BSHI
British Society for Histocompatibility and Immunogenetics

NEWSLETTER 102

ISSUE 1 March 2016

Paul Terasaki-

10 September 1929 to 25 January 2016

A personal reflection:

Professor Phil Dyer OBE, PhD, FRCPath

It is one of the highest honours for an individual to have an everyday item named after them - "hoover, biro, bunsen burner" - with convention dictating that their name is not capitalised. Paul Terasaki invented the terasaki tray used every day in hundreds of H&I laboratories across the world. Paul was an innovator of technical developments in H&I, their application to clinical transplantation and a world leader in data collection and its analysis to inform clinical best practice.

Paul was the leading technical innovator for the identification, classification and subsequent application of HLA proteins and genes to clinical transplantation. Terasaki Labs bristled with machinery, highly skilled and motivated technical staff and scientists all working to increase throughput and quality of HLA testing - at the University of California at Los Angeles - at his company, One Lambda, and at his Foundation. Most developments progressing from serological analysis of HLA proteins through to next generation sequencing of HLA genes were led or improved by Terasaki.

The UK contributed to Paul's career when he spent time in London for a period of research in Sir Peter Medawar's laboratory, for which Paul was always grateful as stated in his chapter in his "must read" anthology "A History of HLA", which is accompanied by his other major compilation "A History of Transplantation". Paul also innovated the world-wide review of developments and

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Editorial

Welcome to the spring edition of the BSHI Newsletter.

The year began on a sad note when the death of Paul Terasaki, one of the pioneers in H & I, was announced in January. We are grateful to Prof Phil Dyer for sharing his memories of Dr Terasaki and celebrating his contributions to transplantation.

Two BSHI Training meetings were held in the autumn – for the BSHI Diploma and the Higher Training Meeting for those preparing for the FRCPath part 1 exam. Reading the reports highlights the quality of training provided by BSHI, given by experts in their fields. Thanks to Jennifer McCaughan and Dan Eggleston for summarising the meetings for us.

Researchers are continuing to make progress in understanding the effects of donor-specific antibodies after transplantation. This issue's Science Watch article examines the contribution of IgG subclasses in antibody mediated rejection of kidneys. David Briggs puts the findings into context for us.

We finish this issue with a thought-provoking case study discussing an unrelated cord blood transplant in an adult BME patient with ALL. More case studies are welcome! Submission details are towards the end of the Newsletter.

Thanks for all the contributions to this Newsletter and we look forward to your articles for the next one!

The Editorial Team

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Paul Terasaki.... continued

activity in transplantation in "Clinical Transplants" published annually.

Collaboration was always a priority for Paul. He took a major role in every International Histocompatibility Workshop and actively encouraged others to contribute and not limit their own developments to publication in journals. The 1980 IHW hosted by Paul in Los Angeles was, arguably, the most innovative and progressive IHW firmly placing HLA protein testing at the centre of effective clinical transplantation by establishing, amongst other developments, the minimisation of HLA-DR protein mismatching between a recipient and their donor as a necessary prerequisite. Leading up to the 1980 IHW, Paul successfully established a world-wide transplant centre database of kidney transplants and reported through the Pre-IHW Newsletters on relevant analyses led by his close colleague Gerhard Opelz. In addition, these helpful Newsletters fed back technical developments established by IHW participating labs. Many will know that Opelz moved to Heidelberg, Germany, to build on his experience from LA and the IHW to establish the clinically unique Collaborative Transplant Study (www.ctstransplant.org).

In 1982, Paul was elected as President of the Transplantation Society - an honour for a scientist in a field dominated by clinicians. At his inaugural address at the Brighton, UK, Conference Centre he called for further international collaboration including exchange of kidneys across national boundaries to create effective transplant options for immunologically challenging recipients. Although prolonged cold storage times might result, Paul had already supported the development of Collins preservation fluid to minimise the impact of storage of kidneys at 4◦C.

When travelling to the 1984 IHW in Munich, a group of UK H&I scientists gathered in a Heathrow departure lounge and whilst conversing about the upcoming conference, Paul and his wife struggled into the room. We whispered "it's HIM". I saw all was not well and decided to approach Paul offering any help and explaining that whilst he would not know us, we all knew him. This was the start of a friendship between us which Paul always made the effort to maintain despite his elevated status in the transplant community. It transpired that his wife had not travelled well from California but thankfully soon recovered on her arrival in Munich. I helped with bags and taxis in Munich but on the first day of the IHW I was taken aback when Paul looked me up in the crowded meeting room to thank me. We met and chatted at subsequent conferences and Paul was always keen to have my thoughts on where clinical transplantation might be heading next. I shared with him the exciting work on post-transplantation sensitisation to donor mismatched HLA proteins which Sue Martin and Judith Worthington pioneered in the Manchester laboratory. This observation, which followed some earlier indicative publications, was subsequently confirmed by many others and inspired Terasaki through his laboratory at UCLA and then at his company, One Lambda, to develop highly specific and rapid tests to detect HLA reactive antibodies in patient serum.

A further important collaborative innovation which Paul pioneered was training workshops often supported financially by his company. These meetings spread across the globe and remain an important aspect for sharing developments in the field. VHBio, as the UK distributor for One Lambda, has provided much appreciated support for BSHI in several aspects, including access

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Paul Terasaki.... continued

to training, often under-appreciated by the NHS where funds for training are scarce.

Paul never retired. After moving on from One Lambda, left in the competent hands of his colleagues (Ayoub, Han, El-Awar, Ordonez and others) who provided much technical and organisational support at the memorable 1980 IHW, he established a Foundation and private laboratory which continued to contribute innovative research findings reported in leading peer review journals and to make significant technical developments. Paul travelled world-wide to deliver important and interesting lectures, often invited as a key-note speaker. He always had something new to say. Paul's Foundation donated very substantial monies to UCLA for a building in the Department of Surgery and endowed a clinical chair there too, again illustrating Paul's generosity.

Paul was gentle, approachable and generous despite his elevated status amongst those of us working in H&I. Several of us from the UK H&I community have fond memories of Paul and all have interesting recollections to share. As you can see in the accompanying photograph when Prof Derek Middleton, myself and Paul attended a One Lambda Workshop in Cape Town, South Africa an important feature was time to relax and chat which was always something Paul was keen to foster knowing that informal conversations are often the most productive.

Of greatest importance was Paul's innovation in many areas directly impacting on clinical transplantation. There are many 'heroes' in this field and the surgical giants of Murray, Hamburger, Starzl, Barnard, Morris and Calne are those associated with the life-saving procedures but we who work in H&I laboratories know there are many others deserving of accolades at the highest level -Paul is one of them. It was an honour and a pleasure for many of us in the UK H&I community to meet Paul, to collaborate with him and to spend time with him. Many transplants recipients alive today will never have heard the name "Terasaki" but every single one owes Paul a big "thanks" and there can be no bigger tribute.

Professor Phil Dyer OBE, PhD, FRCPath

BSHI Founding Chairperson 1990-1993

British Transplantation Society President 2002-2005

H&I Clinical Scientist in Birmingham (1977-78), Manchester (1979-2008) Edinburgh (2008-2012)

For a formal obituary visit www.terasaki.org.

End

Chair's Report

Dear Colleagues,

Welcome to the Spring edition of our BSHI Newsletter.

In February, the sad news of Dr Paul Terasaki's death was announced. His passing is a huge loss to our community, but we are privileged to have shared his company for so long. In my days as a young scientist, one of the main reasons why I was drawn to H&I was that, as a developing discipline, many of the great scientists responsible for fundamental discoveries which advanced our understanding of histocompatibility were still alive. Not only were these "H&I Famous Names" alive, but they were also very approachable, personable people, more than happy to share their expertise. Dr Paul Terasaki was one of these individuals. Several of us had the opportunity to meet him; exchanging ideas in One Lambda-sponsored academic meetings. In the spring of 2010, we had the unusual honour of welcoming him to our laboratory during a rare gap in his schedule. This edition of the newsletter began with an obituary to this great man written by Prof Phil Dyer. Dr Terasaki's love and enthusiasm for H&I were infectious, and I hope that reading about his extraordinary life will be an inspiration to our more junior members.

