor can induce two distinct cell fates (the choice between Granulocyte and Macrophage lineages).

### Methods

We have used two derivatives of an activated h $\beta$ c mutant with an extracellular duplication (F1 $\Delta$ ) where the presence or absence of a single intracellular tyrosine residue (Y577), can specify bi-lineage Granulocyte-Macrophage differentiation or Macrophage-only differentiation respectively (Brown et al., 2004). Transcriptional profiling of these differentiation states has allowed us to identify genes with altered expression associated with either terminal granulocyte or macrophage differentiation. Signalling pathways correlated with transcriptional changes and differentiation states were also examined.

### Results

An examination of the genes displaying expression correlating with macrophage differentiation revealed a potential role for the transcription factor TCF4/TCF7L2 which is a central mediator of the canonical Wnt signalling pathway through its role as the DNA binding co-factor for  $\beta$ -catenin. TCF4/TCF7L2 is also a transcriptional target gene of this pathway. Further examination of signalling in these cells identified that stabilisation of  $\beta$ -catenin was associated with the switch to macrophage-only differentiation and that endogenous GM-CSF signalling also induces  $\beta$ -catenin stabilisation during GM differentiation. Stabilisation of  $\beta$ -catenin and GM differentiation could also be induced using the GSK3 $\beta$  inhibitor BIO (6-bromoindirubin-3'-oxime), indicating that this pathway for regulation of  $\beta$ -catenin protein stability is intact in FDB1 cells.

### Conclusion

Using the FDB1 model of myeloid differentiation we have identified a previously uncharacterised role for  $\beta$ -catenin/TCF signalling downstream of myelopoietic cytokine receptor activation during myeloid differentiation.

*No conflict of interest to disclose*

Brown, AL, Peters, M, D'Andrea, RJ, and Gonda, TJ (2004). Constitutive mutants of the GM-CSF receptor reveal multiple pathways leading to myeloid cell survival, proliferation, and granulocyte-macrophage differentiation. *Blood* 103, 507-516.

A146

Tuesday 20 October  
HSANZ Free Communications 6

1030-1130  
Meeting Rooms 1/2

**O076**

1115

## **Characteristics of Bone Marrow Derived Mesenchymal Stromal Cells in Myelodysplasia**

**Lawrence Jyh Yeu Liew**<sup>1 2</sup>, Marian Sturm<sup>2</sup>, Anna Cook<sup>3</sup>, Kathryn Shaw<sup>2</sup>, Richard Herrmann<sup>2 4</sup> and Benedict Carnley<sup>4</sup>

<sup>1</sup> School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia

<sup>2</sup> Cell and Tissue Therapies Western Australia, Royal Perth Hospital, Perth, Western Australia

<sup>3</sup> School and Biomedical Sciences, Curtin University of Technology, Bentley, Western Australia

<sup>4</sup> Department of Haematology, Royal Perth Hospital, Perth, Western Australia

Immune dysregulation has been implicated in the pathogenesis of myelodysplasia (MDS). Recent studies indicate that a rare population of bone marrow cells, mesenchymal stromal cells (MSC), may play a role in the modulation of normal immune cells and malignant clones in MDS. In this study, MSC from MDS patients (MDS-MSC) were characterised and compared to those of healthy donors.

MSC were isolated from bone marrow aspirates of MDS patients (n=4) and healthy donors (n=6) using density gradient centrifugation. These cells were culture expanded and characterised for the expression of established MSC phenotype of CD73, CD90 and CD105, and lack of haemopoietic markers CD14, CD34 and CD45 using flow cytometry. Growth kinetics of MSC to passage (P) 4 were recorded and the differentiation capabilities of these cells determined. Immune regulatory actions of MSC on peripheral blood mononuclear cells (MNC) were examined using Cell Titre Aqueous One™ proliferation assay and IL-6 production measured using BD FACSAarray bioanalyser™. Cytogenetics and DNA analysis for *FLT3* mutation were performed.

MDS-MSC expressed normal MSC phenotype and underwent multi-lineage differentiation when stimulated. Cytogenetic and DNA analysis of this small cohort of MDS-MSC revealed normal karyotype with no *FLT3* mutation detected. MDS-MSC displayed slower growth kinetics (paired T test; ± standard error of mean (SEM); P<0.05; 88days vs. 56days to reach P4) and produced higher levels of IL-6 in culture, as compared to MSC from healthy individuals (unpaired T test; ± SEM; P<0.05; 2576pg/ml vs. 1406pg/ml at 24hrs; 4676pg/ml vs. 1868pg/ml at 96hrs). In addition, as for normal MSC, MDS-MSC inhibited the proliferation of healthy MNC in co-culture.

Preliminary results indicate that MDS-MSC have a role in the inhibition of immune cells. The observation *in vitro* that MDS-MSC produced significantly higher levels of IL-6 may reflect the *in vivo* MDS bone marrow microenvironment and may contribute to the disease

*No conflict of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 7

1030-1130  
Meeting Rooms 10/11

**O077** **1030**  
**EBV-specific T Cells As Therapy for Relapsed / Refractory EBV-Positive Lymphomas**

**Frank Vari**<sup>1</sup>, Rajiv Khanna<sup>1</sup>, Erica Han<sup>1</sup>, Kimberley Jones<sup>1</sup>, Sanjleena Singh<sup>1</sup>, David Ritchie<sup>2</sup> and Maher Gandhi<sup>1</sup>

<sup>1</sup> Queensland Institute of Medical Research, Herston, QLD

<sup>2</sup> Peter MacCallum Cancer Centre, East Melbourne, Vic

We and others have shown a critical pathogenetic link between Epstein-Barr Virus (EBV) and the development of a range of malignant lymphomas, including Hodgkin's, DLBCL, PTLID and ENKTL. These occur in the immunosuppressed and the 'overtly' immunocompetent who demonstrate a selective impairment of EBV immunity. The presence of EBV within the lymphoma cell is an adverse prognosticator but is also a potential target. Restoration of EBV-specific T cell immunity is an attractive therapeutic option. We hypothesize that adoptive immunotherapy of clinical grade EBV EBNA1-LMP1/2 specific T cells for relapsed / refractory EBV-positive lymphomas is safe, results in reconstitution of anti-viral immunity, and induces tumour lysis. We have recently commenced an NHMRC phase I clinical trial of adoptive immunotherapy of *in-vitro* expanded, EBV-specific cytotoxic T lymphocytes (CTL) in EBV-positive lymphomas. This utilizes a novel replication-deficient adenoviral construct ("AdE1-LMPpoly") that encodes specific EBV proteins expressed by all latency II and III EBV-positive lymphomas. CTL are generated in QIMR's cGMP licensed facility. Previous methodology was slow, technically demanding and resulted in CTL with minimal EBNA1 specificity. Our approach is a new technology that circumvents these limitations and utilizes a highly efficient, but relatively brief, autologous EBV-specific CTL expansion protocol. To date 4 patients have been enrolled (2 Lymphomatoid Granulomatosis [LYG], 1 Hodgkin's, 1 DLBCL). In all cases clinical grade EBV-specific CTL were generated. CTL were re-infused in both LYG patients. In the first a short-lived remission was induced including complete eradication of skin lesions with demonstrable anti-viral efficacy but subsequent relapse of disease, but interestingly no return of skin disease. In the second patient remission was induced and is ongoing. Our data although preliminary, indicates that this approach is potentially feasible, safe and efficacious. The trial is ongoing and aims to recruit a further 16 patients.

*No conflict of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 7

1030-1130  
Meeting Rooms 10/11

**O078**

1045

## **Epstein-Barr Virus Specific Cytotoxic T Cells for Clinical Use in Immune Reconstitution Post Haemopoietic Stem Cell Transplant**

**Emily Blyth**<sup>1</sup>, Leighton Clancy<sup>2</sup>, Upinder Sandher<sup>3</sup>, Rajiv Khanna<sup>4</sup>, David Gottlieb<sup>3</sup>

<sup>1</sup> Westmead Millennium Institute, Westmead, NSW, Australia. <sup>2</sup> Sydney Cellular Therapies laboratory, Westmead, NSW, Australia. <sup>3</sup> Blood and Marrow Transplant Service, Westmead Hospital, Westmead, NSW, Australia. <sup>4</sup> Queensland Institute for Medical Research, Herston, QLD, Australia

### **Introduction**

Uncontrolled EBV replication can lead to life threatening post-transplant lymphoproliferative disorder (PTLD). The incidence of EBV reactivation and PTLD is proportional to the degree of cellular immunosuppression. Treatment with EBV specific cytotoxic T lymphocytes (CTL) effectively controls EBV replication but the generation of CTL using autologous EBV-transformed B cells as stimulators is cumbersome.

### **Aim**

To develop a rapid and reliable method for production of a clinical grade EBV specific T cell product using an adenoviral vector encoding genes for EBNA-1 and immunogenic LMP peptides.

### **Method**

Monocyte derived dendritic cells (DC) were generated from peripheral blood by adherence to plastic and exposure to IL-4 and GM-CSF. DC were transfected with a clinical grade adenoviral vector encoding EBNA-1 and HLA Class I epitopes of LMP-1 and LMP-2a and matured with TNF. Mature DC were used to stimulate non-adherent cells. Cultures continued for 21 days with a second stimulation on day 7 in the presence of increasing doses of IL-2. The cellular product was analysed on day 21 for phenotype, antigen specificity and functional capacity by tetramer staining, cytokine production in response to antigen stimulation and cytotoxicity.

### **Results**

Cellular proliferation was seen in all of 10 EBV seropositive normal donors with a mean fold increase in total cell number of 5.25 (SEM 1.094). In all donors, the cellular product was mainly T cells (mean CD3+ 94.7%, range 81 to 99.4) with both CD4 (mean 65.7% of CD3, range 17.0 to 93.2) and CD8 cells present (mean 29.6%, range 4.4 to 74.4). EBV specificity was demonstrated by tetramer staining or intracellular cytokine detection in 70% of donors. Tetramer analysis of HLA-A2 positive donors showed up to 429-fold expansion of LMP-2a tetramer specific CD8 cells. Cytokine responses to stimulation with EBNA, LMP and adenoviral peptides were present in both CD4 and CD8 cells and showed significant individual variation. Cytotoxic activity was seen with up to 75% specific lysis of EBV antigen coated targets.

### **Conclusion**

The use of an adenoviral vector containing genes encoding EBNA-1 and LMP antigens allows the rapid generation of a clinical grade EBV-specific T cell product from the majority of EBV seropositive normal donors. This technique will permit the incorporation of adoptive immunotherapy for EBV into routine haemopoietic stem cell transplantation.

