

BSBMT NEWS

British Society of Blood and Marrow Transplantation

Issue Number 10 - December 2011

INSIDE...

"Annual income twenty pounds, annual expenditure nineteen nineteen six, result happiness. Annual income twenty pounds, annual expenditure twenty pounds ought and six, result misery."

(Mr Micawber, David Copperfield)

2012 will bring the bicentenary of the birth of Charles Dickens, a man who knew something about debt. Thanks to a perfect storm of financial fecklessness, dishonesty and incompetence, we anticipate frugal times ahead. **Graham Jackson** sets out some of the resulting challenges to transplant practice and calls for the active involvement of the BSBMT membership in maintaining and developing good practice in the service of our patients. **Peter Zarko-Flynn** and **Ulrike Paulus** describe developments in our sister organisations, the Anthony Nolan and the NHSBT while John Snowden and colleagues highlight the effective workings of the Sheffield transplant centre. Elsewhere, challenges in clinical practice are addressed by **Ruth Ashbee** and **Chris Fox**. The future of transplantation depends not only on funding, but on talent: Coming through the ranks are **Venetia Bigley** and **Clare Bennett**, both winners at the annual BSBMT Scientific meeting as well as **Chris Parrish** who provides our journal club selection. Life is not all about work - congratulate Venetia on her new baby and also note that The Harvard Business Review recently featured the benefits of making time off predictable and required, as **Bing Jones** ably demonstrates. Finally, while it may seem foolhardy to believe, as Mr Micawber did, that "something will turn up" in 2012, we should hope for the best but prepare for the worst. Meantime, I wish you a Happy Christmas, untroubled by dreams of Scrooge.

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STREAMLINING THE SEARCH FOR STEM CELLS

Peter Zarko-Flynn, Ann Green and Bronwen Shaw



In December 2010 the Department of Health published a report by the UK Stem Cell Strategic Forum, which was led by NHS Blood and Transplant (NHSBT). The report set out recommendations to save over 200 lives a year by increasing the availability of stem cells for patient transplantation.

Following these recommendations, the Minister for Public Health, Anne Milton MP, announced £4 million in funding to take forward some of these recommendations. This has enabled Anthony Nolan and NHSBT to collaborate on a number of measures - including creating a single registry, enriching the registry by improving the quality of the data held, speeding up the process of identifying a matching donor and collecting more cord blood - which will all help to improve the provision of unrelated stem cell donations in the UK.

The first of these developments is that Anthony Nolan and NHSBT have aligned their unrelated stem cell donor registry in order to streamline the process of donor search and donor provision used by transplant centres in the UK.

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What does this mean in practice?

- This Autumn, Anthony Nolan and NHSBT will begin operating a single UK-wide registry. This means UK transplant centres can now carry out a streamlined search for donors both from the Anthony Nolan register and the British Bone Marrow Registry (BBMR) as well as UK cord blood banks.
- This will be managed by Anthony Nolan, who will be the single point of contact for search requests.
- The centre will receive a search report from Anthony Nolan incorporating BBMR & Anthony Nolan adult donors and cord blood units.
- If a UK transplant centre wishes to request extended typing/confirmatory typing, this will also be done through Anthony Nolan.
- UK transplant centres will still need to contact BBMR or Anthony Nolan to make arrangements for work-up if they select a donor from either registry.
- However, from 2012 Anthony Nolan will be managing all aspects of donor provision. Transplant centres will receive more details on this change nearer the time.
- Posters are being sent to all centres to explain this process and to provide each centre's search coordinator's contact details.

In addition to the single registry, Anthony Nolan and NHSBT are increasing collection hours at their existing cord blood collection centres to 24/7 working patterns, which will mean that local mothers will have more opportunity to donate their cord blood. NHSBT will also be opening a new cord blood collection centre later this year. These measures will result in an additional 2,000 banked cord blood units this year, helping to

achieve a target of 50,000 banked units as recommended by the UK Stem Cell Strategic Forum.

Anthony Nolan and NHSBT are also carrying out high-resolution typing of 20,000 donors with common phenotypes and are developing a genotype prediction system to enhance the search algorithm. This gives an indication of the likelihood of a donor being a high resolution match where a donor is HLA typed at low-medium resolution. The algorithm will be based on HLA haplotype frequencies of thousands of donors in the database typed to the highest level of the resolution.

10,000 of these donors will be newly recruited by Anthony Nolan, which is targeting young people as they are more likely to be selected as a final donor and can stay on the register for longer. This will significantly enhance the donor pool and increase the chance for UK transplant Centres to select a British donor

What are the benefits of the collaboration?

The work being delivered through the collaboration is expected to reduce transplant costs to the NHS by £0.3 million a year as we see: better typing on our donors on the registries, making them more likely to be picked both nationally and internally; and more cord blood in our own banks.

Consequently, we expect to import fewer transplants from abroad.

Future developments

Anthony Nolan and NHSBT aim to continue their innovative collaboration to deliver further improvements in the provision of donor stem cells for transplantation. The initial funding allocated for this year has allowed us to embark upon the first steps to delivering against the UK Stem Cell Strategic Forum recommendations. We will continue to work together to deliver improvements and developments that will lead to better outcomes for patients needing a stem cell transplant.

We have also commenced work to facilitate development of common strategies for donor selection in the UK. Following an initial workshop with H&I labs and UK registries on 29 June 2011 we plan to hold a second meeting to allow the transplant community to share knowledge, experience and best practice with a view to ensuring consistency in practices across the UK.