The UK H&I community has experienced its busiest period ever. A record number of kidney transplants were performed in the UK during 2015, as we move towards the transplantation targets set for 2020. Many of our laboratories and staff are feeling the strain, and workforce issues are the top of BSHI's priority for this year. The Education Board is working hard to adapt existing national training schemes to improve their fitness for purpose. To ensure that the requirements of all our laboratories are addressed, BSHI held a Workforce Development Workshop on 1st March 2016. This offered the opportunity to hear the latest news about H&I training at all levels, and to discuss ways in which we can create a sustainable future for our services.

Further to our announcement at the BSHI AGM in Cambridge, BSHI has now consolidated our secretariat support services, and has moved the management of the BSHI Diploma, and Conference support services to Executive Business Support, who previously managed our accounts. We are confident that bringing all our managerial needs under the control of a single organisation will improve our efficiency as a society. Hopefully as members you will appreciate the benefits of this arrangement very quickly.

This is the time of year when our thoughts turn to the preparation of abstracts for our BSHI Meeting in Keble College, Oxford on 12th-14th September. Details of abstract submission will be announced shortly, and the Local Organisers are working closely with the Research Executive to finalise the programme of what promises to be an outstanding meeting. We are also delighted to announce that our 2017 meeting will be held in Cardiff. This meeting will be held slightly earlier in the year during June or July to avoid a conflict with the 17th International Histocompatibility Workshop in September 2017.

With best wishes,

Kay Poulton

February 2016, Manchester.

End

BSHI Committee Report

Secretary's Report from the meeting held on the 21/01/16.
The following issues were discussed:

Chair's report

- **Welcome to new members of the BSHI Committee:** A warm welcome was extended to the newly elected members of the Committee; Katy Derbyshire has agreed to take on the role of Meetings Secretary, Anna Barker will be the new Membership Secretary and Tom Browne is an Ordinary member of the Committee.

- **Recent engagement with Prof Shelley Heard, Modernising Scientific Careers (MSC) Medical Advisor:** Due to concerns within the H&I community about training posts, workforce planning and future recruitment to senior posts, an H&I workforce plan was submitted to the MSC team a number of months ago. Due to limited engagement from Professor Sue Hill's office, Professor Shelley Heard, Medical Advisor to the MSC team has been approached for advice. Professor Heard suggested that a letter should be written to heads of organisations hosting H&I services and that a business case for funding of HSST should be drawn up. A meeting is being planned between the BSHI Chair and the Chair of the BPAG with Prof Heard to see if there may be other opportunities to raise the profile of H&I within MSC.

- **Report back on AHCS Congress, Edinburgh December 2015:** DT attended the Congress and Council meeting on behalf of BSHI. The congress focused on the role of the Academy to provide 'one voice' for HCS, but there were some comments that the remit of the AHCS is still not widely understood. BSHI need to ensure that a senior member of the community, not necessarily the Chair, is available to attend the AHCS Council to provide the appropriate continuity to this group.

Secretary's report

- **Bursaries 2015:** A total of £6,100 was given to BSHI members as bursary awards in 2015. The majority of this was to help attendance at the BSHI 2015 Cambridge meeting. A budget for bursary allocation in 2016 will be set, allowing funds to be released throughout the year for BSHI, EFI and other scientific conferences/training events.

- **Policy on advertising posts/sending out information by email:** DT is to work on updating the BSHI guidelines for job ads after recent questions to the Committee. We need to clarify what constitutes BSHI business (which will be free) and state the cost per mailshot.

- **CSO Conference 2016;** Leading the Vision for 20/20: KP asked TB if he would like to attend this meeting on behalf of BSHI.

- **Julia Bodmer Award and One Lambda summer meeting:** DT circulated JB award flyer prior to this meeting. The closing date for applicants will be 31/03/16. The process of selecting a recipient of the VHBio award for attendance at the One Lambda summer meeting is being taken forward by the TDE.

Treasurer's report

- **BSHI Accounts:** Current account: £70,697; Savings account: £32,316; Reserve: £3,251

- **New BSHI Bank Account:** The Financial Services Compensation scheme changed on 1st Jan 2016 with the level reducing from £85K to £75K. EBS will open a new account with Santander in the near future and move monies from the current account into the new account so that there is always less than £75K with any one institution.

- **Change from Kingston Smith to EBS:** Handover of many of BSHI's administrational tasks to EBS has been completed. There are a number of storage boxes currently at EBS that will be looked at to see what the Society wishes to keep. The items required for posterity will be electronically archived.

- **Conference Organisation:** EBS have taken on the conference organisation from 2016. The outturn from BSHI 2014 in Manchester was £4153.

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BSHI Committee Report.... continued

Membership Secretary's report

- **Current BSHI Membership:** Active membership looks low as currently in process of collecting monies from members; have 126 paid up members and for 310 we're awaiting payment. There are 11 new members since the 2015 AGM, and a total of 12 retired members.

- **Corporate Membership:** BSHI currently has 7 corporate members. All members of the committee were tasked with approaching companies that may not be aware of corporate membership to see if this number could be raised.

Meetings Secretary's Report

- **BSHI 2015 Cambridge:** The feedback from this meeting was discussed and on the whole was very positive. A common criticism was the space given for the poster viewing which was deemed somewhat inadequate. There were also some requests made for more presentations on HSCT. All of the comments and scores to questions will be made available to the organisers of BSHI 2016.

- **BSHI 2016 Oxford (13th and 14th September):** the organisation for this meeting is progressing well between EBS, the RE, the local organisers and the Meetings Secretary.

- **BSHI 2017 Cardiff:** a report from the local organisers was presented at the meeting. A huge amount of effort already appears to have gone into the selection of potential venues for the meeting and social aspects!

- **Future BSHI meeting venues:** KP is to discuss venues with potential hosts for BSHI 2018 and BSHI 2019. BSHI 2020 will be held as a joint meeting with EFI in Glasgow.

BSHI Education Board Report

- No report was tabled in the absence of the BEB Chair

Professional Advisory Group report

- **H&I Review:** There was a further telecon involving the H&I subgroup of the H&I review on 18/12/15 at which the updated dataset collated by Martin Barnardo was discussed. Concerns exist that a number of centres have not responded to the request to validate data relating to manpower deployed to solid organ workload management. Concerns were also expressed that too complex a dataset was being pursued and that there was a need to reduce this to more simple measures to enable direct comparison and a meaningful analysis. Inconsistency of the part of the dataset relating to clinical activity with that published by NHS-BT was also identified and it was agreed to reference the latter rather than the submitted data in the final report. It was also agreed that certain core data such as the size of the waiting list supported by a laboratory were more indicative indices of 'at-bench' activity than number of transplants supported. A further teleconference is scheduled for 03/02/16. The end of March 2016 has been provisionally set as the deadline for delivery of the agreed dataset to the main review.

Continued on next page

- **Letter to President of AHCS prior to meeting with CMO NHSE:** A request for notification of 'burning issues' by the President of AHCS, Dr Brendan Cooper, for communication to the CMO, Prof Dame Sally Davies was responded to by BSHI indicating the profession's concern that H&I workforce planning and education needs to deliver strategic goals set by the UK strategy for organ transplantation to 2020 had not been meaningfully addressed. Specific concerns in respect of Consultant recruitment and outputs of MSC programmes which are failing to deliver numbers required to sustain service delivery into the future were highlighted. In follow-up to the meeting with the CMO, Dr Cooper sent out a short report identifying it as 'positive and useful' and promising a more detailed account following on. This is still awaited.

- **Letter for circulation to Trust etc Chief Execs re H&I workforce:** Following advice received from Prof Shelley Heard at HEE a letter was provided to heads of labs for forwarding to their CEOs in regard to laboratory capacity in respect of delivery of 2020 transplant targets and underlining concerns for sustainability arising out of failure to proactively plan for these increases. A request for notification of its use to brief CEOs was made in order to determine the level of coverage achieved. Four centres have indicated that the letter was forwarded on.

BSHI Website

- Update to BSHI website: The Committee are keen to progress this, but appreciate the difficulty of such a large task being undertaken by a single member of the Committee (JR). JR is to discuss with EBS to see if they can help with this website development

Newsletter Team Report

- **Submission Schedule 2016:** Volume 102, Issue 1 – 18th January, Volume 103, Issue 2 – 18th April, Volume 104, Issue 3 – 18th July, Volume 105, Issue 4 – 17th October

- **Facebook:** We have continued to post a mixture of BSHI info and items of general interest and will continue to do so for our younger and young at heart members.