*There are no conflicts of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 7

1030-1130  
Meeting Rooms 10/11

**O079**

**1100**

## **Comparison of Cytomegalovirus (CMV) pp65 Specific T Cell Generation from Mobilised Peripheral Blood Stem Cell (PBSC) Collections and Whole Blood**

**Leighton Clancy**<sup>1,3</sup>, Emily Blyth<sup>3,4</sup>, Upinder Sandher<sup>3</sup> and David Gottlieb<sup>1,2,3,4</sup>

<sup>1</sup> *Sydney Cellular Therapies Laboratory, Westmead Hospital, Sydney, Australia*

<sup>2</sup> *Westmead Hospital, Sydney, Australia*

<sup>3</sup> *Westmead Millennium Institute, Sydney, Australia*

<sup>4</sup> *University of Sydney, Sydney, Australia*

### **Introduction**

CMV reactivation post allogeneic haemopoietic stem cell transplant (HSCT) can cause significant morbidity. We have recently conducted two clinical trials of *ex vivo* expanded donor derived CMV specific T cells given prophylactically to HSCT recipients. Our ongoing investigations suggest this strategy is safe and controls reactivation without the need for antiviral therapy. Our approach requires 100mls of donor blood to be collected before stem cell mobilisation. This can result in significant logistical and regulatory obstacles which could be alleviated if a proportion of the mobilised PBSC product in excess of that required for HSCT could be allocated to generate CMV specific T cells.

### **Aims**

The aim of this study was to compare the generation of CMV specific T cells from mobilised PBSC harvests to whole blood obtained prior to stem cell mobilisation.

### **Methods**

Samples consisted of 1.6-1.8ml (<1%) of PBSC products or 100mls of blood from transplant donors. Mononuclear cells were isolated and dendritic cells (DC) generated. DC transfected with a clinical grade vector encoding CMVpp65 were co-cultured with PBMC to stimulate expansion of T cells. Cultures were re-stimulated after 7 days and continued for 14 days.

### **Results and Discussion**

There was a 14.5-17 fold increase in cell number in cultures from PBSC harvests consisting primarily of T cells (range 92.6-98.3%). In one donor, there was a 100 fold increase in T cells recognizing the HLA-A2 restricted epitope NLVPMVATV (49% of CD8 T cells). 15% of CD8 T cells recognised a HLA-A24 restricted epitope in a second donor. In cultures from whole blood we observed a 7.9-10.1 fold increase in cell number. Cultures were mainly T cells (75.2-80%) but contained more NK cells (>20%). Differences were observed in CD4:CD8 ratio and percentage of CMV tetramer<sup>+</sup> cells. This study shows CMV specific T cells can be generated from PBSC harvests, however further work is required to compare T cell function in cells generated from mobilised PBSC harvests.

*No conflict of interest to disclose*

**A150**

**Tuesday 20 October**  
**HSANZ Free Communications 7**

**1030-1130**  
**Meeting Rooms 10/11**

**O080**

**1115**

**Developing a Therapeutic Anti - Dendritic Cell Antibody to Prevent GVHD**

**Derek Hart<sup>2</sup>**, Therese Seldon<sup>1</sup>, Martina Jones<sup>2</sup>, Yonghua Sheng<sup>1</sup>, Anna Palkova<sup>1</sup>, Hannah Cullup<sup>1</sup>, Trent Munro<sup>2</sup>, Alison Rice<sup>1</sup>, John Wilson<sup>1</sup>, Ross Barnard<sup>2</sup>, Stephen Mahler<sup>2</sup>, David Munster.

<sup>1</sup> Mater Medical Research Institute. <sup>2</sup> University of Queensland.

Graft versus host disease (GVHD) following allogeneic haematopoietic stem cell transplantation (alloHSCT) is the major contributor to transplant related mortality. The risk of GVHD limits the application of alloHSCT and current immunosuppressive strategies, which focus on controlling donor T cell responses using nonspecific agents, increase the risk of leukaemia recurrence and post transplant infections, including the reactivation of pre-existing cytomegalovirus (CMV) infections. Host and donor dendritic cells (DC) stimulate alloreactive donor T lymphocytes, and initiate GVHD. We have shown that polyclonal antibody to the DC surface activation marker human CD83 (anti hCD83), which depletes activated DC, can prevent human DC and T cell induced lethal xenogeneic GVHD without impairing T cell mediated anti-leukaemic and anti-viral (CMV and influenza) immunity (J Exp Med 2009; 206: 387). Therefore, we investigated the effect of polyclonal anti mCD83 antibody in both autologous and allogeneic murine HSCT models. The anti mCD83 had no effect on autologous HSC engraftment and we confirmed that it delayed acute GVHD, at least as effectively as cyclosporin A in a fully MHC mismatched combination. We are currently developing humanized mouse models that will, in conjunction with our established mouse alloHSCT models, enable us to test whether the anti leukaemic CTL capacity in anti CD83 treated recipients will control leukaemia recurrence.

Based on these preclinical studies, we are developing a humanized monoclonal antibody against hCD83, to test as a new therapeutic immunosuppressive agent. We have panned single chain variable fragment (scFv) phage libraries on recombinant human CD83 extracellular domain and isolated six phage clones that bind to CD83. After screening for specificity and affinity, the clones are reformatted to human IgG1 and expressed as whole immunoglobulin by transfected CHO cells. The purified antibodies are tested further, including in a functional assay (mixed lymphocyte reaction (MLR)). To date, we have reformatted and tested two of the six clones. One has lost binding affinity for antigen, probably as a result of immunoglobulin variable region glycosylation, which does not occur with prokaryote expressed scFv. The other reformatted anti-CD83 clone binds and is functionally active as it blocks a mixed leucocyte reaction (MLR), by an antibody dependent cellular cytotoxicity mechanism.

This clone and others in the pipeline will be subjected to preclinical testing in the humanized NOD-SCID mouse of human cell induced lethal GvHD. The most effective antibody, which prevents GVHD without impairing the desired graft versus leukaemia effect of alloHSCT will then be developed for phase 1 clinical trials in clinical alloHSCT.

*No conflict of interest to declare*

Tuesday 20 October  
HSANZ Free Communications 8

1030-1130  
Meeting Room 3

**O081**

**1030**

## **Determinants of Survival in Australian Patients With AL Amyloidosis**

**Peter Mollee**<sup>1</sup>, Jill Tate<sup>2</sup>, Kirk Morris<sup>3</sup>, Jeremy Wellwood<sup>4</sup>, Martin Browne<sup>5</sup>, Paula Marlton<sup>1</sup>, Robert Bird<sup>1</sup>, Anthony K Mills<sup>1</sup>, Peter Wood<sup>1</sup>, Sally Mapp<sup>1</sup>, Devinder Gill<sup>1</sup>.

<sup>1</sup>*Department of Clinical and Laboratory Haematology, Pathology Queensland and Princess Alexandra Hospital, Brisbane, Australia*

<sup>2</sup>*Department of Chemical Pathology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia*

<sup>3</sup>*Division of Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, Australia*

<sup>4</sup>*Department of Haematology, Gold Coast Hospital, Southport, Australia*

<sup>5</sup>*Cancer Centre, Coffs Harbour, Australia*

### **Aim**

As there are few reported cohorts of patients with AL amyloidosis in Australia, we aimed to assess the characteristics and outcomes of such patients referred to a single centre.

### **Methods**

A retrospective analysis of consecutive patients with symptomatic AL amyloidosis was performed, identifying prognostic variables and the impact of haematologic and organ responses on survival. AL amyloidosis associated with overt myeloma was excluded. Organ involvement, and haematologic and organ responses were defined as per the International Society of Amyloidoses consensus criteria.

### **Results**

52 pts with AL were referred between Jan'99 and Jun'09: median age 61 yrs; 33% female. AL was lambda light chain restricted in 67% and the FLC ratio was abnormal in 94%. 47% had an ECOG performance status of  $\geq 2$ . Organ involvement: renal 62%; cardiac 69%; liver 22%; and neurologic 41%. Initial therapy was autologous stem cell transplantation (n=12), melphalan and dexamethasone (n=29), other chemotherapy regimens (n=2), and 9 received no treatment. On an intent-to-treat basis 30% achieved haematologic CR, 28% PR and 42% had no response. 29% achieved an organ response at a median of 5 months post-therapy (range 1 to 16 months). With a median follow-up of 19 months, median overall survival was 25 months. In univariate analysis, inferior survival was predicted by worse ECOG performance status ( $p < 0.0001$ ), weight loss ( $p = 0.0005$ ), syncope ( $p = 0.04$ ), absence of renal involvement ( $p = 0.02$ ), cardiac involvement ( $p = 0.005$ ), liver involvement ( $p = 0.004$ ), a postural drop in blood pressure  $\geq 20$ mmHg, and number of organs involved ( $p = 0.05$ ). Amongst treated patients, haematologic response ( $p < 0.0001$ ) and organ response ( $p < 0.0001$ ) strongly predicted survival, although CR did not provide additional benefit over PR.

### **Conclusions**

Patients with AL amyloidosis continue to have a poor prognosis which is predominantly influenced by performance status and extent of organ, particularly cardiac, involvement. Achievement of a haematologic PR is a powerful predictor of survival and is the critical initial goal of therapy.

*No conflict of interest to disclose*

**A152**

Tuesday 20 October  
HSANZ Free Communications 8

1030-1130  
Meeting Room 3

**O082**

1045

## **Bone Marrow Plasma Cells at Diagnosis of Waldenstrom's Macroglobulinemia**

**Sant-Rayn Pasricha**<sup>1</sup>, Andrew Lim<sup>2</sup>, David Westerman<sup>2,3</sup>, Surender Juneja<sup>1,2,3</sup>, Neil Came<sup>1,2,3</sup>

1. *The Royal Melbourne Hospital (RMH), Parkville, Victoria, Australia.*
2. *Peter MacCallum Cancer Centre (PeterMac), East Melbourne, Victoria, Australia.*
3. *University of Melbourne, Parkville, Victoria, Australia.*

### **Aim**

The diagnostic and prognostic significance of the bone marrow plasma cell (PC) component in Waldenstrom's Macroglobulinaemia (WM) is unknown. Because WM lacks a hallmark immunophenotype or molecular-cytogenetic abnormality, we investigated whether the PC compartment offers useful additional information at diagnosis.