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The key recommendations from the UK Stem Cell Strategic Forum are:

- reducing the time taken to identify a matching donor, through better tissue typing and exploiting new technology platforms. Currently a significant number of patients die or deteriorate physically while waiting for their transplant
- increasing the UK cord blood inventory to 50,000 clinically validated units
- increasing collaboration between the UK registries and cord blood banks
- a collaborative approach with third sector organisations to engage with donors from ethnic minority communities

LANGERHANS CELLS REGULATE CUTANEOUS INJURY BY LICENSING CD8 EFFECTOR CELLS RECRUITED TO THE SKIN

Clare L. Bennett, Farnaz Fallah-Arani, Thomas Conlan, Celine Trouillet, Hugh Goold, Laurent Chorro, Barry Flutter, Terry K. Means, Frédéric Geissmann and Ronjon Chakraverty



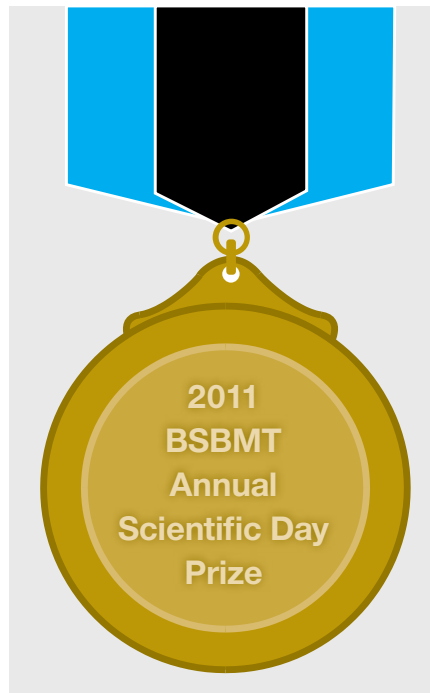
Skin graft-versus-host disease (GVHD) is a major cause of morbidity after allogeneic stem cell transplant.

Within the target organ, Langerhans cells (LC), which are the most numerous dendritic cells in the skin, form a contiguous network throughout the epidermis.

We were particularly interested in LC because they are relatively radio-resistant and persist in patients after transplant-related conditioning. Therefore, LC provide a pool of allo-antigen in the skin, and may be highly efficient at presenting this antigen to donor T cells.

In this study, we employed a tractable model of cutaneous GVHD, induced by topical application of a Toll-like receptor agonist, to explore the role of LC in the development of tissue injury.

By adapting this model to permit inducible and selective depletion of host LC, we found that GVHD was significantly reduced when LC were absent. However, LC were not required either for CD8 T-cell activation within the draining lymph node or subsequent homing of effector cells to the epidermis.

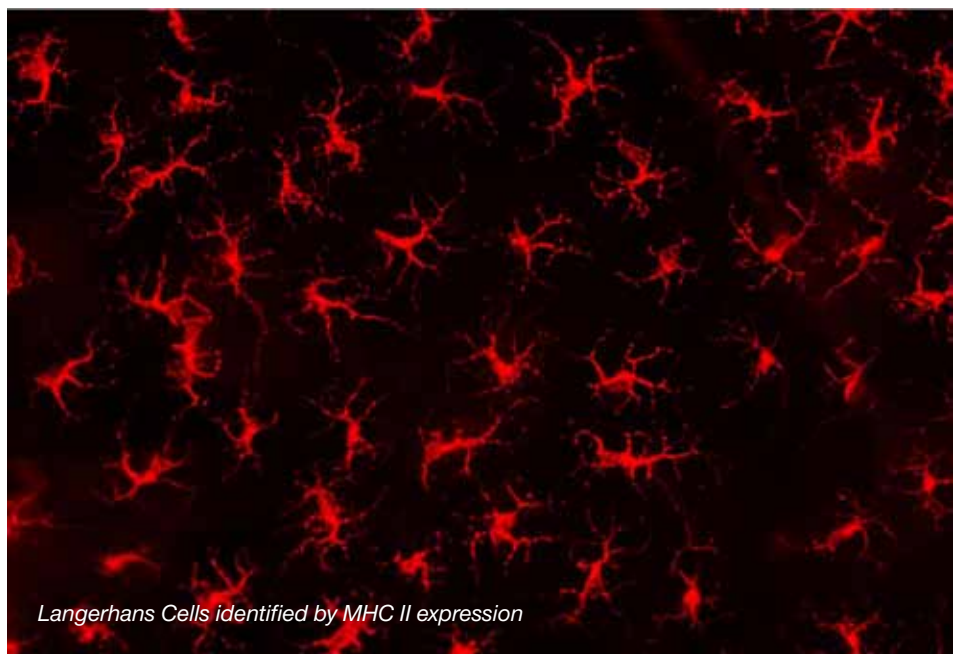


Instead, we found that LC were necessary for inducing transcription of IFN- γ and other key effector molecules by donor CD8 cells in the epidermis, indicating that they license CD8 cells to induce epithelial injury.

These data demonstrate a novel role for epidermal LC in driving the development of cutaneous GVHD due to direct activation of host-reactive effector T cells in the skin.

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Langerhans Cells identified by MHC II expression



ONE FOR THE JOURNAL CLUB

Blaser, B. W., Kim, H. T., Alyea, E. P., Ho, V. T., et al.

Hyperlipidemia and Statin Use after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant (2011).



The long-term follow-up of haemopoietic stem cell transplant (HSCT) patients touches on a great many aspects of clinical medicine. Amidst such pressing haematological concerns as disease relapse and graft-versus-host disease lie endocrine

dysfunction, secondary malignancies and psychological morbidity. Lurking in the mélange is a considerable body of evidence that cardiovascular disease, already reaching epidemic proportions in our society, is more prevalent still amongst the survivors of SCT.