AoB

- **Election of ordinary Committee member:** Due to JR's period on the committee coming to an end at BSHI 2016, an election will need to be held over the summer. Details will be sent out in due course by DT.

End

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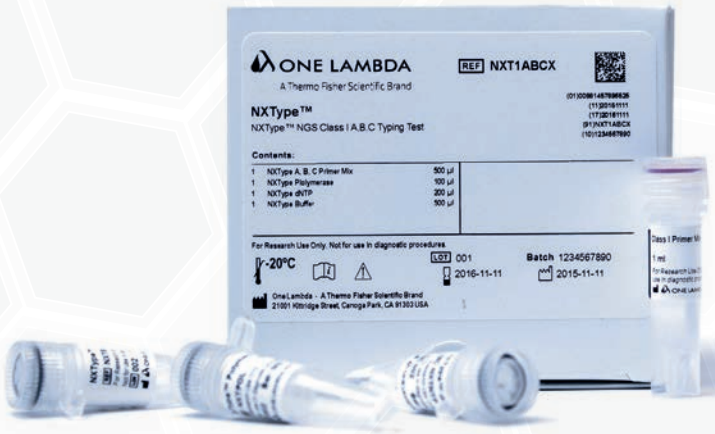

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TABLE 1. NXTYPE GENE COVERAGE

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HLA-B	Full gene
HLA-C	Full gene
HLA-DRB1	Exon 2 - Intron 3
HLA-DRB345	Exon 2 - Intron 3
HLA-DQB1	Exon 2 - Intron 3
HLA-DQA1	Full gene
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Science Watch

Donor-specific antibodies: *vive la difference!*

Lefaucheur, Carmen, Denis Viglietti, Carol Bentlejewski, Jean-Paul Duong van Huyen, Dewi Vernerey, Olivier Aubert, Jérôme Verine et al. "IgG donor-specific anti-human HLA antibody subclasses and kidney allograft antibody-mediated injury." J Am Soc Nephrol: 2016 Jan; 27: 293 - 304.

Donor HLA-specific antibodies (DSA) are known to cause damage to organ transplants. The question of how much antibody is required to cause significant harm (eg via Fc-mediated activities) remains unanswered for two main reasons. Firstly, no one has yet managed to properly quantify HLA-specific antibodies in serum or plasma. Measuring the amount of DSA binding to donor leukocytes (eg as in a flow cytometric crossmatch) is perhaps the best we can do at the moment but of course this is unlikely to be equivalent to their binding to the various tissues in a transplanted organ. Secondly, DSA are heterogeneous, varying with specificity, affinity, glycosylation and isotype; all of these factors are likely to contribute to the overall pathogenicity of the collected, circulating DSA. Many researchers are therefore investigating these properties and IgG subclass analysis is gaining particular interest; single antigen bead assays make this possible, the biology of human IgG subclasses is well understood, and there is the considerable heterogeneity in IgG1-4 composition in HLA antisera: there is something to shoot at.

This paper by Lefaucher, et al [1] proves that this interest is justified. This group are not the first or only ones to demonstrate the relevance of HLA-specific IgG subclass in organ transplantation (Kaneku et al have shown how IgG3 relates to chronic rejection of liver grafts [2] and we have shown that the presence of preformed IgG4 DSA can predict early rejection [3], for example) but what makes this work so important is the detail of the combined analysis of antibody and histological data. Three clinical and histological patterns were defined, aABMR, sABMR and ABMR-free and each was found to associate with different IgG subclass patterns. In particular, they assert that, in their transplants, aABMR was mainly driven by IgG3 DSA while sABMR was driven by IgG4 DSA: IgG3 associated with manifestations of early rejection, IgG4 with later graft injury.

The statistical and mathematical methodologies used to explore their data are also an important feature of this study. As a clinical and scientific community we are going to have to embrace and use this type of mathematical approach not least because of the complexity (depth and breadth) of the information we now generate (HLA is, of course, intrinsically complex). Mathematical modelling, machine learning, decision trees, principle component analysis (used here) and more are methodologies with which we need to become familiar, if not understand, and with these we can exploit our vast data reserves as well as undertaking useful R&D. The clear clustering of differential clinical symptoms and outcomes with differences in the quality of specific antibodies, which are easily measurable, offers the potential to better understand the underlying immune processes, predict outcomes, and to design and develop targeted interventions.

Predicting outcomes with reasonable certainly and risk stratification models based on the properties of DSA is an exciting and generally practical prospect. However, as far as this study is concerned, a flaw in its design does limit such use. It is clear from the information given that many of the assays were done on samples taken after the rejection events. This limits conclusions about the predictive or causative nature of specific IgG isotypes. If we do not know whether a DSA was present at the time or before the clinical event we cannot distinguish between it causing the event and being caused by the event. A crucial successor to this study must involve a prospective

Continued on next page

collection of samples designed to span potential events of interest. We then need to build models around all the relevant, measureable features of HLA specific antibodies. Unfortunately measurement of one of the most significant factors, antibody amount, is still not satisfactorily resolved. MFI values from single antigen bead assays are widely used despite many shortcomings using this to compare the strength of different antibodies.

A concluding paragraph must mention one of the great pioneers in our field because of his unique contribution to transplantation, without which this study would not have been possible. We have come a long way with the late Paul Terasaki since he alerted transplanters to the dangers of HLA-specific antibodies [4]. We are now close to being able to understand the why, when and how of these apparent obstacles to transplantation; why are DSA sometimes a contra-indication and sometimes not; when should we treat a donor-specific post-transplant humoral response; how can we manage DSA and ABMR. We have the tools to investigate these and of course many of these tools have continued to be developed and provided by Terasaki and his colleagues.

David Briggs
Chair, BSHI RE
H&I, NHSBT, Birmingham

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End

BSHI National Higher Training Meeting

Manchester Transplantation Laboratory on the 12th and 13th November 2015.

Jennifer McCaughan

The BSHI National Higher Training Meeting was held at the Manchester Transplantation Laboratory on the 12th and 13th November 2015. Over the course of the two days, a wide range of topics relevant to Histocompatibility and Immunogenetics were covered.

The course commenced with a presentation by Dave Lowe on epitope matching. In this talk, Dave discussed the platforms for, and potential utility of, epitope matching in solid organ transplantation. He also critically appraised the use of additional antibody analysis techniques, such as C1q assays and antibody isotype analysis, in risk stratification. In the afternoon, Martin Howell provided a comprehensive overview of the role of HLA in disease risk. It was particularly interesting to hear of the recently published research which proposes a molecular mechanism for the long recognised associations between HLA class II antigens and rheumatoid arthritis and type 1 diabetes mellitus. The remainder of the first day had a clinical flavour with a presentation on the options for immunosuppression following kidney transplantation and an interactive session with Professor Robert Wynn, Honorary Clinical Professor of Paediatric Haematology and Cellular Therapy in Manchester, who discussed the role of haematoprogenitor cell transplantation in Paediatrics and the importance of appreciating the "risk of transplanting" versus the "risk of not transplanting" for each individual patient.

The second day began with a session from John Goodwin on platelet immunohaematology. The current guidelines for the management of patients with platelet refractoriness were discussed and some time was spent in small groups interpreting the HLA type and antibody results for an individual with platelet refractoriness and selecting potential platelet donors. One of the aims of the National Higher Training Meeting is to prepare candidates for FRCPath Part 1 and Stephen Sheldon from the Manchester laboratory gave a talk on negotiating this exam. This was followed by an interactive session in small groups where questions from past papers were discussed and an approach to addressing these questions was developed. Each group was led by individuals who had passed the FRCPath Part 1 exam and who were able to offer guidance on this process. The final session of the afternoon covered the role of an H&I laboratory in haematoprogenitor cell transplantation. This presentation provided a summary of the important criteria which should be taken into consideration when selecting donors.