### **Method**

Percentage and topography of B-lymphocytes and PCs in the marrow were defined in 5% increments by consensus between two observers interpreting immunohistochemistry in patients presenting with WM between 1999-2009 at RMH and PeterMac. B-lymphocytic infiltration was classified as: Scattered-nonaggregated, interstitial, peri-sinusoidal, nodular, and diffuse. PC infiltration was classified as: Scattered-interstitial, peri-vascular, microaggregates ( $\geq 10$  non-peri-vascular PCs), permeative (occupying at least one inter-fat space), or nodular (effacement of fat-space/s). Associations between percentage and pattern of marrow B-lymphocytes, PCs, and monoclonal serum IgM were also investigated.

### **Result**

Thirty-nine patients (10F:29M) presented with monoclonal serum IgM between 4-64g/L (median 21g/L). The most common pattern of B-lymphocytic infiltration was interstitial (33/39, 84.2%); 12/39(28.9%) demonstrated a nodular component; 8/39(21.1%) paratrabeular; and three (7.9%) peri-sinusoidal. PC burden ranged between 1-30% (median 5%) and was  $>5\%$  in the majority (33/39, 85%). Distribution was peri-vascular in 37/38(97.4%); scattered-interstitial, 22/38(57.9%); micro-aggregates, 7/38(18.4%); and permeative, 4/38(10.5%). Plasma cells outnumbered B-lymphocytes in 4/39(10.3%). No nodules were identified. Notably, bone marrow PC percentage was positively associated with serum IgM ( $p < 0.01$ , Spearman's rank), as was the character of the infiltrate (microaggregates  $p < 0.05$  and permeative  $p < 0.05$ , Wilcoxon rank sum; interstitial and perivascular, no association). B-lymphocyte percentage was not associated with paraprotein level.

### **Conclusion**

Marrow plasmacytosis at time of diagnosis of WM is usually modest and often peri-vascular. However, higher PC burden, presence of microaggregates, and permeative changes all appear related to higher IgM. Changes to PC compartment following treatment and their correlation with outcome in WM require evaluation.

*No conflict of interest to disclose*

Tuesday 20 October  
HSANZ Free Communications 8

1030-1130  
Meeting Room 3

O083

1100

## Borderline High Serum Free Light Chain (FLC) Kappa:Lambda Ratios Are Seen Not Only in Dialysis Patients, But Also in Non-Dialysis Dependent Renal Impairment and Inflammatory States

George Marshall<sup>1</sup>, Jill Tate<sup>1</sup>, Peter Mollee<sup>2</sup>

<sup>1</sup>Department of Chemical Pathology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia

<sup>2</sup>Haematology Department, Pathology Queensland, Princess Alexandra Hospital, Brisbane, Australia

### Aim

An abnormal FLC ratio (normal range 0.26-1.65) is "diagnostic" of clonal plasma cell or lymphoproliferative disorders, although renal reference intervals (extending ULN from 1.65 to 3.1) are required when interpreting the FLC ratio in patients on dialysis. As we have noted other patients with false positive borderline FLC ratios we further characterised the clinical features of these patients.

### Methods

We performed a retrospective audit of FLC assays performed between 1/1/2006 and 13/9/2008 at three hospitals and correlated cases with a borderline abnormal ratio (arbitrarily defined as 0.13-0.25 and 1.66-3.2) with their renal function, laboratory measurements of inflammatory parameters, serum and urine protein electrophoresis, clinical features and their final clinical diagnosis.

### Results

2524 FLC assays were requested in 955 patients. Of these, 374 tests in 214 patients had a borderline FLC ratio of which 324 tests were from 167 patients known to have a plasma cell dyscrasia. Thus, 47 patients (4.9%) had a borderline abnormal ratio and no known plasma cell disorder: median age 71yrs; median eGFR 34mls/min/1.73m<sup>2</sup> (range 5-90); median clinical follow-up post FLC assay 264 days. All 47 patients had a borderline high kappa:lambda FLC ratio ranging from 1.67 to 3.2, median kappa FLC 110mg/L (range 12 to 580) and median lambda FLC 49mg/L (range, 7 to 300). No patient without clonal disease had a borderline low ratio. 33 patients (72%) had eGFR < 50ml/min/1.73 m<sup>2</sup>, six being dialysis dependent. Other diagnoses besides renal impairment included infection or gangrene (n=9), chronic liver disease (n=7), malignancy (n=3), colitis (n=2), vasculitis (n=1) and rheumatoid arthritis (n=1). 56% of patients had features on serum protein electrophoresis suggestive of an inflammatory process.

### Conclusions

Patients without plasma cell dyscrasias may have borderline high FLC ratios in the setting of non-dialysis dependent renal failure as well as in patients with a polyclonal inflammatory response even in the absence of renal impairment.

*No conflict of interest to disclose*

A154

Tuesday 20 October  
HSANZ Free Communications 8

1030-1130  
Meeting Room 3

**O084**

1115

**The Potential role of Curcumin (diferuloylmethane) in Patients with MGUS [Monoclonal Gammopathy of Undetermined Significance]**

**Terry Golombick** and Terry Diamond  
*Dept Endocrinology, St George Hospital*

**Aims**

To determine whether curcumin can decrease paraprotein load and reduce bone resorption in MGUS patients.

**Methods**

26 patients randomised into 2 groups on a 2:1 randomisation: Group A patients administered curcumin at the start, then crossed over to placebo. Group B patients administered placebo, then crossed over to curcumin. Full blood count, B2 microglobulin, serum paraprotein and immunoglobulin electrophoresis determined. Urine was collected for uNTx measurements.

Group values expressed as the mean  $\pm$  standard error of the mean. Data from different time intervals within groups compared using paired student t-test. Statistical significance assigned as  $P < 0.05$ .

**Results**

Serum paraprotein concentration ranged from 8-36g/L, with a median value of 20g/L. Of the 17 patients who were commenced on curcumin, 10 had a baseline serum paraprotein level  $\geq$  to 20g/L and 7  $<$  20g/L. In patients with a serum paraprotein  $\geq$  20g/L, fifty percent of these had a 12-30% decrease in serum paraprotein levels in response to curcumin. The most significant decrease was seen at V2 ( $p < 0.05$ ). This decrease remained stable in most patients until they were crossed over to placebo. Patients with a baseline serum paraprotein  $<$  20g/L did not show a response to curcumin. In contrast to a decrease in serum paraprotein seen in patients initiating curcumin therapy, patients receiving placebo demonstrated stable or increased serum paraprotein levels. Twenty seven percent of patients showed a decrease in their uNTx levels when taking curcumin, but the change in uNTx did not reach statistical significance.

**Conclusions**

Currently no treatment is recommended for MGUS. Given the uncertainty of disease progression to multiple myeloma, early intervention with the aim of reducing the paraprotein load and the potential negative effects on the skeleton would provide an innovative therapeutic tool. Our pilot study suggests that curcumin may decrease both serum paraprotein and uNTX in a select group of patients with MGUS (paraprotein levels  $\geq$  20 g/L). These findings warrant further investigation.

*No conflict of interest to disclose*

Tuesday 20 October  
ASTH Free Communications 2

1030-1130  
Hall D

O085

1030

## **Lepirudin Use and Laboratory Monitoring in Patients on Chronic Haemodialysis with a history of Heparin-induced Thrombocytopenia(HIT)**

**Chee Wee Tan**<sup>1,2</sup>, Margaret About<sup>1,3</sup>, Tim Pianta<sup>4</sup>, Christopher Ward<sup>1,2</sup>

<sup>1</sup>*Northern Blood Research Centre, University of Sydney, NSW, Australia*

<sup>2</sup>*Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, St. Leonards, NSW, Australia*

<sup>3</sup>*Pacific Laboratory Medical Services (PaLMS), Royal North Shore Hospital, St. Leonards, NSW, Australia*

<sup>4</sup>*Department at Renal Medicine, Royal North Shore Hospital, St. Leonards, NSW, Australia*

### **Aim**

The use of anticoagulants to maintain circuit patency in chronic hemodialysis patients with a previous history of HIT remains challenging. A worldwide shortage of danaparoid has led to increasing use of the direct thrombin inhibitor, lepirudin, which accumulates in renal failure. We report the use of lepirudin, and subsequent monitoring via the activated partial thromboplastin time(APTT) and ecarin clotting time(ECT) in 2 patients. Actin FS was the APTT reagent used.

### **Method**

Both patients were on long-term hemodialysis via polysulfone based high flux haemodialysers (studies have shown these membranes to be permeable to lepirudin). Lepirudin was commenced at a dose of 0.1 mg/kg pre dialysis (2-3 times/week). Pre and post-dialysis blood samples were obtained from the arterial needle of the arterio-venous fistula/graft. Pooled normal samples were used to obtain a normal range for APTT and ECT. Lepirudin concentrations of patient samples were obtained via interpolation of a standard curve obtained by spiking pooled normal samples with increasing lepirudin concentrations.

### **Results**

Elevations in APTT and ECT occurred in both patients, suggesting systemic absorption of lepirudin. Initially, there was increased bleeding (epistaxis) in one patient, accompanied by raised APTT. There was persistent clotting of the dialysis circuit in the other patient. Dose adjustments occurred in both patients. At sub-therapeutic to near therapeutic concentrations of lepirudin (0.1-0.6ug/mL), APTT appeared to be more sensitive to dose changes than ECT. With increasing lepirudin concentrations, the linear dose response was maintained with ECT, whereas a plateau response was observed with APTT.

### **Conclusion**

The use of lepirudin in chronic haemodialysis is safe in this setting. It requires frequent laboratory monitoring, with lepirudin retention in the systemic circulation post dialysis and unpredictable lepirudin loss during dialysis. At sub-therapeutic to near therapeutic lepirudin concentrations, APTT is more sensitive to dose adjustments than ECT.