In a retrospective analysis of 2574 patients surviving more than 5 years after SCT at the Fred Hutchinson Cancer Research Centre, Martin et al. reported an excess rate of cardiovascular deaths of 7% by comparison to sex- and age-matched controls¹. Examining patients surviving more than 2 years, Abou-Mourad et al. found hypertension in 21.4%, dyslipidaemia in 8.9% and diabetes in 7.6%². Baker et al compared 1089 SCT survivors to sibling controls and found an increased prevalence of diabetes and of hypertension (3.65 and 2.06 times respectively)³. These findings are not unusual; many other authors report similar findings.

However, there is evidence that this cardiovascular risk can be modified. In a recent article in *Biology of Blood and Marrow Transplantation*, Blaser et al. found incidences of hypercholesterolaemia and hypertriglyceridaemia within 2 years of SCT of 73.4% and 72.5% respectively⁴. They reported that statin use in 29% of patients was associated with a significant net reduction in total cholesterol, triglyceride and low density lipoproteins without significant adverse effects. Whilst cardiovascular risk estimates such as the Framingham score have not been validated specifically in the HSCT population, their prognostic power in other settings is strongly suggestive that such measures should improve cardiovascular outcomes.

In their 2010 review, Griffith et al. suggest that in the light of accumulating evidence, all SCT patients aged over 40 with one or more risk factors should be considered to have a high risk of cardiovascular disease. They outline a suggested approach for screening and management of dyslipidaemia⁵. Many centres will have extended of this sort of approach to encompass hypertension and diabetes mellitus as well as lifestyle issues such as diet, exercise and smoking.

The natural history of atherosclerotic disease dictates that endothelial lesions precede the development of clinically evident cardiovascular disease, often by decades. However, screening for appropriate risk factors through long-term follow-up offers the opportunity to modify them, and is likely to gain ever greater importance as the haematological outcomes of SCT continue to improve.

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SHOULD WE MEASURE SERUM AZOLE LEVELS?



The azole antifungals are undoubtedly an important group of drugs in both prophylaxis and treatment of fungal infections in

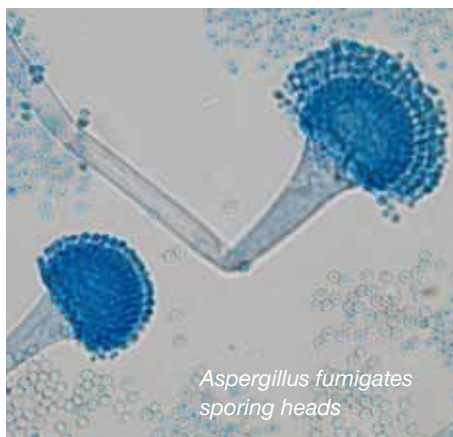
patients who have undergone haemopoietic stem cell transplant, but there are still many uncertainties which complicate their use. They have significant drug interactions with a wide range of drugs, their absorption is very variable and their uptake and metabolism are affected by genetic polymorphisms. With such variability between patients, should therapeutic monitoring be carried out routinely in patients receiving these drugs?

There are several issues to consider. The first is whether there is compelling evidence that the level of drug measured in serum correlates with either prophylactic efficacy or treatment outcome. For itraconazole, early studies showed that neutropenic patients with trough levels $< 0.5\text{mg/L}$ were significantly more likely to develop breakthrough infections and in those who died of those infections, the last trough level was significantly lower than in those who survived. Beneficial outcomes in aspergillosis, oral candidosis and cryptococcosis also correlate with higher serum levels. For voriconazole, several studies have shown improved outcomes with serum trough levels above $1\text{-}2\text{mg/L}$, mainly in patients with aspergillosis, but also for some patients with candidosis and other mould infections.



For posaconazole prophylaxis is most effective when serum levels exceed 0.7mg/L and for treatment of aspergillosis when levels exceed 1.25mg/L .

The second issue is whether therapeutic monitoring is available locally, the frequency with which the



test is done and the method used. For levels to be helpful in guiding therapy, the results must be available quickly and the method used must differentiate azoles from other interfering drugs. Use of HPLC and mass spectrometry methods have largely overcome the problem of interference which was seen in bioassays, but assays need to be performed at least twice weekly and results should be telephoned to the requesting centre. Validation of assays is still very variable but guidelines produced by the US Food and Drug Administration and the establishment of national and international quality assurance schemes should now improve the standardisation and reliability of assays.

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Assuming you have access to the relevant assays and timely results, the next issue is how often to carry out the tests and what are the indications for testing? Once azole therapy begins or after changing the dose, testing trough levels 5-7 days later is advisable as a guide to absorption and any effects of interacting drugs. Other indications will vary with the drug, but include starting or stopping any interacting drugs, uncertain drug compliance, any signs or symptoms of toxicity (particularly for voriconazole), lack of response or possible breakthrough infection, gut-associated graft versus host disease or other causes of diarrhoea or reduced oral nutrition (particularly for itraconazole and posaconazole).

If patients achieve levels above the target and do not experience any of the problems in the preceding list, then levels probably only need to be monitored monthly or when any problem arises.

As further data emerge, the exact role and frequency of therapeutic monitoring for each drug will become clearer, but for the present, monitoring offers some reassurance that patients taking azoles are achieving serum levels which are sufficient to provide the protection that they need.

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SCOTTISH NATIONAL CORD BLOOD BANK OPENS

The Scottish National Blood Transfusion Service (SNBTS) has established a public Cord Blood Bank at its West of Scotland - Regional Transfusion Centre in Glasgow.