One of the most stimulating aspects of this meeting was the opportunity to meet colleagues from throughout the UK with a range of areas of expertise. The discussion which occurred around the various presentations was both interesting and educational and there were opportunities for each person attending to learn from the other attendees as well as the presenters. This was facilitated further by the regular coffee and lunch breaks which were much appreciated. Thank you to Alison Logan and her team for all their work in making this such a worthwhile event.

End

H&I Part 1 Study Forum

A closed facebook group has been created to link scientists from all labs studying towards their RCPath Part 1 exam in H&I. It is an informal forum to explore themes, share ideas and exchange study skills. All welcome to join.

Any queries, please email *Natalia.DiazBurlinson@cmft.nhs.uk* or send me a message via facebook.

BSHI Diploma Training Day
Manchester Royal Infirmary, 27th November

Dan Eggleston, Anthony Nolan Laboratories

This year's BSHI Diploma Training day was held at the Manchester Royal Infirmary on 27th November. There were 5 lectures, given by speakers from laboratories all over the country. The theme of the day was 'Management of the difficult patient' and covered a range of topics from STR analysis, to KIR genotyping.

Post-transplant Engraftment Monitoring by STR Analysis

After an early morning trip up to Manchester, everybody settled down with a cup of tea and some Quality Streets (other brands of chocolate are available) for the initial session: engraftment monitoring post-transplant through the use of STR analysis with Dr Helena Lee. Dr Lee explained that STRs are short tandem repeats - small nucleotide sequences that are repeated throughout the genome. There are many STR loci present in the human genome and the number of repeats at each locus varies between individuals (except monozygotic twins). These highly polymorphic STRs can be mapped, giving each person a unique profile that can be used post-transplant as a way of identifying the degree of chimerism between donor and recipient cells. Pre and post-transplant samples can be compared with a donor sample to determine the percentage of donor cells present post-transplant. The technique's sensitivity can be increased by cell lineage separation, as chimerism can vary between different leukocyte populations. An increase in recipient derived cells can imply engraftment failure or disease relapse while increased proportions of donor cells reflect successful engraftment. Interestingly, recipients can be stable with mixed chimerism, depending on their condition.

Provision of Platelet Support

After a quick refreshment break, it was over to Dr Colin Brown for a session on Platelet Support. When a patient's platelet count does not increase significantly in response to platelet transfusions (an increase of <10000/mL is considered a failure to increment), then they are considered refractory. These patients are then referred for HLA antibody screening. If HLA antibodies are found, HLA selected platelet units can be recommended. If no HLA antibodies are found, the patient is most likely to have non-immune refractoriness, potentially stemming from splenomegaly, bleeding, infection or even certain antibiotics.

Cord Blood Unit Selection

Just before lunch, Dr Ann-Margret Little crossed the border to cover considerations when carrying out a cord blood transplant. A graft derived from umbilical cord blood can be advantageous due to better tolerance of mismatches, no risks to donor, reduced GvHD and off the shelf availability. However there is no possibility of Donor Lymphocyte Infusions, the stem cell dose is lower and the risk of infection post transplant can be higher due to delayed engraftment. All of these factors are considered by clinicians when choosing the best graft source for a patient.

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HLA Antibodies and Risk Stratification

The penultimate session was delivered by Professor David Briggs who discussed hazard and risk, particularly in the context of HLA antibodies, kidney transplantation and rejection. Current guidelines aim to quantify the risk of transplant based on known hazards. Antibodies are considered the primary hazard in kidney transplantation. Using Luminex, CDC or flow tests, many antibody characteristics can be identified including their specificity, titre, subclass and capacity for complement binding. All these results can be used in risk stratification. However, the risk of organ rejection when transplanting should be weighed up against the potential benefit to the patient of receiving the organ and the harm caused by inaction. Furthermore, strategies can be employed to reduce the risk of rejection. HLA Matchmaker can be used to epitope match, reducing HLA donor/ recipient differences and refining antibody specificity. Patients can also undergo desensitisation and immunosuppression to reduce antibody titres. Professor Briggs finished by stating that he felt the role of H&I scientists was to facilitate transplant by managing risk, not to veto by identifying risk.

KIR Genotyping in HSCT

Last, but by no means least, Alison Logan discussed developments in the field of KIR typing. Killer Cell Immunoglobulin-like receptors are expressed by Natural Killer cells and can be activating or inhibitory. KIRs have been shown to interact with HLA proteins, particularly through the 'missing ligand' hypothesis. In this, the lack of an HLA molecule, as can be caused by viral infection, can initiate a cell's destruction by a Natural Killer cell. KIRs recognise a number of HLA antigens and can be broadly split into 2 groups based on HLA-C recognition (C1 or C2). Mismatching HLA-C and KIR during a transplant can mimic this absence of an HLA molecule, causing NK initiated cell death so increasing GvL. Therefore matching of KIR types prevents the destruction of recipient cells. Current haploidentical transplants use T cell depleted grafts in order to reduce the risk of GvHD. However, this also results in a decrease in GvL and so increases the possibility of disease relapse. Mismatching at KIR may be an effective strategy to increase the GvL effect in these recipients.

The day was rounded off with a BSHI trainee forum hosted by Dr Sharon Vivers, the BSHI Trainee Representative. This session allowed trainees to ask questions and feedback on their experience of the BSHI Diploma. A significant amount of discussion was generated around essay marking and this will be fed back to the TDE at their next meeting.

The whole day was very well received and it was great to have so many diverse lectures from such a simple theme. Final thanks must go to Ben Adams for all his effort in organising such an engaging training day.

End

Case Study 1:
Unrelated Cord Blood Transplant in an Adult ALL Patient

Natalia Diaz Burlinson, Transplantation Laboratory, Manchester

Case Selection

Case study 1 was chosen early in my preparation for the RCPath Part 2 examination. I had recently been appointed to my position as Head of the Molecular Section and, although routinely selecting cord blood units (CBU) for paediatric patients and stem cell donors for both paediatric and adult patients, I found identifying suitable CBU for adult patients a challenge. This was due to the usual requirement of 2 CBU to obtain a sufficient cell dose for an adult patient's weight. My training manager at the time recommended I prepare this case study as an aid to my routine clinical practice.

Introduction

SN is a male patient of Indian ethnicity who was diagnosed with Philadelphia positive acute lymphoblastic leukaemia (ALL) in September 2006 at the age of 27. His white cell count was 29.2 – the normal reference range is 4-11 $x10^9$/l. His cerebrospinal fluid was positive. His blood group is B RhD positive and he is CMV positive.

ALL is a rare condition occurring at 1-1.5 per 100,000 individuals. The term ALL encompasses a range of malignancies resulting from the proliferation and expansion of lymphoid blasts in the bone marrow, blood and other organs. In 5-7% of patients, there is central nervous system (CNS) involvement which can be detected using cerebrospinal fluid (CSF) cytology or flow cytometry. Patients with CNS involvement have been shown to have lower survival rates than patients with no CNS involvement (Jabbour 2010).

The presence of the Philadelphia chromosome (Ph+) is the most frequent karyotypic mutation present in adults with ALL, occurring in 20-30% patients, rising to 50% in patients over 50 years old (Thomas 2007). The Philadelphia chromosome is a translocation between the breakpoint cluster region (BCR) gene on chromosome 22 and the Abelson tyrosine kinase (ABL) gene on chromosome 9 [t(9;22)(q34;q11)] which results in a constitutively active tyrosine kinase protein, BCR-ABL.

Prior to tyrosine kinase inhibitors (TKI) such as imatinib mesylate, survival rates for adults with Ph+ ALL were not high: one report suggests complete remission rates of 70% and 5-year overall survival rates of 20% (Ohno 2008). Allogeneic haematopoietic stem cell transplantation (HSCT) performed when the patient achieved first complete remission (CR1) offered the highest likelihood of cure, but this was often limited to patients with an HLA-matched sibling or volunteer unrelated donor (VUD). A study of Ph+ ALL patients who received an allogeneic HSCT had a 5-year relapse risk of 32%, compared with 81% in those patients who were treated with chemotherapy alone or autologous HSCT (Goldstone *et al* 2001).

TKI therapy works by binding to the inactive BCR-ABL and partially blocking the binding site of ATP, thus preventing the conformational change to the activated oncoprotein. However, imatinib resistance has become an issue in certain patients, mainly due to the acquisition of point mutations in the ABL tyrosine kinase domain that prevents binding of the drug. Unfortunately, in up to 20% imatinib-resistant patients, there is also resistance to one of the 2nd generation TKI, dasatinib (Pfeiffer *et al* 2007).