*No conflict of interest to disclose*

A156

Tuesday 20 October  
ASTH Free Communications 2

1030-1130  
Hall D

**O086**

1045

## **Heparin-induced Thrombocytopenia (HIT): Evaluation of Soluble Platelet Glycoprotein VI as a Biomarker for HIT**

Huy Tran,<sup>1</sup> Mohammad Al-Tamimi,<sup>2</sup> George Grigoriadis,<sup>1</sup> Hatem Salem,<sup>1,2</sup> Ross I Baker,<sup>3</sup> Erica Malan,<sup>4</sup> Michael C. Berndt,<sup>5</sup> Robert K. Andrews,<sup>2</sup> and **Elizabeth E Gardiner**<sup>2</sup>  
<sup>1</sup>Haematology Department, Alfred Hospital, and <sup>2</sup>Australian Centre for Blood Diseases, Monash University, Alfred Medical Research & Education Precinct (AMREP), Melbourne, Victoria, Australia; <sup>3</sup>Department of Haematology, and Centre for Thrombosis and Haemophilia, Murdoch University, Royal Perth Hospital, Perth, Australia; <sup>4</sup>Monash Medical Centre Haematology Laboratory Clayton Campus, Melbourne Victoria; <sup>5</sup>College of Medicine and Health, University College Cork, Cork, Ireland

Heparin-induced thrombocytopenia and thrombosis (HITT) is a serious adverse event associated with the widespread use of heparin as an inexpensive, fast-acting and reversible anticoagulant. The final diagnosis of HIT is still based on clinical suspicion as not all heparin/PF4 antibodies cause HIT, and the results from currently available assays for HIT-related Ig or its functional effects on platelets may be negative despite a convincing clinical picture. Consequently, it is difficult to distinguish HIT patients at risk of thrombosis from non-thrombotic HIT. Our previous studies showed that the platelet-specific receptor, glycoprotein (GP)VI, is stable on normal circulating platelets, but undergoes metalloproteinase-mediated ectodomain shedding in response to Fc $\alpha$ R1IIa-mediated platelet activation to HIT antibodies *in vitro*.

### **Aim**

To determine whether soluble GPVI (sGPVI) is an early biomarker of HIT pathology.

### **Methods**

We used an enzyme-linked immunosorbent assay (ELISA) to measure shed sGPVI in plasma from patients at risk or confirmed to have HIT.

### **Results**

Initial studies showed sGPVI levels in plasma from 192 healthy individuals (19.5 $\pm$ 15.4 ng/mL) were independent of age, gender and common GPVI polymorphisms (associated with Gln317/Leu). In contrast, sGPVI levels in HIT patients ranged from normal to >180 ng/mL (mean 81 $\pm$ 37.9 ng/mL) in plasma samples collected at the onset of thrombocytopenia. Levels of sGPVI tended to be higher in confirmed HIT with high anti-heparin/PF4 antibody compared to low antibody levels.

### **Conclusions**

These findings suggest a potential correlation between HIT-related Ig and plasma levels of sGPVI *in vivo*, consistent with experimental data. Current studies will assess whether sGPVI levels are predictive of thrombosis.

*No conflict of interest to disclose*

Tuesday 20 October  
ASTH Free Communications 2

1030-1130  
Hall D

O087

1100

## Rapid Diagnosis of Heparin-induced Thrombocytopenia by Whole Blood Impedance Aggregometry

Marie-Christine Morel-Kopp<sup>1,3</sup>, Margaret Aboud<sup>1,2</sup>, Chandima Kulathilake<sup>3</sup>, Chee Wee Tan<sup>1,3</sup> and Christopher Ward<sup>1,3</sup>

<sup>1</sup> Northern Blood Research Centre, University of Sydney. <sup>2</sup> Pacific Laboratory Medical Services (PaLMS), <sup>3</sup> Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, NSW Australia.

### Aim

Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin use. IgG antibodies to complexes of platelet factor 4 (PF4) and heparin trigger the clinical manifestations of HIT. Only a subset of these antibodies will activate platelets, and these can only be identified with platelet functional assays; most of those being time-consuming and complex to perform. We have developed a whole blood impedance (WBI) test using the new Multiplate<sup>®</sup> analyser to simplify HIT diagnosis confirmation step.

### Methods

All samples (N=107) referred to our laboratory over a 10 month period were screened for heparin-PF4 antibodies by an ELISA method (Zymutest HIA IgG). The 4T's score was used to assess HIT pretest probability. Antibody positive samples were further tested by all three functional assays: LTA, SRA and WBI.

### Results

Twenty out of 107 samples were Zymutest positive. Thirteen out of twenty samples were positive by LTA (10 patients) and 15 by WBI (11 patients). SRA, considered to be the gold standard, was used as a confirmatory test and 12 were found to be positive (10 patients); the three discrepant samples were weakly positive by LTA or WBI. The prevalence of a positive functional test was strongly correlated with the 4T's clinical risk score, but a small number of low-risk patients had positive functional assays.

### Conclusion

In this study, the WBI assay detected all SRA and LTA-positive samples, and was positive for three others, suggesting greater sensitivity. The WBI is easy to perform with rapid turnaround time, and should be considered as an alternative confirmatory assay for platelet-activating HIT antibodies.

*No conflict of interest to disclose*

**Tuesday 20 October**  
**ASTH Free Communications 2**

**1030-1130**  
**Hall D**

**O088**

**1115**

## **Heparin-Induced Thrombocytopenia: evaluation of ELISA assays**

**Marie-Christine Morel-Kopp**<sup>1,3</sup>, Margaret Aboud<sup>1,2</sup>, Chandima Kulathilake<sup>3</sup>, Chee Wee Tan<sup>1,3</sup> and Christopher Ward<sup>1,3</sup>

<sup>1</sup> Northern Blood Research Centre, University of Sydney. <sup>2</sup> Pacific Laboratory Medical Services (PaLMS), <sup>3</sup> Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, NSW Australia

Heparin-induced thrombocytopenia (HIT) is a rare immuno-allergic complication of anticoagulant treatment by heparin and is triggered by the production of antibodies to complexes of heparin (H) and platelet factor 4 (PF4). Enzyme linked immunosorbent assays (ELISA) are designed to detect these antibodies. A critical subset of these antibodies actually mediate HIT *in vivo*, and laboratory evidence for this subset relies on platelet functional assays: 14C-serotonin release assay (SRA) and light transmission aggregometry (LTA).

### **Methods**

In evaluating four ELISA assays (Stago Asserchrom IgGAM, GTi PF4 IgG and Hyphen HIA IgGAM and IgG) to detect antibodies against H-PF4 complexes, we used patient sera from 111 consecutive requests for laboratory screening for HIT. ELISA assays have high sensitivity for the detection of heparin-dependent antibodies. Specificity for the antibody that confers high risk of triggering HIT was assessed by further testing all ELISA-positive samples by SRA and LTA.

### **Results**

10 samples were positive by SRA (the positivity of one sample was not suppressed by 100U/mL of heparin rendering it potentially non-specific). Of these 10 SRA positive samples, 8 were also positive by LTA.

All four ELISA assays clearly identified these 10 potentially clinically significant positive results.

Non-specific positivity was similar in the four assays (Stago IgGAM 14, GTi PF4 IgG 8, Hyphen HIA IgGAM 8 + 4 equivocal, Hyphen IgG 7 + 3 equivocal).

### **Conclusion**

All assays had well-defined cut-off ODs, with the Stago and GTi assays yielding no equivocal results. One patient with a non-specific positivity in the Stago assay had a clearly demonstrated lupus anticoagulant. As all assays satisfactorily identified all clinically significant antibodies, our decision in favour of the Hyphen IgG ELISA assay was based on cost-competitiveness. The ELISA assays are suitable for screening patient plasma for heparin-dependent antibodies, but a more specific functional assay is recommended to confirm the laboratory diagnosis of HIT.

*No conflict of interest to disclose*

Tuesday 20 October  
Nurses Symposium: Consent in Blood Transfusion

1030-1130  
Hall A  
1030

## Consent in Blood Transfusion Symposium- ANZSBT Survey

**K Robinson<sup>1,2</sup> & R Hunt<sup>1</sup>** on behalf of ANZSBT Clinical Practice Improvement Committee

1. *BloodSafe Program, Adelaide, South Australia*

2. *Australian Red Cross Blood Service, Adelaide, South Australia*

### Introduction

The NH&MRC/RCNA blood component administration guidelines recommend that patient consent be gained for transfusion and this has been incorporated into ACHS EQulP 4 standards.

Aim: To determine current transfusion consent policy and practice across Australian and New Zealand hospitals. To pilot a standardised audit tool usable by hospital staff without specific expertise in transfusion.

### Method

An online survey tool was developed to assess hospital transfusion policy and practice and included a retrospective audit of up to 25 medical records of patients transfused between July 2008 & 2009. An invitation to participate was placed in the ACHS newsletter and sent out to ANZSBT members and through local networks.

Results: Table 1 summarises the results to date from 63 Australian and 11 New Zealand hospitals. 73% of respondents reported having a hospital transfusion consent policy. 57% of transfused patients audited had a signed consent form and 10% had other medical record documentation. 30% had no documented consent for transfusion.

Table 1

Results to 22/6/2009	Overall
Metropolitan Location	54%
Public Hospital	66%
Private Hospital	22%
Public/private combination	12%
Hospitals with a transfusion practitioner	40%
Hospitals with a specific transfusion committee	58%
Hospital transfusion consent policy	73%
Requirement for a signed consent form	58%
Medical Record Transfusion Consent Audits:	
Documented on consent form	57%
Documented in medical record	10%
Documented consent unable to be gained	1%
No documented consent	30%

### Conclusion

The ANZSBT consent survey has proved a meaningful and practical tool to assess and benchmark current transfusion consent policy and practice.

*No conflict of interest to disclose*

**A160**

**Tuesday 20 October**  
**Nurses Symposium: Consent in Blood Transfusion**

**1030-1130**  
**Hall A**  
**1100**

## **A Patient's Perspective - The Patient from Hell**

### **Shannon Farmer**

*WA Department of Health Patient Blood Management Program; Medical Society for Blood Management; School of Surgery, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia; Centre for Population Health Research, Curtin Health Innovation Research Institute (CHIRI), Curtin University, Perth, Western Australia.*

Complex issues surround contemporary transfusion medicine. The precautionary principle and vigilant efforts to protect the blood supply from infectious agents have resulted in supply challenges and burgeoning costs. New and re-emerging infectious agents present an ongoing challenge to blood safety efforts. Transfusion-related circulatory overload (TACO), transfusion-related acute lung injury (TRALI), wrong blood component transfused, acute transfusion reactions and bacterial contamination of blood remain the leading causes of transfusion-related death and major morbidity. Greater safety issues may relate to the growing literature implicating transfusion in short- mid- and long-term adverse patient outcomes. Patient informed consent relating to transfusion risks, benefits and alternatives is also becoming an important issue in health care. With greater access to medical information, patients are now demanding more say in health care decisions and requesting explanations on options and alternatives. This talk will dramatise the modern informed patient who has done his/her research and is seeking information on transfusion risks, benefits and alternatives. It highlights challenges and opportunities presented by the modern information age where medical information is the most retrieved on the internet and where surveys suggest consumers outweigh clinicians in accessing sites intended primarily for clinicians. An article in the *British Medical Journal* states, "The fact that patients have access to the same databases as clinicians leads to increased consumer knowledge, which is pushing clinicians to higher quality standards and evidence based-medicine."