The Bank has obtained HTA-accreditation in May 2011, and is now ready to issue cords for clinical transplantation nationally and internationally. These are made available via listing at the British Bone Marrow Registry and in due course the Anthony Nolan Registry.

Cords are being collected by dedicated, fully trained midwives in a Glasgow maternity unit, and processed and banked with the state of the art equipment of the Regional Transfusion Centre in Glasgow. All testing is undertaken in Scotland, by a combination of SNBTS- and NHS - laboratories.

The Cord Blood Bank is aiming to bank a minimum of 800 cords per year, and has started to work towards FACT-accreditation.

This bank will hopefully make a valuable contribution towards meeting the needs of transplant patients in the UK and worldwide.



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DEPARTMENTAL SPOTLIGHT

SHEFFIELD: 35 YEARS OF BMT IN THE STEEL CITY

John Snowden, Sharon Barrott, Leona Pickersgill, Khaled El-Ghariani, Chris Dalley & Ajay Vora



Members of the North Trent Adult programme

The first BMT procedure in Sheffield was performed in a paediatric patient in 1976, shortly after the appointment of Dr (now Professor Sir) John Lilleyman. Subsequently, the BMT service in Sheffield was developed by John Lilleyman, David Winfield and Barry Hancock in the 1980s and 1990s. Since then, almost 1200 patients have undergone BMT in the Sheffield programmes, including over 60 unrelated cord blood procedures, and, like other tertiary adult and paediatric centres, BMT is now very much a routine and integral component of the regional haematology and cancer services.

BMT in Sheffield is contained within two individual but close working programmes sited at the neighbouring Sheffield Teaching Hospitals (Royal Hallamshire Hospital) and Sheffield Children's Hospital Foundation Trusts, working with the Sheffield NHSBT centre.

The adult and paediatric services together currently perform well over 100 transplant procedures per year, including unrelated and cord blood procedures. All aspects of HSCT Programme are JACIE accredited. There are also close links with the regional extracorporeal photopheresis service in nearby Rotherham.

Adults

The North Trent Adult BMT Programme provides autologous and allogeneic BMT services principally to the hospitals within the North Trent Cancer Network i.e. Sheffield, Barnsley, Rotherham, Doncaster and Bassetlaw, and Chesterfield, which are linked by weekly video-conferenced MDT links to facilitate referrals. The programme covers approximately 2 million population within a relatively population dense network.

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The consultant team includes John Snowden, Chris Dalley, Nick Morley, Josh Wright, John Reilly and Linda Evans, who work closely with our BMT co-ordinators, Helen Jessop, Aileen Nield and Sue Simpson. Quality management is led by Leona Pickersgill, who succeeded Carole Charley (now working part-time for JACIE in her retirement). Our data managers, Laura Scott and Alison Sellars do a tremendous job in the never-ending task of EBMT reporting. Our recently upgraded inpatient facilities include TYA accommodation and an expansive day-case unit incorporates the regional apheresis unit and the evolving ambulatory programme.



Paediatrics

The BMT Programme at Sheffield Children's Hospital (SCH) is the sole paediatric allogeneic HSCT service in the Trent region, and provides autologous and allogeneic services for children and adolescents for a population of over 6 million in South Yorkshire, Humberside, Derbyshire, Nottinghamshire, Lincolnshire and Leicestershire (an area of 19,000 square kilometres).

The paediatric consultant team includes Ajay Vora, Jenny Welch and Jeanette Payne with Sisters Shan Rush and Julie Marples as transplant co-ordinators, and are supported by quality manager, Sharon Barrott, and data manager, Janet Williams. Inpatients and day

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cases are cared for on a 14 bedded haematology/oncology unit and outpatient clinics are held in the recently refurbished Haematology/Oncology Clinic in the Roald Dahl Haematology Centre. Bone marrow harvesting and apheresis services are performed within SCH. SCH was the first centre in the UK to perform an unrelated cord blood transplant in 1998. The patient, who had JMML, remains alive and in complete remission.

Sheffield NHSBT

The adult and paediatric BMT services work closely with the Sheffield based NHSBT centre, who provide stem cell processing (Victoria Day and Anatole Lubenko) along with H&I and unrelated donor and cord blood identification services (Noel Collins, David Smilie and Andrea Hamer). Stem cell collection services, led by Khaled El-Ghariani, Bing Jones and Christine Birchall, are provided for adults by NHSBT within the day-case facilities of the Royal Hallamshire Hospital. Sheffield has been a longstanding BBMR unrelated harvesting centre, and, recently, the collaboration has extended with Sheffield becoming the first site outside of London to become an Anthony Nolan unrelated donor apheresis and bone marrow collection centre.

Late Effects Clinic and Late Effects Group Sheffield (LEGS)

One further feature that links the paediatric and adult programmes is the well-established Late Effects services in Sheffield. Led by Dr Diana Greenfield, the UK's first nurse consultant in Late Effects, with paediatric nurse specialist input from Tanya Urquhart, the late effects clinic provides structured and systematic follow up for all transitional patients and high risk adult oncology patients, including BMT patients. Clinics are held concurrently with BMT clinics, in conjunction with consultant endocrinology, reproductive medicine and liaison psychiatry colleagues. The service supports an active research and educational programme.

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Service developments and academic interactions

All current consultants and other key staff involved in BMT in Sheffield are primarily NHS employed, and are proud of the NHS service provision for our local population, many of whom live in some of the most economically deprived areas of the country. Current nationally funded service development and quality assurance projects relevant to BMT include clinical and health economic evaluation of ambulatory transplantation and intensive chemotherapy, led by Chris Dalley, and BMT related NEQAS schemes in immunophenotyping and molecular genetic/chimaerism testing, led by John Reilly. We have active roles in the EBMT and JACIE, as well as BCSH Guidelines committees and the NCRI Haemato-oncology Clinical Studies Group and disease specific sub-groups.