Clinical History

Following diagnosis in September 2006, SN received chemotherapy treatment in India, as per the UKALLXII trial. This involved:

- Vincristine
- Asparaginase
- Daunorubicin
- Prednisolone

He also received consolidation treatment consisting of high dose Ara-C (cytarabine). This is administered after remission is achieved following initial treatment and is used to destroy any remaining malignant cells. SN received cranial radiotherapy in November 2006.

SN returned to Barts and the London NHS Trust (BLT) in early 2007 for maintenance therapy, administered to reduce the risk of relapse:

- 6-mercaptopurine (6MP)(daily)
- methotrexate (weekly)
- Imatinib

At this stage, if an HLA-matched donor (sibling or unrelated) could be identified, SN would receive an allogeneic transplant.

In December 2007, SN was no longer considered for allograft as no donor had

Continued on next page

Case Study 1.... continued

been identified for him. He continued to receive 6-MP, methotrexate and imatinib until March 2009 when this was reduced to imatinib alone.

SN subsequently relapsed. One cycle of salvage re-induction therapy was necessary in 2010 but SN suffered a subdural bleed. Allogeneic transplantation options were then revisited. In February 2010, the levels of BCR-ABL detected in SN's blood were rising and a bone marrow aspirate was performed. This showed 4/200 cells contained the Philadelphia chromosome, consistent with low level cytogenetic relapse. His dose of imatinib was increased. A mutation screen showed no obvious BCR-ABL mutation. An application to his Primary Care Trust for dasatinib – another TKI used when imatinib is no longer effective - was rejected. SN's BCR-ABL levels continued to rise and in August 2010 he underwent another bone marrow aspirate which showed morphological relapse with 20% blasts. At this point, SN's full blood count and lactate dehydrogenase (LDH) were normal; LDH levels can be elevated as a result of tissue damage, especially haemolysis, as LDH is present at high levels in red blood cells and is a marker of ALL.

Methodology

SN's sample was received in the Clinical Transplantation Laboratory (CTL), Royal London Hospital (RLH) for extended HLA typing in May 2007 in accordance with transplant policy requirements for an allograft, which are higher than the European Federation of Immunogenetics (EFI) mandatory minimum of HLA-A, -B and –DRB1 (Nunes *et al* 2011). It was tested by Luminex® technology and polymerase chain reaction with sequence-specific primers (PCR-SSP) (high resolution Class II, intermediate resolution Class I).

HLA type:

A*02:11/69, 03:01+

B*07:05/06, 35:03/36

C*03:03+, 04:01+

DRB1*10:01, 16:02

DRB5*01:01+

DQB1*05:01, 05:02

The '+' after the HLA allele indicates a string of alleles in accordance with laboratory reporting policy for intermediate resolution results. In these circumstances, it is highly likely that the allele present is the first allele in the string; Luminex® technology is able to separate other common alleles e.g. in SN, A*02:11/69 does not fall under the more frequent A*02:01+ string, whereas he possesses A*03:01+ which (if sequenced to high resolution) is likely to prove to be the A*03:01 allele. The CTL reporting policy adapts to the presence of a synonymous mutation, where this may mask the presence of the most likely allele later in the allele string e.g. the B*44:02:11+ string indicates the more likely B*44:03 allele. Such an elaborate reporting policy that adapts to regular nomenclature updates is necessary due to limitations with the current laboratory information management system and the need to report intermediate resolution results in an accessible format.

The best donor option for HSCT is a fully HLA-matched sibling. In a non-consanguineous family, there is a 25% chance of a sibling being matched to the patient. For SN, 1 sibling was HLA tested at the DRB1 locus, which was mismatched so no further work was performed, in accordance with laboratory policy.

Due to the genetic proximity on the short arm of chromosome 6, many HLA genes travel 'en bloc', with linkage disequilibrium (LD) frequently seen between the loci, especially HLA-B and –C and HLA-DRB1 and –DQB1. LD is defined as the presence of certain HLA combinations in the population at higher frequencies than would be expected if the loci segregated independently. In addition to LD between specific loci, haplotypes of certain HLA alleles are frequently seen in different populations as they are inherited together. As not all populations are represented on the VUD registries – HSCT being an expensive treatment option not available in many countries – patients possessing less usual allele combinations can struggle to find a suitable unrelated donor. In SN, HLA-B*35:03 is seen in many populations in association with HLA-C*04:01. However, HLA-B*07:05 has been described with HLA-C*03:03 only in Indian populations with a frequency of 2.4%, which is much less frequent than the more common association with HLA-C*15:05 (Gonzalez-Galarza *et al* 2011). It is likely, therefore, that any donor that may be HLA matched at the other loci will be mismatched at HLA-C.

When SN's sibling was identified as mismatched, a Bone Marrow Donors Worldwide (BMDW) (www.BMDW.org) search was performed to assess the number of potential stem cell donors available. BMDW is a free internet-based tool which gives HLA typing of potentially compatible donors and indicates which donor registry they are listed on but gives no further details (eg. gender, age etc). A formal donor search is required to request verification typing (VT) samples. BMDW search results below:

- x1 A,B,DRB1 (DRB1*16:02)
- x1 A,B,DR (DRB1*16)
- x2 A,B,DR (DRB1*15/16)
- x4 A,B,DR (DR2)
- x49 1A mismatch

The internal short-hand notation for BMDW or formal search report results

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Case Study 1.... continued

differentiates between donors identified as known allelic matches at the DRB1 locus (recorded as DRB1 above) from those matched at the first field only (recorded as DR above). Due to the technologies available when stem cell donor registries were established, some donors were only tested by serology at the DRB1 locus; this is recorded with the serological specificity in parentheses eg. DR (DR2). The HLA-A and –B loci were tested by the donor registries at low resolution. No HLA-C testing was available. Based on these results, a formal donor search of the British (Anthony Nolan Trust [ANT], British Bone Marrow Registry [BBMR] and Welsh Bone Marrow Donor Registry [WBMDR]) and international donor registries was initiated in June 2007 - search results below recorded in internal short-hand notation:

- ANT: x1 A,B,DR (DR2)
- Italy: x1 A,B,DR (DR2)
  x1 A,B,DR (C mismatch)
- NMDP (USA):
  x1 A,B,DRB1
  x7 A,B,DR (DR15/16) where the DRB5 association suggests these donors will be DRB1*15 not 16.
- Caitlin Raymond (USA):
  x1 A,B,DR (DR2)
- Canada: x1 A,B,DR (DR2, C mismatch)
- Germany: x1 A,B,DR (C mismatch)

VT samples were requested from x2 donors in June 2007 as these were the most likely to be a 10/10 match (donors 1 & 2 – see Appendix 1).

In March 2008, x3 cousins were tested at the HLA-DRB1 locus. They were all mismatched to SN so no further work was performed.

After having been removed from the transplant list in December 2007 as no donor had been identified, in June 2008, SN was again considered for allograft. A re-search was performed but no new donors were identified. At this point, 1 antigen mismatched donors at HLA-A,-B,-C,-DRB1,-DQB1 (9/10) were considered so VT samples were requested on x2 HLA-C mismatched donors in July 2008 (donors 3 & 4 - see Appendix 1). Local DRB1 typing - performed by the registry on stored DNA - was also requested on 2 other donors:

- Caitlin Raymond: x1 A,B,DR (DR2), Male, 42 yrs. This donor was deleted from the registry in September 2008.
- Italy: x1 A,B,DR (DR2), Male, 46 yrs. Local typing indicated this donor was DRB1 mismatched so VT samples were not requested.

Local typing of a single locus performed by the donor registry on stored samples is cheaper than requesting VT samples. However, if a HSCT is required urgently, this can add precious extra weeks to a donor being identified, as under EFI accreditation standards, all donors must be HLA tested prior to transplant in the same laboratory as the patient (EFI standard [v6.1] I4.3.2.1). Also, depending on the procedure of the donor registry involved, the donor may not be contacted at the time of testing on stored material. Therefore, a potentially matched donor may then subsequently be deleted from the registry if unwilling or unable to donate.