Tuesday 20 October  
ANZSBT: Ruth Sanger Oration

1130-1230  
Hall C

## **Falsifiability of Component Therapy – Karl Popper, Thomas Kuhn and the Common Sense of Transfusion Medicine**

**Albert Farrugia**

*Plasma Protein Therapeutics Association, Annapolis MD, USA*

Falsifiability is an important concept in the philosophy of science. Its main developer and proponent was Karl Popper, who asserted that a proposition is scientific only if it is falsifiable, that is, that it can be shown false by observation or experiment. That something is "falsifiable" does not mean it is false; rather, that if it is false, then this can be shown by observation or experiment. Conceptually, Thomas Kuhn's development of paradigm shifts as a way of explaining scientific developments complements and furthers the concept of falsifiability, in that scientists work within a conceptual paradigm that strongly influences the way in which they see data, and will go to great length to defend their paradigm against falsification, by the addition of ad hoc hypotheses to existing theories. Changing a 'paradigm' is difficult, as it requires an individual scientist to break with his or her peers and defend a heterodox theory.

This presentation will assess key concepts in transfusion medicine, including component therapy, haemovigilance and the safety-supply balance in the light of falsifiability and the evolution of the current transfusion paradigm. The overall framework of blood policy and decision making in the author's experience over the past thirty years will be reviewed. It is suggested that there is a need to examine current dogma, asserted as common sense by many, in relation to many of these key concepts as a necessary prelude to the development of a new, more relevant and productive paradigm, which, in its turn, should be falsifiable and conducive to further development....when the time comes.

**Tuesday 20 October**  
**HSANZ Symposium: Risk Adapted Therapy**

**1330-1500**  
**Hall C**  
**1330**

## **Myeloma**

**Thierry Facon**  
*CHU Lille, France*

The concept of risk-adapted therapy has largely emerged with the availability of new prognostic factors and the use of novel agents (specifically thalidomide, bortezomib and lenalidomide). Theoretically, treatment choice could be adapted to individual patient characteristics (for example eligibility for autologous stem cell transplantation (ASCT), preference for one of the novel agents based on comorbidities) or to the risk of the disease (different treatment approaches for low-risk or high-risk MM). In many countries, cost will also effect treatment choice.

### **Patient- based risk-adapted therapy**

Eligibility for ASCT is somewhat variable across countries and is still under debate in patient subgroups, e.g., in patients >65 years of age and in those with renal failure. The use of novel agents, such as MP with or without thalidomide or bortezomib, in frail elderly patients is also a matter of debate, especially in community hospitals.

In limited cases, the patient's history strongly suggests the use of a specific agent. For instance, a history or risk of DVT may indicate treatment with bortezomib, while a history of peripheral neuropathy may point to the use of lenalidomide. Other treatment considerations warrant careful consideration, such as the use of bortezomib in patients with renal failure or the use of lenalidomide or thalidomide in patients living far from a hospital.

Recently assays have been developed, using GEP to identify patients likely to respond in the early courses of therapy (bortezomib study conducted at the UAMS)

### **MM risk-adapted therapy**

Despite major advances in identifying risk factors, using cytogenetics, FISH and more recently GEP and CGH, selecting definitive treatment based on cytogenetic abnormalities (IMW 2009 consensus panel 2) is premature. Targeted therapies that can reverse primary cytogenetic changes do not yet exist for MM. Risk-directed trials have been rare. This concept was probably pioneered by the IFM group 10 years ago in the IFM 99/02 and IFM 99/03-04 trials, for low/intermediate and high-risk patients, respectively (based on beta-2-microglobulin and del13). At the present time, the only example of trials researching GEP-defined, risk-directed therapies appears to be the total therapy programs TT4 and TT5 from UAMS.

**Tuesday 20 October**  
**HSANZ Symposium: Risk Adapted Therapy**

**1330-1500**  
**Hall C**  
**1400**

**Lymphoma**

**Martin Dreyling**

Abstract not received at time of going to print

**Tuesday 20 October**  
**HSANZ Symposium: Risk Adapted Therapy**

**1330-1500**  
**Hall C**  
**1430**

## **Monitoring Response in Chronic Myeloid Leukaemia**

**Tim Hughes**

In CML, close monitoring of response is needed to enable early recognition of drug resistance and disease progression. The risk of imatinib resistance is strongly related to the phase of disease with almost universal resistance in blast crisis and a very low risk of resistance in de-novo chronic phase CML. Resistance can be either primary or secondary. Primary resistance, seen in less than 10% of newly diagnosed CML patients is poorly understood and rarely attributable to kinase domain mutations. Poor intracellular uptake of imatinib and suboptimal plasma levels may be important contributors to primary failure. Secondary resistance emerges in about 10-15% of CML patients treated with imatinib first-line. Around 60% of cases have kinase domain mutations. To address the problem of imatinib resistance two second generation ABL kinase inhibitors, dasatinib (BMS) and nilotinib (Novartis) have been developed and assessed in CML patients. These drugs have several potential advantages over imatinib that may allow them to overcome drug resistance. They are both much more potent than imatinib so that if imatinib resistance is mediated by additional copies of the Ph-chromosome or overexpression of BCR-ABL, enhanced potency may lead to greater efficacy. Nilotinib and dasatinib are also less vulnerable to resistance mediated by kinase domain mutations. Whereas imatinib is partially or totally resistant to over 90 amino acid substitutions in the kinase domain of BCR-ABL, dasatinib and nilotinib are vulnerable to a limited spectrum of mutations. The emerging evidence from clinical trials in imatinib-resistant patients is that in-vitro sensitivity studies using mutant constructs of BCR-ABL are predictive of clinical resistance to second-line therapy. It is also evident that treatment of imatinib resistance when it is still only cytogenetic is more effective than treatment of hematologic resistance. This strengthens the argument for close molecular and/or cytogenetic monitoring. The indications for regular mutation screening include imatinib failure, advanced phase disease and in any patient being considered for a second line tyrosine kinase inhibitor

Tuesday 20 October  
ANZSBT Nurses Combined Symposium: Blood Management

1330-1500  
Hall B  
1330

## Do Transfusion Guidelines Reduce Transfusion Requirements

**Dafydd Thomas**

*Abertawe Bro Morgannwg University NHS Trust, Swansea, Wales, UK*

There are numerous examples of transfusion guidelines available in many languages and many countries. As a doctor working in the UK I have been involved and am therefore aware of guidelines that have been produced to help guide my clinical practice. More recently I have been involved as a representative of the Royal College of Anaesthetists with a number of guidelines aimed at promoting appropriate use of red cells, fresh frozen plasma and platelets in addition to the management of massive haemorrhage.

The surprising result of this involvement is my increased awareness of how few of my colleagues back at my base hospital are unaware or not interested in these guidelines. They most certainly do not therefore incorporate the recommendations suggested in these guidelines into their clinical practice.

Why then is there such poor awareness about transfusion guidelines amongst the multidisciplinary groups within our clinical environment. There is no doubt that many healthcare workers are overwhelmed by information and guidelines need to be succinct, up to date and evidenced base to have any impact. They also have to be made easily available to busy clinicians and incorporated into local guidelines and standard operating protocols.

Of course even when this is achieved change is never easy or quick. Many authors have described a lag time of implementation of even the best evidenced base practice which can take 15 to 20 years to become embedded in practice. In my presentation I will give examples of how practice and patient care has changed in response to guidelines - albeit over a predictable 15 year period.

**Tuesday 20 October**  
**ANZSBT Nurses Combined Symposium: Blood Management**

**1330-1500**  
**Hall B**  
**1400**

## **Where Does All Our Blood Go?**

**Rachel Whitford**

*Department of Health, Government of South Australia*

### **Background**

Blood transfusion is a common clinical procedure essential for treatment of specific patient groups. Ageing populations and advancing medical care are driving an increasing demand for red cells against a decreasing donor pool. Electronically linked pathology, clinical and patient epidemiological databases can be useful in developing data systems to monitor, compare and model transfusion practices.

### **Methods**

A linked electronic database was developed using clinical, epidemiological and red cell transfusion data from twenty five public hospitals across South Australia. Data were electronically extracted from four pre-existing databases on all hospital admissions during the 2006 calendar year. Data analysis included aggregation of blood usage by surgical and medical procedures (ICD-10-AM codes), speciality related groups (SRGs), patient demographics and type of admission.

### **Results**

Of the 327,995 admissions, 12,803 (3.9%) received a total of 40,124 red cells (average: 3.1, range: 1 to 64). Patients >65 years accounted for 56.9% used. Red cells were transfused in 6.4% of surgical admissions, accounting for 46.1% of total use and in 3.3% of medical admissions, 47.6% of total use. The remaining 6.3% use was associated with various types of endoscopic procedures. Red cells were transfused in 5.5% of emergency admissions, 61.9% of total use and in 2.8% of non-emergency admissions, 38.1% of total use. SRGs related to the treatment of haematological malignancies, orthopaedics, GIT endoscopy, cardiothoracic surgery, medical oncology, colorectal and vascular surgery formed the largest clinical entities, accounting for 55.0% of all red cells transfused, but only represented 19.1% of all admissions.

### **Conclusion**

The electronic linkage of laboratory, epidemiological and clinical data into a single database has provided baseline information on red cell use in relation to patient diagnoses, clinical procedures and demographics. The study highlights patterns of blood use and will provide useful input into blood contingency planning based on known disease trends, patient profiling and transfusion audits.

*No conflict of interest to disclose*

Tuesday 20 October  
ANZSBT Nurses Combined Symposium: Blood Management

1330-1500  
Hall B  
1430

## Developing a Blood Management Program

**Sherri Ozawa**

*Englewood Hospital and Medical Center, Englewood, New Jersey, USA*

The pressing issues surrounding blood transfusion, including ever increasing costs, emerging pathogens, inadequate supply, and the association of poor clinical outcomes has prompted numerous institutions across the world to implement organized patient blood management programs. Such programs approach appropriate transfusion practice from a number of different angles. Current blood use patterns by physicians and specific clinical areas must be analyzed, blood ordering practices must be scrutinized, and measures must be taken to ensure that patients for whom blood is not an option have their wishes and needs sufficiently addressed. Ethical and legal aspects of patient blood management must be taken into consideration and appropriate documentation and procedures must be created to address the specific needs of this population.