In our spare time, we do have some academic interests, but, as this is limited by our NHS commitments, we have always been very happy to support our academically-based colleagues elsewhere in the country with patient enrolment onto their national clinical trials in acute leukaemia, myeloma and lymphoproliferative disease. The North Trent Cancer Research Network has one of the highest recruitments into the NCRI portfolio, many of which have a BMT component performed in Sheffield. Locally in the University of Sheffield, we also have active and productive collaborations with Professor Sam Ahmedzai in the Academic Department of Supportive Care, and with Professors Rob Coleman and Penella Woll within the ECOMC badged Cancer Clinical Trials Unit. In addition, work by our basic scientific colleagues in myeloma bone disease, and in MRD and drug metabolism in ALL has led to the award of an LLR Centre of Excellence. We hope to appoint to the first ever senior clinical academic post specifically in haemato-oncology by the end of 2011.

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DEPARTMENTAL SPOTLIGHT

Some recent BMT related publications with Sheffield involvement

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PTLD: THE ENEMY WITHIN

Chris Fox

Isolated reports of 'immunoblastic sarcomas' of donor origin, arising in the early months following allogeneic stem cell transplant (SCT), emerged in the late 1970s and early 1980s¹. A series of 15 patients who developed a histological spectrum of Epstein-Barr virus (EBV)-associated lymphomas at a median of 77 days following myeloablative SCT was subsequently reported². The majority of cases were shown to arise from donor B cells and the mortality rate was almost 90%. The consistent finding of EBV genomes (figure 1) within such tumours implicated the virus in tumorigenesis³.

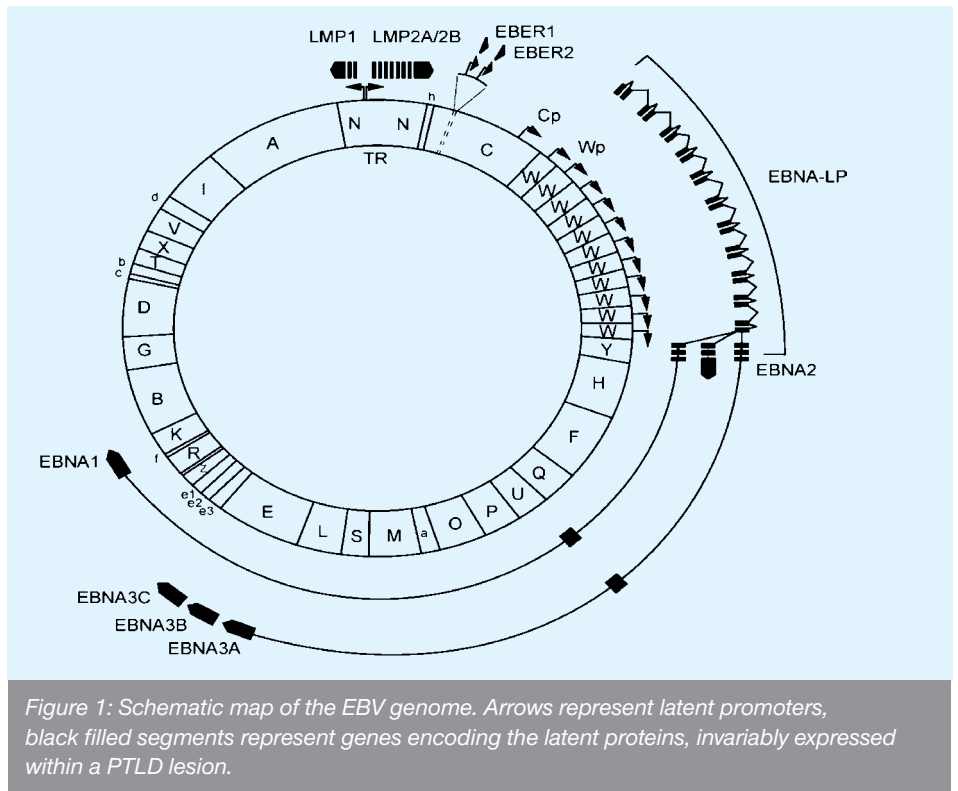


Figure 1: Schematic map of the EBV genome. Arrows represent latent promoters, black filled segments represent genes encoding the latent proteins, invariably expressed within a PTLD lesion.

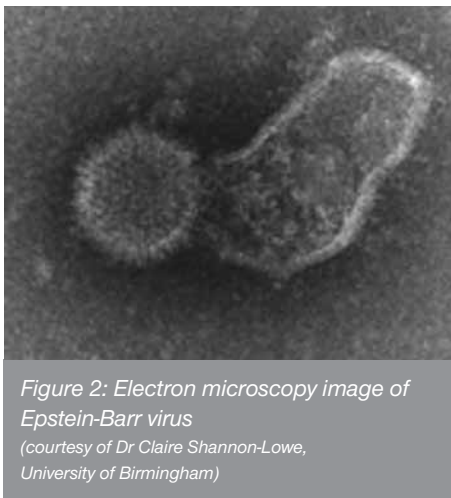


Figure 2: Electron microscopy image of Epstein-Barr virus (courtesy of Dr Claire Shannon-Lowe, University of Birmingham)

EBV is a γ herpesvirus, (Figure 2) that has co-evolved with our ancestors over millions of years and is found widespread in the human population as a lifelong and largely asymptomatic infection. However, the seemingly benign character of this ubiquitous herpesvirus should be reconciled with its potent growth-transforming ability and success as a lymphoid and epithelial tumour virus.