In January 2009 VT samples were requested from donor 5 (see Appendix 1). The donor medical consent form for one of the donors highlighted that the donor requested had received a bone graft from a deceased donor 6 years previously and had also tested positive for Hepatitis B surface antigen in one test, although subsequently tested negative. SN's clinicians decided to proceed with the VT request as no other donors were available. Although it was acknowledged that the donor was unlikely to pass the medical test prior to donation, this donor was a potential chance to find a match and SN's clinicians wished to explore every possible option. Donor re-searches were performed every 3 months to identify any new donors that may have registered since the last search.

In August 2010, the ANT contacted two VUD registries in India, not listed on the BMDW. They had no potential donors.

In September 2010, SN's consultant requested a cord blood search as a double cord transplant was now being considered under a new protocol organised by the British Society for Blood and Marrow Transplantation on reduced intensity conditioning with umbilical cord blood transplantation (BSBMT RIC UCBT 2009). The protocol requirements are either a single or x2 units with up to x2 mismatches at low resolution HLA-A, -B and high resolution HLA–DRB1 (4/6, 5/6 or 6/6); if x2 CBU are infused, the intercord compatibility must also be a minimum of 4/6 match; a total nucleated cell dose (TNC) of 3 x 10^7 cells/kg, with each CBU not being less than 1.5 x 10^7 cells/kg. SN's weight was 90kg (01/11/10). Therefore, each individual CBU must have a TNC of 135, with an overall TNC of 270. A BMDW cord search performed on 20/09/2010 resulted in no potentially matched or single antigen mismatched CBUs. However, there were potential CBUs with x2 antigen mismatches (4/6).

A re-search of the stem cell registries in October 2010 resulted in no new donors. However, x1 VT sample was requested (donor 6 - see Appendix 1). The age and low resolution HLA typing of this donor indicates why VT samples were not requested earlier.

In December 2010, SN was considering a haplo-identical transplant at another centre. He opted for a cord transplant

Continued on next page

and his consultant wished the transplant to occur in 2-2.5 months (February-March 2011). As SN had received multiple platelet transfusions which can act as sensitisation events, a serum sample was screened for HLA antibodies to ensure he had no HLA antibodies to the mismatched antigens in the CBU under consideration. He was HLA antibody negative.

In May 2011, funding for a double cord transplant under the BSBMT RIC UCBT protocol was agreed. The two cords identified from the Italian (ICB) and New York (NYCB) cord banks were requested on 28/06/11 for infusion on the 28/07/11. A DNA aliquot was sent from the cord banks to the CTL in advance of cord shipment to verify the HLA typing. SN's pre-transplant conditioning did not start until the CBU were received at the stem cell laboratory at the Royal London Hospital. As no segments were available on the CBU, after infusion the empty cord packs were given to the CTL for bioidentity verification testing to ensure the correct CBU had been shipped. Ideally, this would have occurred in advance of infusion, but it is not always logistically possible.

Results

In November 2010, medium resolution HLA-A,-B & -C and high resolution HLA-DQB1 were requested on x2 1DRB1 antigen mismatched 5/6 CBUs with a TNC of 171 and 149 (see Table 1). Due to the scarcity of material for testing and the inability to release samples to individual transplant centres until a CBU has been formally requested for transplantation, HLA typing was performed by the appropriate cord registries on stored DNA. The extended HLA types are below and the mismatches to the patient - at both first field and allele levels - are shown in Table 1. Mismatches are highlighted in Figure 1.

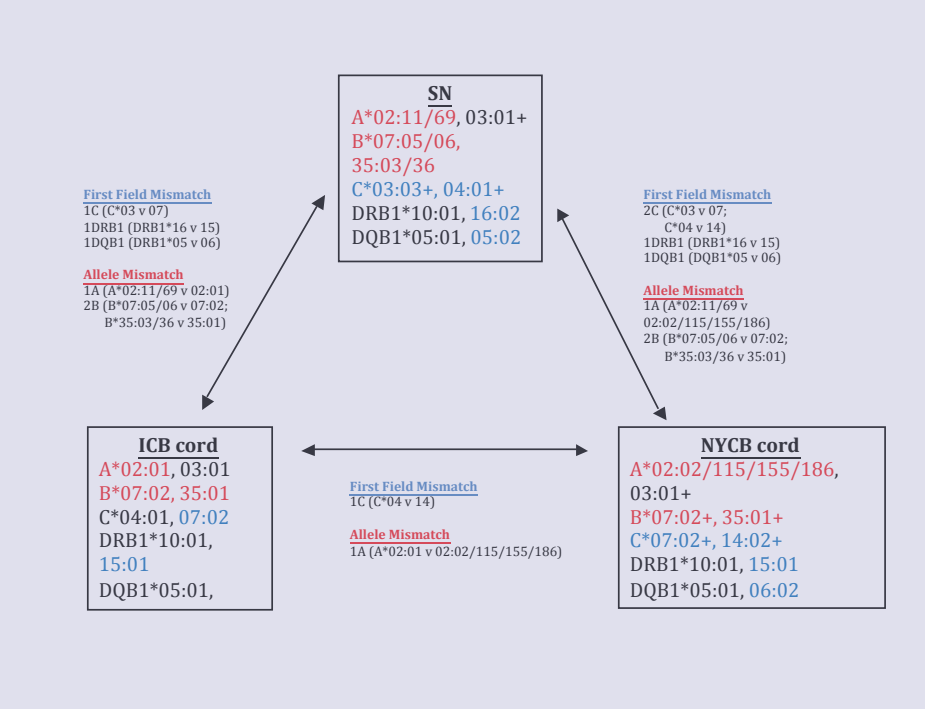

Figure 1: mismatches between SN and selected cord units

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Case Study 1.... continued

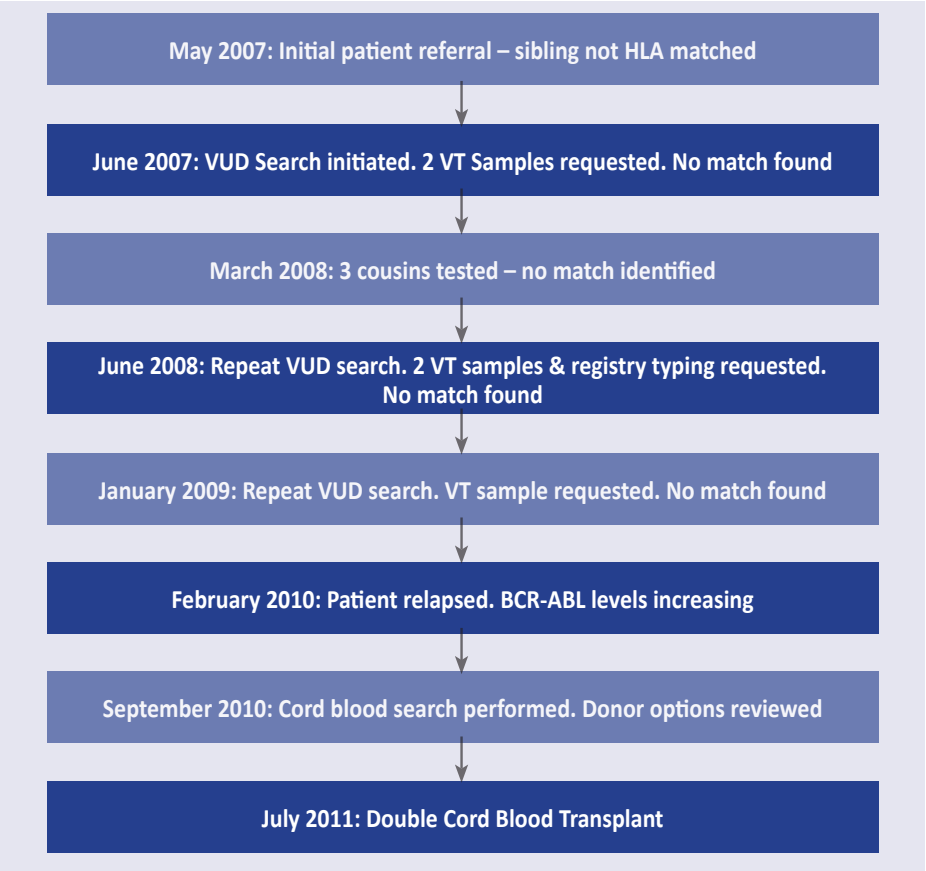
Cord Bank	Mismatch Identified on Search Report	Total Nucleated Cell Count	First Field Mismatch	Intermediate Resolution Allele Mismatch	Low Resolution First Field Match	Intermediate Resolution Allele Match	Demographics
ICB (Italian Cord Bank)	1DRB1 antigen	149	1C antigen 1DRB1 antigen 1DQB1 antigen	1A allele 2B alleles	5/6, 7/10	2/6, 4/10	Female Blood group A+ Birth: 2002 Viability: 99.2%
NYCB (New York Cord Bank	1DRB1 antigen	171	2C antigens 1DRB1 antigen 1DQB1 antigen	1A allele 2B alleles	5/6, 6/10	2/6, 3/10	Female Blood group O+ Birth: 2008 Viability: 100%
ICB v NYCB intercord	-	-	1C antigen	1A allele	6/6, 9/10	5/6, 8/10	-