The implementation of such programs requires the acquisition of knowledge, manpower, equipment, and ongoing education to be successful. An entirely new mindset is necessary in the culture of the institution, a mindset which views transfusion as an invasive procedure that should be carefully undertaken only when evidence of benefit outweighs risk, it is acceptable to the patient, and no alternative is available. This requires a dramatic change in practice for many physicians who have been trained to use allogeneic transfusion as a default treatment to manage anemia, even when safer options exist. Hospitals that implement such programs often see dramatic reduction in financial expenditures for blood products, improved provider and patient satisfaction, and improved clinical outcomes.

**Tuesday 20 October**  
**ASTH Symposium: Rare Bleeding Disorders**

**1330-1500**  
**Hall D**  
**1330**

## **Platelet Function Disorders – Mechanism and Diagnosis**

**Marco Cattaneo**

*Clinica Medica, Ospedale San Paolo, Università degli Studi di Milano. Milano, Italy*

Inherited platelet disorders can alter circulating platelet numbers, function or both. These conditions are typically manifested by symptoms of excessive mucocutaneous bleeding and rapid onset, excessive bleeding following invasive surgical and dental procedures or trauma. Disorders of platelet function include defects of: 1) platelet receptors for adhesive proteins (e.g., Bernard-Soulier Syndrome, Glanzmann Thrombasthenia), 2) platelet receptors for soluble agonists (e.g., defects of P2Y<sub>12</sub>), 3) platelet granules (e.g., storage pool deficiency); 4) signal transduction pathways (abnormalities of the arachidonate/thromboxane A<sub>2</sub> pathway, of the stimulatory G-protein alpha-subunit), 4) procoagulant phospholipids (Scott syndrome). The diagnostic laboratory assessment for evaluation of a suspected platelet function defect should include an assessment of blood counts, a careful evaluation of the blood smear, and an evaluation of platelet size (mean platelet volume). Assessments of platelet function, by assays of aggregation and secretion, are commonly used for the diagnostic evaluation of platelet disorders. More specialized tests are helpful to confirm conditions that have been suspected based on the results of the initial screening tests. Therapy is not warranted for bruising. Platelet transfusions should be reserved for individuals with serious bleeding unresponsive to medical therapies. Recombinant Factor VIIa is useful in the treatment of bleeding episodes of patients with alloimmunization from platelet transfusions. Desmopressin and fibrinolytic inhibitors are useful for treatment of less severe bleedings. Treatment of menorrhagia needs to be individualized, and should take into consideration the individual's wish for pregnancies or contraception.

Tuesday 20 October  
ASTH Symposium: Rare Bleeding Disorders

1330-1500  
Hall D  
1410

## Factor XIII Deficiency

**Elizabeth M Duncan**

*Haematology Division, Institute of Medical and Veterinary Science, Adelaide, SA, Australia*

Factor XIII (FXIII) is a transglutaminase that circulates in plasma as a tetramer, comprising two catalytic A sub-units (FXIII-A) and two carrier B-subunits (FXIII-B). In fibrin, activated FXIII-A catalyses the covalent cross-linking of adjacent  $\alpha$  and  $\beta$  chains of fibrinogen to stabilise the clot. It also incorporates antifibrinolytic factors into fibrin, to improve resistance to fibrinolysis. Inherited, severe FXIII deficiency is a rare, homozygous recessive condition (1 per 2 million) with patients characteristically showing delayed bleeding and poor wound healing. Commonly reported clinical symptoms include umbilical stump bleeding, intra-cranial haemorrhage and spontaneous abortion. Both cryoprecipitate and a highly purified formulation of FXIII-A provide effective treatment, and a new recombinant product is currently undergoing clinical trials. Prophylaxis prevents bleeding, with levels as low as 5% sufficient to prevent spontaneous bleeding and maintain pregnancy. In the non-bleeding patient FXIII has a half-life of ten days, but this may be shorter in the bleeding patient and the levels required to support haemostasis much higher. The prothrombin time and APTT will not detect a deficiency of FXIII, and test requests should be guided by clinical symptoms. Quantitative measurement of FXIII-A is preferred for laboratory diagnosis, using methods to measure FXIII activity or antigen levels. These methods differ in degree of automation, levels of accuracy at low levels of FXIII and cost. Clot lysis tests are still commonly used to screen for FXIII deficiency but they will only detect a severe deficiency, may give a false positive result and cannot be used to monitor treatment. With more than 60 mutations of the A-subunit gene and 4 mutations of the B-subunit gene described, genetic analysis can be of value to confirm a diagnosis. Acquired deficiency of FXIII, e.g. secondary to auto-antibodies or liver disease, is also a clinically significant disorder requiring diagnosis and suitable treatment.

*No conflict of interest to disclose*

**Tuesday 20 October**  
**ASTH Symposium: Rare Bleeding Disorders**

**1330-1500**  
**Hall D**  
**1435**

## **Paraproteinemia and Coagulation Disorders**

**Simon McRae**

*SA Pathology Royal Adelaide Hospital, Adelaide, SA, Australia*

Abnormal screening coagulation tests are frequently observed in patients with underlying plasma cell disorders, with the majority of such patients having no bleeding history. The mechanism of the prolongation of clotting time remains unclear in the majority of these patients. However, a small percentage of such patients will have rarer conditions that are associated with a clinically significant coagulopathy, such as acquired von Willebrand Syndrome, amyloid associated acquired factor Xa deficiency, and inhibitors directed against other coagulation factors. The incidence, diagnosis, and management of the paraprotein related acquired coagulopathy will be discussed, including examples of recent single centre experience with managing such patients around the time of major surgery.

Tuesday 20 October  
HSANZ Symposium: Drug Approval

1530-1630  
Hall C  
1530

## Access to New and High Cost Drugs in Australia - Some Insights

**Andrew Roberts**<sup>1,2,3</sup>

<sup>1</sup>*The Walter & Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia.*

<sup>2</sup>*Department of Clinical Haematology, The Royal Melbourne Hospital, Parkville, Victoria, Australia.*

<sup>3</sup>*The University of Melbourne, Parkville, Victoria, Australia.*

In Australia, the TGA licences pharmaceuticals for sale and use after a formal evaluation of efficacy and safety. However for most new drugs, access by the general population relies on the Federal Government including the drug on the Pharmaceutical Benefits Scheme. For the past three decades, inclusion on the PBS has required a formal evaluation by an expert committee, the PBAC. By legislation, no item can be listed on the PBS without a positive recommendation by the PBAC. Successive Australian governments have tasked the PBAC to consider the cost-effectiveness of medications as a key element within the decision-making process. I will outline the current processes and highlight how cost-effectiveness is evaluated, with particular reference to how this applies to haematology-related drugs.

**Tuesday 20 October**  
**HSANZ Symposium: Drug Approval**

**1530-1630**  
**Hall C**  
**1550**

## **New Zealand Experience**

**Peter Browett**

Abstract not received at time of going to print

Tuesday 20 October  
HSANZ Symposium: Drug Approval

1530-1630  
Hall C  
1610

## Challenges to New Drug Development and Approval: Experience and Opinion of an Industry Medical Director

**Kevin P Lynch**

*Celgene Pty Ltd, Melbourne, Australia*

In an environment characterised by an ageing population, technological advances enabling new target identification, rapidly emerging economies of third world countries and a lifestyle contributing to an epidemic of chronic disease, one would speculate that the Pharmaceutical Industry would be very buoyant indeed. However, an understandable and increased level of scrutiny by regulators and payors, enormously high development costs, and fierce competition for patients and resources provides substantial constraints to this enthusiasm. Indeed, despite large increases in investments, the number of new medical entities approved by authorities such as the FDA and TGA has roughly halved in the last decade. Identification of lead compounds for clinical development is less of a bottleneck, especially in the field of cancer medicine where hundreds of new compounds targeting recently understood oncogenic pathways are in development. The challenge is more focused on efficient completion of Phase I and II studies utilising better biomarkers, codevelopment of molecular diagnostics, and rigorous attention to translational questions that can help design the pivotal studies as well as feeding clinical information all the way back to the discovery programme. Adoption and acceptance of flexible designs for registration studies, often using less conventional statistical techniques, may be crucial to more efficient late stage development programmes. Demonstrating improvement in survival outcomes at this stage is made more complex by the confounding features of additional lines of therapy and the sometimes contentious inclusion of a cross-over design. In this respect, the understanding and support from academic investigators and regulatory authorities is key. Fundamental to the process of drug development is a recognition that regulatory approval of a drug does not equate with access. Australian and New Zealand have in some ways lead the way as countries that demand convincing health economic data before approving funding for new medicines. It is only reasonable that the Industry in seeking funding for high cost medicines, should bring to the use of a drug a high level of confidence that it will work in the selected population. This will only be possible through close attention to disease biology, drug mechanism of action and appropriate patient selection. Early and consistent engagement of the academic research community is critical to this effort.

*The opinions expressed in this abstract are those of the author alone and do not necessarily reflect those of Celgene nor of the Pharmaceutical Industry more broadly*

**Tuesday 20 October**  
**ANZSBT Symposium: IVIg – Have We Got It Right?**

**1530-1630**  
**Hall B**  
**1530**

## **A National Overview**

**Alison Turner**

Abstract not received at time of going to print

Tuesday 20 October  
ANZSBT Symposium: IVIg – Have We Got It Right?

1530-1630  
Hall B  
1550

## A View from the Australian Red Cross Blood Service

**Marija Borosak**

*Australian Red Cross Blood Service (ARCBS), Melbourne, Victoria, Australia*

Intravenous immunoglobulin (IVIg) is a unique and precious plasma derived product used in immune replacement and immune modulation for a number of clinical indications. In Australia ARCBS collects plasma from volunteer, non-remunerated donors, the plasma is pooled and fractionated by CSL Bioplasma. Currently Australia is not self-sufficient in IVIg, and imported IVIg supplements domestic supply.

IVIg has been managed intensively for over a decade as IVIg demand has been increasing, in recent years at about 14% per annum. ARCBS has been an integral participant in this management and actively manages IVIg clinical review and supply.