Indeed, EBV was first discovered in cultured cells from a disaggregated Burkitt lymphoma biopsy, flown to the UK from Kampala, Uganda in 1964⁴.

Primary infection with EBV

Following primary infection, EBV replicates in the oropharynx and enters B lymphocytes, resulting in an expanded population of lymphoblastoid B cells in the tonsil, coinciding with large numbers of infected B cells in the blood. Many of these proliferating cells are eliminated by the immune response, but a minority survive by hijacking normal B cell differentiation and suppression of immunogenic viral proteins during germinal centre transit. Thereafter, imperceptible to host immunity, latent EBV persists in the long-lived memory B cell pool at a frequency of approximately 1:10,000 to 1:100,000 in the peripheral blood of healthy carriers.

The healthy carrier state of EBV-immune individuals is associated with substantial levels of EBV-specific (predominantly CD8+) T cells in peripheral blood, with evidence of dynamic trafficking to secondary lymphoid tissue and sites of viral replication. Indeed 1-3% of the total circulating CD8+ T cell pool in healthy individuals is EBV-specific, increasing up to 10-15% in some individuals over 60 years of age. Such robust cellular immune responses are critical to maintain a stable virus: host balance.

EBV immunity after allogeneic stem cell transplant

Deficiencies in T cell numbers and function following alloSCT render the transplant patient at risk of a range of opportunistic infections, including disease caused by members of the herpesviridae family.

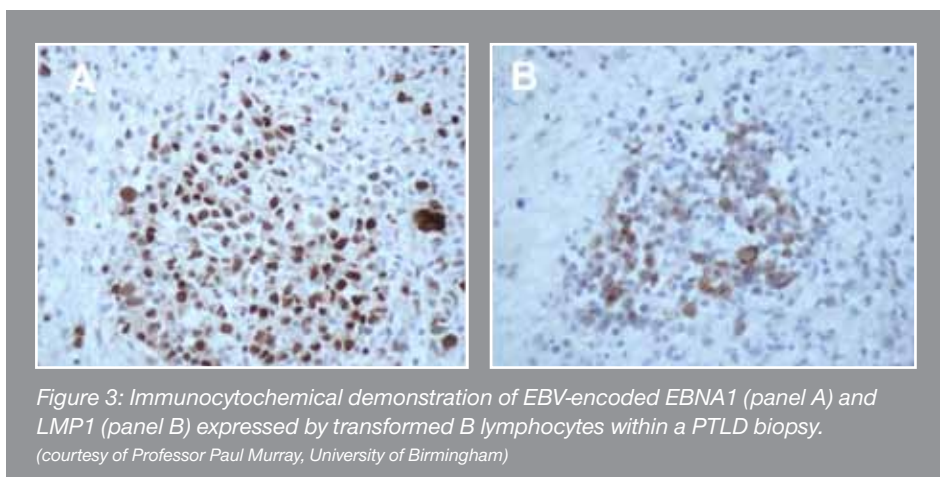
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EBV-specific T cell recovery is particularly delayed in the context of in vivo T cell depletion with Alemtuzumab, where EBV-specific responses are rarely detected within six months of SCT⁷.

Accordingly, EBV reactivation is relatively common in the early months following SCT and the risk of PTLD development increases with the degree of (in vitro or in vivo) T cell depletion⁵. Careful delineation between asymptomatic EBV reactivation and EBV-associated disease is of central importance to the clinical management of this complication. The box shows definitions that have been recently introduced in the setting of SCT⁶.

- **EBV-DNA-emia** ≡ detection of EBV-DNA in the blood.
- **Probable EBV disease** ≡ significant lymphadenopathy (or other end-organ disease) with high EBV-DNA load in the blood, in the absence of an alternative aetiology.
- **Proven EBV disease** ≡ EBV detected from an organ by biopsy together with symptoms and/or signs from the affected organ.

In most cases of PTLD the proliferating cells express the full spectrum of EBV latent proteins (latent membrane proteins LMP1, LMP2A/2B and nuclear antigens EBNA1, 2, 3A/3B/3C/LP and BHRF1), although both inter- and intra-tumour heterogeneity is recognised (Figure 3). Collectively, these viral proteins not only drive cell growth but also constitute the target antigens through which, in healthy EBV carriers, virus-transformed cells are recognised and destroyed by virus-specific T cell surveillance.



Clinical management of PTLD post-allogeneic stem cell transplant

Historically, a dismal outcome for patients developing PTLD following SCT was anticipated with mortality rates in excess of 80%⁷. However, 2 major developments over the last decade have resulted in a paradigm shift in the management of PTLD, leading to significantly improved outcomes. First, the therapeutic use of the humanised monoclonal anti-CD20 antibody Rituximab has dramatically improved response rates and survival for a large proportion of patients diagnosed with PTLD⁸. Second, the clinical availability of quantitative PCR (qPCR) assays for EBV genome copy number in peripheral blood samples has revolutionised both PTLD diagnosis and routine monitoring following SCT. However, although qPCR monitoring for EBV reactivation post-HSCT is now commonplace, its diagnostic and predictive value remains unclear. Combining EBV qPCR data with measures of T cell reconstitution may better identify patients at risk of subsequent PTLD development; this requires further study.

A UK collaborative study has recently examined the clinicopathological features of PTLD occurring in 62 patients following an Alemtuzumab-based allogeneic SCT.

The median age at onset was 50 years (16-62) and 17 patients received myeloablative (MA) whilst 45 received reduced-intensity (RI) conditioning. Forty-four cases occurred following an unrelated donor alloSCT. The median time from HSCT to PTLD onset was 120 days. Substantial clinicopathological heterogeneity was observed but fever was manifest in 80% and extra-nodal disease was frequent (60%). Interestingly, lymphadenopathy was clinically inapparent in 38% cases; such patients were diagnosed late and had a significantly higher risk of death from PTLD.