Table 1: cord blood units selected for transplant

Pre-transplant conditioning was initiated 7 days before cell infusion. This consisted of: fludarabine, cyclophosphamide and total body irradiation (200cGy single fraction). GvHD prophylaxis consisted of: cyclosporine and mycophenolate mofetil (MMF).

Summary of unrelated donor search

A summary of SN's progress from initial referral to transplant is shown in the flow diagram opposite.



Post-transplant management

SN received his double-cord infusion on 28/07/11. Despite receiving the anti-fungal prophylactic drug Posaconazole and even though microbial cultures were negative, SN suffered fevers during his post-transplant in-patient stay. These were treated successfully with the anti-fungal drug AmBisome. He was prescribed the granulocyte-colony stimulating factor, Lenograstim, daily until his neutrophil count reached 2.5 on 2 consecutive days. In addition, SN received MMF for 1 month and Cyclosporine until day 101, when tapering would begin (if there was no evidence of GvHD). He also received the anti-viral prophylaxis, Acyclovir for 1 year and the combination antibiotic, Co-trimoxazole for 6 months. He was tested weekly for CMV, EBV and adenovirus up to day 180. SN suffered recurrent episodes of chest sepsis and, as Acyclovir is not effective for CMV prevention and the CBU cells infused were naïve, he also had CMV reactivation. Post-transplant monitoring using chimerism analysis commenced on day 7 post-infusion. His chimerism tested on day 14 indicated he was 64% ICB donor. SN was discharged on day 21 post-infusion. He suffered from Grade IV liver GvHD which responded to steroids and MMF. In March 2012, SN stopped MMF and was reported as in molecular remission. As of May 2012, SN was 100% donor chimerism with the ICB cord. SN is now back to enjoying life and riding his motorbike.

Discussion

According to the BSBMT Indications for Bone Marrow Transplantation table, an allograft with either sibling or VUD is Standard of Care for patients with Ph+ ALL. Therefore, efforts were concentrated to find SN a suitable unrelated donor when it became clear that no family donor was available. Extensive searching of the international stem cell registries over a prolonged period and subsequent testing of likely candidate donors yielded no success. The disparity in suitable unrelated donors for patients from Black and Minority Ethnicities (BME) compared to Caucasian patients has been documented (Barker *et al* 2010; Dehn *et al* 2008). Contributory factors include the frequency of HLA haplotypes in BME groups compared to Caucasian; the overwhelming presence of Caucasian donors and lack of coverage of BME donors on VUD registries; and the lack of VUD registries in countries of origin of BME patients. With the introduction of the BSBMT RIC UCBT protocol in August 2009, the utilisation of cord blood became a possibility as the HLA matching requirement for UCBT is lower than that for adult stem cell donors, therefore the likelihood of finding a suitable CBU was higher (Elia *et al* 1999).

As the cell dose per kilo bodyweight infused is critical to the engraftment of cord blood stem cells, UCBT has seldom been an option for adult patients. One of the earliest studies by Sanz *et al* (2001) found that adult patients had 1-year disease-free survival of 53% (73% in patients less than 30 years old), yet the transplant-related mortality (TRM) rate was high at 43%; a figure commented on by the authors as a common occurrence post-UCBT. Of note, the median TNC in this study was 1.71 x 10^7/kg – approximately half of the current recommended level. This low cell dose may have contributed to the high TRM reported. Another early report – also infusing single CBU – found that the CD34+ cell count was associated with improved event-free survival and that rates of GvHD were low despite the presence of HLA mismatches (Laughlin *et al* 2001). The indication of UCBT in adult patients continued: a higher cell dose was obtained by infusing x2 CBU (dUCBT) and shown to be an effective treatment option for patients for whom a suitable adult VUD was not available (Barker *et al* 2005). Although the TNC dose obtained by a combination of two units is required to ensure stem cell engraftment occurs, evidence demonstrates that in most cases only one of the CBUs dominates. It currently cannot be predicted which CBU will dominate, but both CD34+ cell viability and CD3+ cell dose have been shown to have a significant impact, whereas HLA high resolution matching has been shown not to affect unit dominance, despite the presence of multiple HLA mismatches (Avery *et al* 2011).

The tolerance of UCBT to multiple HLA mismatch has extended the allograft option to BME patients who do not have an HLA-matched sibling. A recent prospective study reported that between VUD and UCBT/dUCBT, only 5% of their total patient cohort were unable to receive an allograft due to lack of suitable donor, however significant numbers of these patients were of African or mixed ethnicity (Barker *et al* 2010). SN's ethnicity considerably reduced the likelihood of finding a suitable stem cell donor. However, the tolerance of dUCBT to multiple HLA mismatches permitted this patient to receive an allograft where previously this option may not have been available. However, despite an accepted CBU selection criteria matching at HLA-A and –B to the first field level and HLA-DRB1 to high resolution and permitting

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Case Study 1.... continued

up to 2 mismatches, a recent study indicated that additional mismatches at HLA-C result in significantly increased TRM (Eapen *et al* 2011). The recommendation from this group is that HLA-C should be taken in to account for cord selection and that mismatches at this locus should be avoided, where possible. As the recommendations for HLA matching in CBU selection approaches that for adult stem cell donors, BME patients are likely to become disadvantaged once again, as the likelihood of finding x2 CBUs that fulfil these criteria – as well as sufficient cell dose and CD34+ cell count - will decrease. The issues of HLA matching for BME patients will only be resolved by increased recruitment of BME donors to the international VUD registries and cord blood banks.

The release of the Cancer Research UK & University College London UK Haplo trial has opened another possible donor avenue (CRUK & UCL UK Haplo). All biological parents and offspring share one haplotype. Although there is only a 25% chance that a sibling will be HLA compatible, there is a 50% chance that a sibling or half-sibling will share a haplotype. This increases the potential donor pool.

Learning Outcomes

As conditioning regimens improve and post-transplant complications are becoming increasingly well managed and overcome, and identification of molecular genetic mutations are used to stratify a patient's risk, HSCT as a treatment of choice is being offered more widely. The case of SN highlights the difficulties that can be encountered when attempting to find a suitable donor for patients from BME groups. Developments in alternative donor sources for patients who would benefit from allograft but for whom a suitable donor is not available has allowed patients to be successfully transplanted using umbilical cord blood or haplo-identical donors. As more transplants are performed with these donor sources and outcomes are analysed, the criteria to select compatible donors that will ensure a successful outcome are becoming clearer. The focus by VUD registries and cord blood banks on donor recruitment from BME groups will increase the available donor pool and ensure equity of access for this life-saving treatment. The reality of the modern donor search is a multi-pronged effort: investigations into sibling / family donor (either HLA compatible from extended family or haploidentical), search of the UK and international VUD registries and also of the international cord blood banks. Depending on the patient's disease status and timeframe available, these searches may all occur concurrently in an attempt to identify a compatible donor as rapidly as possible.

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BSBMT Indications for BMT version Feb 2012

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Continued on next page

Case Study 1.... continued

Appendix 1: Unrelated Donor Verification Testing (VT) Samples Requested for SN

Testing at CTL uses Luminex® technology to HLA type Class I at medium resolution and Luminex® / PCR-SSP for Class II at high resolution.