In December 2007 new Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (the Criteria) were approved by Australian Health Ministers with input from clinical experts, professional colleges, societies and other organisations including substantial input from the ARCBS Transfusion Medicine Team (TMS). The Criteria were implemented from March 2008 with a six month transition phase and have ensured more equitable access to IVIg supplied across Australia under the National Blood Agreement, providing a consistent framework for jurisdictions by which all IVIg requests are assessed. The Criteria identifies clinical conditions where IVIg can be used provided qualifying criteria are met. The introduction of the Criteria has led to a period of change with some reclassification of patients according to Criteria labels, as well as increased use of IVIg due to changes to disease indications included for access to IVIg under the National Blood Agreement. The ARCBS TMS team, review requests and outcomes as required according to the Criteria. Data on requests, issues, outcomes and complications of therapy are recorded in the national STARS database.

Overall there has been successful implementation of the Criteria with opportunity to build further on a good foundation. The review of the Criteria is anticipated to commence within the next 12 months.

*No conflict of interest to disclose*

**Tuesday 20 October**  
**ANZSBT Symposium: IVIg – Have We Got It Right?**

**1530-1630**  
**Hall B**  
**1610**

## **A Clinician's Perspective**

### **Robert Heddle**

*SA Pathology, IMVS Campus, Adelaide, Australia*  
*Clinical Immunology Unit, Royal Adelaide Hospital, Adelaide, Australia*

**Aim:** Descriptive analysis of difficulties experienced in managing IVIg as (1) head of a Clinical Immunology Unit in a major teaching hospital (2) Chairperson of SA IVIG Users' Group

**Methods:** Review of emails, correspondence considered in role as chairperson of IVIG Users' Committee. Discussions with clinical and ARCBS colleagues

### **Results**

#### *Generic problems*

- 1) Difficulties in promoting to clinicians the December 2007 Criteria
- 2) "Grandfathered" patients; IVIg started on criteria no longer current
- 3) Reluctance of many clinicians to communicate details of prospective IVIg recipients
- 4) Diversity of gate-keepers (in SA)
- 5) Major difficulties in meeting review criteria- diversity of criteria, poor understanding, logistic difficulties of follow up/communication and poor definition of pre- and on-treatment clinical criteria.

#### *Condition specific problems*

- 1) Specific antibody deficiency- deals with subjects with recurrent sino-pulmonary infection/bronchiectasis with normal total IgG but suspected inadequate antibody responses. Little consensus on "what" antibody responses to measure, let alone "how" or normal ranges; propose more emphasis on rigorous clinical criteria
- 2) Acquired hypogammaglobulinaemia secondary to haematological malignancies. Low IgG inherent to both criteria but frequently not determined. Review criteria suggest trial off IVIG- this has been performed rarely; is it a reasonable review criterion?
- 3) Adult ITP. Criteria for ongoing IVIg require adequate trials of other therapies and need to maintain platelet count >30,000. These details are often missing from requests.

### **Conclusions**

The December 2007 Criteria represent a necessary attempt to advance evidence based use of a limited resource. The criteria are necessarily developmental and their application difficult. Authorities need to continue to review the utility of criteria. Clinicians cannot be helped unless they communicate relevant clinical details.

*No conflict of interest to declare*

Tuesday 20 October  
ASTH Symposium: Acquired Platelet Disorders

1530-1630  
Hall D  
1530

## The Good and the Bad - Plasma Lipoproteins in Coagulation and Venous Thrombosis

**Natalie Pecheniuk**

*School of Pharmacy and Molecular Sciences, James Cook University, Townsville, QLD, Australia*

It is widely accepted that high density lipoproteins (HDL), the good cholesterol, shows inverse correlation with atherothrombosis. The role of HDL in venous disease however has only recently become evident. The molecular mechanisms of HDL's beneficial antithrombotic qualities observed in both venous and arterial thrombosis remain to be elucidated but evidence suggests that HDL and not LDL shows activated protein C (APC) cofactor activity. HDL particles appear to enhance the protein S-dependent APC pathway down-regulating thrombin generation via enhanced proteolysis of factor Va. Strong correlations are observed in both biochemical and translational clinical studies between HDL particles, in particular the larger HDL particles, with decreased thrombotic potential and venous thromboembolism (VTE). These findings suggest molecular components of the HDL particle may contribute to these beneficial observations. In particular, elevated levels of the major apolipoprotein in HDL, apolipoprotein AI, appear to correlate with reduced VTE recurrence. Recent studies have also suggested that apolipoprotein AI incorporation into lipid vesicles ablates the procoagulant effect of anionic lipids. Further, many enzymes such as lipases, CETP and PLTP are involved in lipoprotein metabolism and contribute to the flux of cholesterol, lipid and protein components between lipoprotein particles. Genetic associations with polymorphisms of CETP have been observed in VTE and these specific genotypes known to associate with an unfavourable lipoprotein profile and elevated plasma CETP were observed to be more prevalent in VTE subjects. Interestingly, elevated plasma CETP antigen has recently been shown to contribute to blood coagulability. The potential benefits of HDL particles stem further than its well described role in reverse cholesterol transport and includes anti-inflammatory, anti-oxidant, anti-apoptotic and anti-thrombotic properties, all of which have a role in the aetiology of venous thrombus formation.

**Tuesday 20 October**  
**ASTH Symposium: Acquired Platelet Disorders**

**1530-1630**  
**Hall D**  
**1600**

## **Stroke, Thrombotic Thrombocytopenic Purpura and ADAMTS13 Activity**

**Ross Baker**, Grace Gilmore and Jim Thom

*Centre for Thrombosis and Haemophilia, Murdoch University, Department of Haematology, Royal Perth Hospital, Perth, Australia*

ADAMTS13 plays an important role in preventing arterial thrombosis and thrombotic thrombocytopenic purpura (TTP) by cleaving the thrombogenic ultralarge high molecular weight von Willebrand factor (ULvWF) multimers to less active forms. When the enzyme is deficient, circulating ULvWf causes thrombosis by the formation of intravascular aggregation of platelets in the microcirculation and at sites of high shear flow associated with blood vessel damage. Diagnostic assays for ADAMTS13 antigen, function and autoantibodies are now becoming more widely available but their utility for clinical practice is uncertain.

Generally patients with idiopathic TTP have low ADAMTS13 activity when compared to those with other causes of secondary TTP such as metastatic tumours, organ transplantation or the use of drugs such as mitomycin C or cyclosporine. The secondary causes of TTP do not tend to respond to plasma exchange probably because the TTP is caused by the massive endothelial stimulation and release of ULvWf rather than ADAMTS13 deficiency.

Around 75% of patients with idiopathic TTP have severe deficiency of ADAMTS13 (less than 5%) at diagnosis. Recent data suggests that patients with idiopathic TTP with normal or deficient ADAMTS13 activity had a similar response rate to plasma exchange and short term survival. However, those who have severe ADAMTS13 deficiency had a significant increased risk of relapse. In smaller studies the detection of auto-antibodies to ADAMTS13 was also associated with refractory disease, higher mortality and an increased risk of relapse. Rituximab has been reported to benefit some patients with primary TTP particularly those with detectable auto-antibodies.

During plasma exchange around a third of patients will have persisting ADAMTS13 deficiency despite a good clinical response. Around 60% of these patients will relapse. In those who had severe ADAMTS13 whose levels are corrected with treatment, relapse almost is always associated with a falling ADAMTS13 level.

Low of ADAMTS13 and high vWf are strongly associated with risk of cardiovascular disease and in experimental models infusing recombinant ADAMTS13 reduces mortality without increasing haemorrhage.

Measuring ADAMTS13 activity may provide clinicians with useful biomarker for prognostic information in patients with TTP and a rationale for targeted therapy with recombinant ADAMTS13 in those severely deficient or with a vascular event.

Tuesday 20 October  
Nurses Free Communications 6

1530-1630  
Hall A  
1530

**O089**

## **A Changing Model of Care – The Role of the Blood Transfusion Clinical Nurse Consultant**

**Emily Allen**

*Prince of Wales Hospital, Randwick, NSW, Australia*

### **Aim**

As a changing model of care the CNC for transfusion was introduced to Prince of Wales Hospital in September '07. The aim was to develop, implement and establish a sustainable role that can initiate and maintain an ongoing process of improvement in quality and safety of transfusion practices at Prince of Wales Hospital. Since this role commenced a number of initiatives have been introduced to the hospital and Area Health Service.

### **Methods**

3 monthly red cell appropriateness audits of 20 consecutive transfusion episodes in specific high use clinical areas, and yearly appropriateness audits of 1 week red cell transfusion episodes hospital wide are carried out, as well as yearly audits of documentation and knowledge surveys.

An education and assessment process is provided by Bloodsafe e-learning and regular education sessions on blood and blood products, transfusion safety and up to date practices in transfusion medicine.

Communication improvement initiatives include the publication of a monthly transfusion newsletter, 'Bloodflash', providing timely transfusion news via Northern Network email and participation in local and Area Health Service transfusion committees.

### **Results**

Hospital wide audits identify a significant improvement in inappropriate transfusion rates – 32% in March '08 compared to 21% in March '09. 3 monthly audits in one specific high use clinical area show a marked improvement in inappropriate transfusions from 25% in February '07 to 5% in September '08.

Documentation audits in September '07 compared to June '09 show considerable improvements in the consenting process from 28% to 64%.

### **Conclusion**

There have been some convincing developments in transfusion practices at Prince of Wales Hospital and by continuing to support the initiatives that have been implemented by the CNC it is hoped that there will be further reductions of inappropriate transfusions and an increase in quality and safety in transfusion practices around the hospital.

*No conflict of interest to disclose*

**A180**

**Tuesday 20 October**  
**Nurses Free Communications 6**

**1530-1630**  
**Hall A**  
**1545**

**O090**

## **Collaborative Nurse Led Transfusion Clinic – 18 months On!**

### **Charlene McLaren**

*Clinical Nurse Specialist, Haematology Outpatients, Canterbury District Health Board, Christchurch, New Zealand*

#### **Introduction**

In 2006 there were increasing numbers of elderly frail patients causing increased stress and frustration for medical staff in the Haematology Outpatient service at Christchurch Hospital. This highlighted the need for change to occur within the service and the introduction of a Collaborative Nurse Led Transfusion Clinic was proposed and implemented in November 2007.

#### **Aim**

The aim of this clinic was to allow a nurse who had completed appropriate post graduate qualifications to carry out comprehensive assessments for transfusion dependant patients who had stable haematological conditions or were palliative.