The median viral load at the onset of PTLD was 49,300 copies/ml (range 50 - 65,200,000 copies/ml). Notably, the viral load was $\leq 10,000$ and $\leq 40,000$ copies/ml in 23% and 45% of cases respectively; below currently applied thresholds for pre-emptive therapy and challenging current paradigms for monitoring and intervention. With a median follow-up of 20.4 months, mortality attributable to PTLD was 31% (19/62). Eleven cases were post-mortem diagnoses or died rapidly after initiation of therapy. The majority of the 51 evaluable cases were initially treated with Rituximab-monotherapy, with a 70% response rate.

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Patients failing Rituximab responded poorly to chemotherapy, but donor lymphocyte infusions appeared to be an effective salvage therapy. The overall response rate was 78% and although there were no documented relapses, all those with progressive disease died of PTLD at a median of 33 days (13-257 days) from diagnosis.

A body of work from Houston, Texas has clearly demonstrated the long-term safety and efficacy of EBV-specific cytotoxic lymphocyte infusions (generated in vitro from the EBV-immune stem cell donor, (Figure 4) for the prevention and treatment of PTLD⁹. Nevertheless, questions as to the optimal role of this cellular therapy still remain, owing to the limited availability, labour and cost implications.

Future directions

Future research should focus on the early events in virus: host pathobiology in the context of alloSCT to enable accurate identification of patients at highest risk of PTLD development, and help inform a 'smarter' strategy of pre-emptive intervention with B-cell specific monoclonal antibodies. In the case of established PTLD, a clearer understanding of the clonal evolution of virus-transformed B cells, along with better characterisation of EBV's role in the acquisition of cellular mutations, should be sought. For the subgroup of patient with biologically aggressive disease, unresponsive to Rituximab, alternative therapeutic approaches are urgently required.

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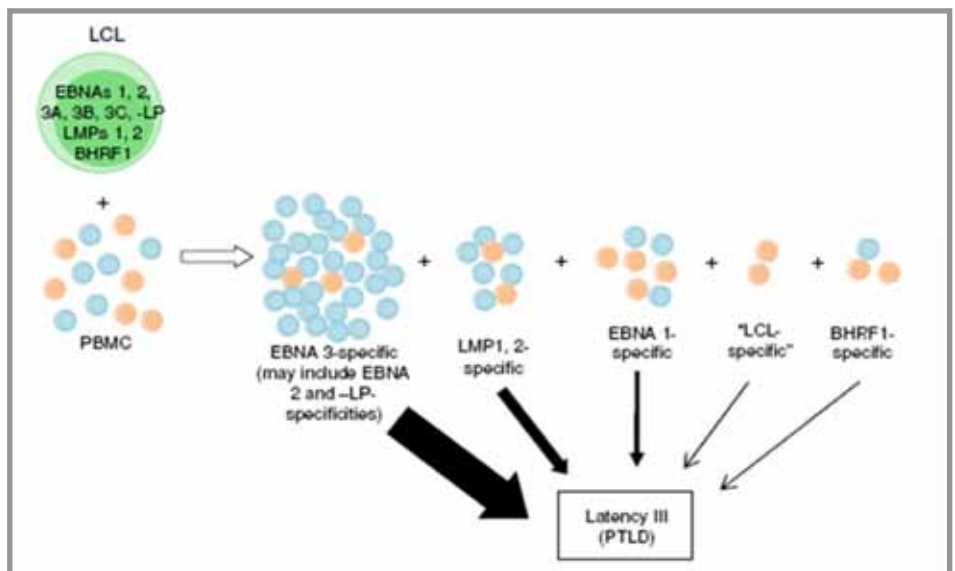


Figure 4: A schematic representing the specificities and frequencies of effector T cells generated in vitro by stimulation with EBV-transformed B cells (lymphoblastoid cell lines, LCLs). CD8+ T cells of indicated specificity are shaded blue, whilst CD4+ effectors are orange; the number of cells shown indicates their relative frequency within the polyclonal populations. The width of each arrow represents the potential contribution of the respective T cell sub-population to target PTLD tumours expressing the full range of latent viral protein targets.

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PLURIPOTENT HAEMATOLOGISTS: BALANCING BLOOD AND ART

Bing Jones



I wonder what you do to offset the stresses and strains of bone marrow transplantation? My life has a novel mix. For half the week, I work for NHS Blood & Transplant with much of it working alongside the BMT team, here in Sheffield. For the other half of the week, I paint portraits... as a business. It is an odd mix but I have got used to it over the decades. Patients and portraits are strangely complementary activities.

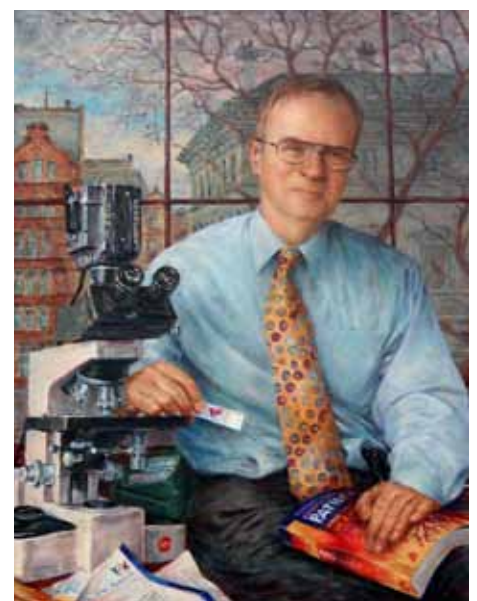
As a doctor, I spend my time collecting stem cells, counselling allogeneic donors and managing poorly patients who need plasma and red cell exchanges... and living with quality systems. Quality surrounds me, both in Transfusion and Transplantation. But then I pick up my brushes and paint portraits, involving the age-old crafts of oil painting, figure drawing and the

great mystery of catching a likeness. Here, there are no documents, no rules and no deaths. Only the quiet, the colours and the dangerous business of what the sitter will say when it's done. But there's a kind of quality that I need to find in the pictures too...