There was a need to improve patient assessment pre transfusion and improve patient management plans. The nurse was able to do a full holistic assessment addressing a range of problems relating to the needs of frail elderly patients. The establishment of this clinic decreased medical loads and department fiscal costs. This also created increased self autonomy and opportunities for the nurse who had advanced haematology clinical knowledge.

#### **Conclusion**

Now 18 months on this has been extremely exciting for the Haematology Service. The clinic is continuing to improve and expand with positive patient experiences. It also will create further opportunities for other senior nurses to expand their roles while providing a more holistic service for our patients thus continuing to improve Outcomes for the out patients in the Haematology Outpatient service.

*No conflict of interest to disclose*

Tuesday 20 October  
Nurses Free Communications 6

1530-1630  
Hall A  
1600

**O091**

## **Influencing Factors on Chelation Compliance in Transfusion Dependant Haemoglobinopathy Patients**

**Emily Allen**

*Prince of Wales Hospital, Randwick, NSW, Australia*

### **Aim**

Complications of iron overload are thoroughly documented in the literature and methods of chelating excess iron are effective when administered as prescribed. Regularly transfused patients are required to take full responsibility in complying with their prescribed chelation regime at home although there are a number of physical and psychological issues that impact on the patients' ability to comply with their treatment. By understanding these issues, providing relevant education and support health professionals can work with the patient to develop strategies that may help to improve their compliance. Improving the patients understanding of haemoglobinopathy and related complications can lead to an increased autonomy in the management of their condition and demonstrate a positive influence on patient compliance.

Patient case studies will be utilised to illustrate some of the issues, methods implemented, and their latest outcomes.

### **Methods**

One to one patient support sessions are provided to identify issues, provide education and improve the patients' knowledge. Presentation of graphs showing individual patient ferritin levels and T2\* measurements are utilised as a visual aid and educational tool during these sessions and facilitated patient focus groups are held quarterly to provide patients with the opportunity to voice issues and concerns.

### **Results**

Influencing factors include site problems with subcutaneous infusions, patients feel too busy to prepare or forget to take tablets among others.

Preliminary results of mean ferritin levels indicate an overall reduction from 2680ug/L in Jan '07 to 1551ug/L in May/June '09. Recent T2\* results show a decrease in iron stores following appropriate changes to chelation therapy regimes combined with improved compliance.

### **Conclusion**

This work in progress has provided the foundation to explore the clinician's understanding of the issues affecting patient compliance to chelation therapy and in turn encourage the patients' active participation in the management of their haemoglobinopathy to prevent or reduce iron overload.

*No conflict of interest to disclose*

**A182**

**Tuesday 20 October**  
**Nurses Free Communications 6**

**1530-1630**  
**Hall A**  
**1615**

**O092**

## **So You Think Giving a Blood Transfusion is Easy!**

**Linley Bielby**<sup>1,2</sup>, Erica Wood<sup>1,2</sup>, Russell Hunt<sup>3</sup>, David Roxby<sup>3</sup>, David Westerman<sup>2</sup> and Axel Hofmann<sup>4</sup>

<sup>1</sup>*Australian Red Cross Blood Service, Melbourne, Victoria, Australia,* <sup>2</sup>*Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia,* <sup>3</sup>*Flinders Medical Centre, Adelaide, South Australia, Australia,* <sup>4</sup>*Medical Society for Blood Management, Vienna, Austria*

### **Introduction**

Administration of red cells is a common activity, especially for Haematology/Oncology Nurses, however many would not consciously consider the risks, time and complexity-associated costs related to transfusion.

### **Methods**

To determine the real cost of red cell transfusion in Australia, each step of the transfusion process was mapped including phlebotomy, specimen delivery, laboratory procedures, collecting units for transfusion and bedside administration. Nurses play key roles in many of these steps.

### **Results**

The process maps demonstrated the complexity (number of steps involved in each aspect of the transfusion process) and points where critical failures can occur. In clinical areas these include: phlebotomy, requiring 35 process steps; collection of the unit from the laboratory, 20 steps or more; and actual administration of the unit; >120 process steps. Critical points where failure can occur include checking correct patient identification (ID) before pre-transfusion sample collection and administration. Incorrect patient/sample ID and cross-match sample documentation required an average 4% of patients to be re-bled at one centre. Sample collection time ranged from 3.5 – 11 mins. The average time to collect a red cell unit from the blood bank for transfusion was 12 mins and the average associated nursing time for administration of this red cell was 28 mins, with extra time required for additional precautions (~2-3 min each additional intervention). Preliminary financial data attributed to each of process step indicates that the cost is AUD\$650.00-\$690.00 for administration of a single red cell unit.

### **Conclusions**

The transfusion process is complex, time-consuming and involves many individuals and resources. Nurses have key roles in the transfusion process and by understanding the real risks and costs related they can encourage better transfusion practice, to optimise red cell utilisation, to improve patient outcomes, and to reduce risks and costs of unnecessary transfusions.

*This study was funded by an unrestricted grant from Amgen, Australia.*

Tuesday 20 October  
HSANZ Masterclass 7

1630-1730  
Meeting Rooms 1/2

## Myeloma - from Genetic Abnormalities to Targeted Therapy

**Thierry Facon**

*CHU Lille, France*

Our understanding of multiple myeloma (MM) disease biology has increased substantially over the recent years and has led to the identification of a number of factors that are associated with a poor prognosis. The 2009 International Myeloma Workshop consensus panel 2 summarized that the specific cytogenetic abnormalities considered as poor risk comprise cytogenetically detected deletion of chromosome 13 (del13), translocation(4;14) and deletion of chromosome 17 (del17p), as well as detection by FISH of t(4;14); t(14;16) and del17p.

A number of studies have investigated the novel agents in patients with poor-risk cytogenetic factors to establish if these agents may offer the possibility of improving outcomes in these patients over traditional treatments. These studies have many limitations: 1) they are usually post-hoc subgroup analyses of phase 3 studies or expanded access programs, 2) limited number of patients, 3) in most studies response was evaluated but TTP, PFS and OS were not reported. Bortezomib in MM patients with cytogenetic abnormalities was investigated in several studies. In a retrospective analysis of the SUMMIT and APEX trials, response and survival appeared to be similar in bortezomib-treated patients with and without del(13). In the front-line setting, similar results have been obtained. Bortezomib induction regimens achieved similar response rates in patients with or without cytogenetic abnormalities. In the IFM bortezomib/dexamethasone vs VAD study, the combination of bortezomib and dexamethasone resulted in a significantly higher VGPR rate than VAD in patients with del(13) and t(4;14) and/or del(17p). In addition, in patients with newly diagnosed MM not eligible for transplantation, who were treated with bortezomib plus melphalan and prednisone (MPV), response, TTP and OS were not negatively affected by the presence of t(4;14), t(14;16) and del(17p). Collectively, these data suggest that bortezomib may overcome, at least partly, the poor prognostic impact of del13 and t(4;14).

Data from several lenalidomide studies suggest that del(13) and t(4;14) do not influence response rate or EFS. However, a recent report by the IFM group indicated that in patients treated with lenalidomide plus dexamethasone, the presence of del(13) and t(4;14) resulted in a significant reduction in response rate, PFS and OS compared with patients without cytogenetic abnormalities.

Overall, further studies with larger patient numbers and longer follow-up are needed to confirm these encouraging results and to assess the effect on PFS and OS.

**Tuesday 20 October**  
**HSANZ Masterclass 8**

**1630-1730**  
**Meeting Room 3**

**Waldrenstrom Macroglobulinaemia – What’s New?**

**Martin Dreyling**

**Notes:**

Tuesday 20 October  
ANZSBT Masterclass 10

1630-1730  
Meeting Room 4

## Haemodilution – The Role in Transfusion Practice

**Paul M Ness**

*Transfusion Medicine Division, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA*

Acute normovolemic haemodilution (ANH) has been advocated to reduce or eliminate the need for volunteer blood during surgery. The principle of ANH is to reduce the patient's haematocrit by phlebotomy prior to surgical blood loss so that, for a given volume of surgical bleeding, a smaller mass of red cells will be lost. Since the amount of blood saved can be small, another important mechanism by which ANH might reduce transfusion requirements is by providing fresh autologous platelets and plasma that can correct the acquired perioperative haemostatic deficiencies.

Despite its introduction over three decades ago, ANH has not emerged as a standard intervention, nor has it been discredited. The use of ANH began in cardiac surgery and was driven by a desire to reduce blood required to prime the extracorporeal pump. The AIDS epidemic shifted the focus to minimizing exposure to homologous blood and its adverse effects. In this context, ANH has been advocated as a more cost effective means of avoiding transfusion than preoperative autologous donation (PAD) or intraoperative salvage.

The benefits of ANH may be quite modest, depending on the magnitude of surgical blood loss and patient characteristics. The benefit increases with the extent of haemodilution. Moderate ANH has generally been carried to a haematocrit of 25-35%, based on the concept that oxygen delivery is maximal at a haematocrit of about 30% and a reluctance to accept the risks of more extreme ANH. Even with optimal implementation, blood conservation is modest in the absence of extreme haemodilution. On the other hand, we have demonstrated that aggressive ANH can be performed with a blood substitute, so-called augmented ANH, in aortic aneurysm patients. Since ANH has been proposed as an effective alternative to transfusion. Ness attempted to assess its value compared in a prospective, randomized, controlled trial of ANH versus PAD in radical prostatectomy; no differences in transfusion utilization or perioperative morbidity were found but there was no untreated control group.

Often discussed but little explored is the impact of ANH on the hemostatic mechanism. One of the touted benefits of ANH has been the preservation of coagulation factors and platelets, since blood removed in the operating room is not cooled. We provided limited evidence that blood collected by ANH may reduce postoperative bleeding in cardiac surgery compared to control patients.

A final concern about ANH is whether it is cost effective. In addition, the resources to perform ANH in the operating room require training and reliable protocols and it is not clear that many hospitals have set up the appropriate systems so that ANH can be offered as a reliable alternative to blood transfusion in elective surgery. If a safe blood substitute becomes available, augmented ANH may become a feasible option for high risk cases or religious objectors in the future.

**A186**

**Tuesday 20 October**  
**ANZSBT Masterclass 11**

**1630-1730**  
**Meeting Room 5**

**Preparation and Implementation of a Practical Hospital Based Blood Shortage Contingency Plan**

**Taher Rad**

**Notes:**

**Tuesday 20 October**  
**ASTH Masterclass 12**

**1630-1730**  
**Meeting Room 11**

**Managing Patients with Venous Thrombosis**

**Paul Kyrle**

**Notes:**