So, medically, I see a marvellous mix of the very fit and the very poorly, of SOPs and ethical dilemmas, of Hospital and Transfusion Centre. There's a very hilly ride between the two sites. I clump about in the hospital in my funny cycling shoes, with more or less lycra, depending on the time of year, amidst laughter at my kneecaps and apologies for my perspiration. But when the phone rings, it is as likely to be about a portrait as a plasma exchange and then it's on with the helmet and back to the studio.

People and quality: here are two links between the painting of a portrait and that tortuous process called transplantation. People are the real reward at the hospital: watching patients' ups as they get better and their downs as they get worse, talking to donors helping siblings or distant, unrelated recipients. And people are my focus in the studio too. Just think of the privilege of spending quiet hours looking at and getting to know one's sitter. I have famous people and leaders of their field coming for 5 or even 10 sittings to make a big oil painting to hang in some prestigious setting. I have children and young people sitting with the intimate freshness of their faces waiting to be captured. I paint whole families in their living spaces with their dogs, their troubles and their achievements.

Continued on page (14)



Professor Sir James Underwood, Past President of the Royal College of Pathologists. The original hangs at the College in Carlton House Terrace.



Professor Barry Hancock OBE, Emeritus Professor of Clinical Oncology, University of Sheffield. The original hangs in the Lecture Theatre in Weston Park Hospital, Sheffield. (Recognise the cell in the background?)

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They too are a fund of humanity and my prize is to capture just a smidgeon of their essence and to encapsulate it into the paint or the chalk to make a picture that will outlast both me and my sitter.

Quality is a nice concept. It links both art and doctoring. It helps us to weather the dangers of transplantation and helps me separate my portrait from the thousands of competing pictures. The technology of portraiture is intense; I use twenty different colours and four different media to mix the colours in. I use linseed and poppy oil, egg tempera and dammar varnish. I paste thick layers of paint on some of the picture and then glaze over other parts, sometimes when it is wet and sometimes when it is dry, using transparent colours. I scrape away and dab with my thumbs, scratch with the wrong end of the brush and

somehow, sometimes, I can remake a solid head on a flat surface with all its bumps, its eyes and hair, all in roughly the right place. I can sometimes even make the colours glow and the composition satisfy. When I can do that with the face looking out, actually like the sitter, I am a happy man.

Curiously, the best paintings are quiet, they look like ordinary people. They are a bit like the quiet miracle of a patient returning many years after a transplant... with nothing to report beyond an ordinary life.

Bing Jones

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Website www.bingjones.co.uk

Recent BMT related publications include:

van Walraven SM, Nicoloso-de Faveri G, Axdorph-Nygell UA, Douglas KW, Jones DA, Lee SJ, Pulsipher M, Ritchie L, Halter J, Shaw BE;

WMDA Ethics and Clinical working groups. Family donor care management: principles and recommendations. Bone Marrow Transplantation. 2010; 45:1269-73.

THE PRESIDENT'S COLUMN



As we approach the end of 2011 there is no doubt that the current economic climate is beginning to impact on stem cell transplantation. It is likely that these pressures will increase through 2012. It is also clear that there is some variation across the country and we must act nationally to protect transplant centres

locally. As I see it we have to vigorously fight any move to remove funding for CO transplants. We have an adjudication committee very ably run by David Marks. This committee is increasingly busy assessing transplants where local funding cannot be agreed. We are close to completing an up-date of the indications table.

In our discussions with purchasers we also have to make the argument that the alternatives to transplantation are likely to be increasingly expensive both in terms of drug costs and morbidity.

I have also heard a lot of criticism that the transplant community has failed to embrace clinical trials and this is something we all need to address. It can be difficult sometimes to get transplant studies on the books because they are complex and frequently recruit small numbers but we all need to fight to get these studies approved within our centres. Speaking personally we have had problems getting some of these studies approved as trust go for 'value for money' cheap high recruiting studies, especially when CTOs are NHS funded.

I am looking forward to closer ties with other transplant organisations such as the Nolan and NHSBT. I get a sense that we have a common purpose and can work together to help improve the delivery of transplantation throughout the UK. One example of this is our upcoming joint symposium on alternative donor transplantation which will be held on the 23rd Feb 2012. This includes a key note speech from Anne Milton MP Public Health Minister and many excellent talks – put the date in your diary.

Have a great holiday and a very happy new year.

Graham Jackson

President of BSBMT

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FORTHCOMING EVENTS

More information on all these meetings will be found at the BSBMT website <http://bsbmt.org/>

Royal Society of Medicine meeting and BSBMT:

Bench to bedside: Blood and Marrow Transplantation.

Friday 16th December 2011 at the Royal Society of Medicine, London

BSBMT, NHSBT & Anthony Nolan

Symposium of Alternative Donor Transplantation: State of the Art

23rd February 2012, Telford Lecture Theatre, Westminster, London

University of Sheffield & Sheffield Teaching Hospitals

Late Effects in Cancer Survivors

8th & 9th March 2012, Cutlers' Hall, Sheffield