Number	Date VT Requested	Donor Registry	Donor Demographics	HLA match on Search Report *	Mismatches present	Comment
1	June 2007	Anthony Nolan Trust (ANT), UK	Female, 51 yrs	A,B,DR (DR2)	1A allele, 1B allele, 2C, 1DRB1,1DQB1	Donor released
2	June 2007	National Marrow Donor Program (NMDP), USA	Female, 29 yrs	A,B,DRB1	Not performed	Donor deleted from registry in September 2011
3	July 2008	Germany	Male, 44 yrs	A,B,DR	1A allele, 1B allele, 1C, 1DQB1 allele	Donor released
4	July 2008	Italy	Female, 35 yrs	A,B,DR	Not performed	Donor deleted from registry in February 2010
5	January 2009	Canada	Male, 54 yrs	A,B,DR	1A allele, 2B alleles, 1C, 1DRB1, 2DQB1	Donor released
6	October 2010	ANT, UK	Female, 59 yrs	1Amm (DR2)	Not performed	Donor deleted from registry in January 2011

*Standard CTL policy for recording potential donor matches from search reports:

- DR = low resolution match at the DRB1 locus (serological broad antigen in brackets, if applicable)
- DRB1 = allelic match at the DRB1 locus
- A,B = low resolution match at these loci
- 1Amm = 1 overt mismatch at the locus recorded; other loci are presumed to be matched at low resolution.
- Information regarding C/DQB1 loci is seldom listed on search reports, especially where donors have been tested many years ago. Therefore this information is not recorded routinely unless specified.

End

Meetings diary

10th International Congress on Autoimmunity,
April 6 – 10 2016,
Leipzig, Germany.
http://autoimmunity.kenes.com/

42nd Annual Meeting of the EBMT,
April 3 – 6 2016,
Valencia, Spain.
www.ebmt2016.org

30th European Immunogenetics and Histocompatibility Conference,
May 11- 14 2016,
Kos, Greece.
http://efi2016.org/

An Introduction to Immunology,
July 18 – 19 2016,
University of Warwick.
http://www2.warwick.ac.uk/fac/sci/lifesci/study/shortcourses/immunology/

26th International Congress of The Transplantation Society,
August 18 – 23 2016,
Hong Kong
http://tts2016.org

27th Annual BSHI Conference,
September 13 – 14 2016,
Keble College, Oxford.

42nd Annual ASHI Meeting,
September 26 – 30 2016,
St. Louis, Missouri
http://2016.ashi-hla.org/

17th International HLA and Immunogenetics Workshop,
September 6 – 10 2017,
Pacific Grove, USA.
http://ihiws.org/

BSHI Continuing Professional Development

Journal Based Learning

The CPD JBL questions can be found on the BSHI website, and you must now submit your answers electronically via the website.

CPD Points

The question/answer cards will be marked and scored by an assessor appointed by the PDE. Points will be awarded on the basis of: 0-10 answers correct – 0 points, 11-14 correct – 1 point, 15 – 19 correct – 2 points, all 20 correct – 3 points.

How to participate

If you are registered on the BSHI CPD scheme, then you are eligible to participate in the Journal Based Learning scheme. All you need to do is read the reference article given at the top of the answer card, and then answer the question statements by choosing true or false for each of the 20 statements relating to the article.
Go to http://www.bshi.org.uk/members/cpd_questions.html

Then fill in your name, contact address, e-mail address and BSHI membership number.
Simply click on your choice.
Any answers that are not clear, or are ambiguous, will not score.

Luke Foster,
NHS Blood and Transplant,
Luke.foster@nhsbt.nhs.uk

The deadline for submission of completed cards for this cycle is: 29th April 2016

Your answers will be assessed and returned to you with the number of CPD points earned, for inclusion in your BSHI CPD folder. Any members not currently registered on the CPD scheme, but interested in joining should contact the BSHI CPD Co-ordinator; details in the Newsletter

If you have any comments or suggestions about the journal based learning series and the topics/articles
Luke.foster@nhsbt.nhs.uk

Journal Based Learning Cycle 57

Paper title & reference:
A prospective investigation of cell dose in single-unit umbilical cord blood transplantation for adults with high-risk hematologic malignancies. Bone Marrow Transplantation (2015) 50, 1519-1525.

All CPD returns to be made by the BSHI internet link. Deadline for submission of completed answers: **29th April 2016.**
All journals are available through the BSHI access or are open access journals.

1.	One percent of patients had undergone previous stem cell transplant (SCT) with a matched unrelated donor (MUD).	**True**	**False**
2.	A minority of patients, 16%, had low-risk disease.	**True**	**False**
3.	$CD34^+$ viability by flow cytometry was performed at the time of unit collection.	**True**	**False**
4.	Less than 10% of patients were HLA-matched at 6/6 loci.	**True**	**False**
5.	The median neutrophil engraftment was longer for patients receiving a (Total Nucleated Cell) TNC dose of ≥ 2.5 $x10^7$ NC/kg compared with those receiving a dose of ≤ 1.5$x10^7$ NC/kg.	**True**	**False**
6.	HLA match and conditioning regimen had a significant impact on neutrophil engraftment.	**True**	**False**
7.	The median platelet engraftment for patients receiving a $CD34^+$ cell dose of ≥1.5$x10^5$/kg was 60 days and for patients receiving a $CD34^+$ cell dose of <1.5$x10^5$/kg was 39 days.	**True**	**False**
8.	Patients receiving the lowest TNC dose (1-1.5$x10^7$ NC/kg) had similar survival as the entire cohort, 73% at 100 days and 46% at 1 year.	**True**	**False**
9.	In univariate analysis, faster platelet engraftment was predicted by lower $CD34^+$ cell dose.	**True**	**False**
10.	TNC dose and HLA match had a significant impact on neutrophil engraftment after adjusting for other variables included in the model.	**True**	**False**
11.	The primary aim of this study was to investigate the effect of TNC and $CD34^+$ cell dose on engraftment outcome.	**True**	**False**
12.	A TNC dose of ≥ 2.5 $x10^7$ NC/kg is recommended for HLA-mismatched grafts for an adult patient.	**True**	**False**
13.	Preliminary studies suggest HLA-C antigen matching in UCBT may be beneficial in terms of engraftment and transplant-related mortality.	**True**	**False**
14.	A reported challenge is the lack of standardised $CD34^+$ cell measurements amongst different cord blood banks.	**True**	**False**
15.	Patients receiving very low TNC of 1-1.5$x10^7$ NC/kg had poor outcomes as shown by the 100-day and 1-year OS.	**True**	**False**
16.	Analysis of the data suggests $CD34^+$ cell dose should have a role in single cord unit selection, despite lack of standardisation of $CD34^+$ measurements	**True**	**False**
17.	Using the authors' technique of diluting the cells with albumin-dextran instead of washing may allow selection of units as low as 1$x10^7$ NC/kg in the absence of larger units and still produce favourable outcomes.	**True**	**False**
18.	TNC and $CD34^+$ cell dose had a significant effect on engraftment but not OS and PFS.	**True**	**False**
19.	Patients with a TNC < 1.5$x10^7$ NC/kg, receiving a myeloablative conditioning regimen and having a personal history of prior transplant, had significantly worse NRM.	**True**	**False**
20.	This investigation shows positive outcomes in patients receiving lower than the recommended TNC dose of 2.5$x10^7$ NC/kg for an adult patient.	**True**	**False**

Scoring
CPD points will be awarded as follows:

0-10 correct 0 points	11 – 14 correct 1 point	15 – 19 correct 2 points	20 correct 3 points

Journal Based Learning Cycle 56 Answers

Paper title & reference:
Integration of humoral and cellular HLA-specific immune responses in cord blood allograft rejection.
Hanajiri R et al., 2015 Bone Marrow Transplantation. 50:1187-1194.

All journals are available through the BSHI access or are open access journals.

1.	Recipient-derived cellular immune responses are regarded as the primary contributors of graft rejection.	**True**
2.	Plasma exchange, platelet transfusion and rituximab have not previously been proposed as strategies to prevent antibody mediated graft rejection.	**False**
3.	The 53-year old patient who received an unrelated cord blood transplant was a high resolution HLA-C match to the cord.	**False**
4.	In the same patient, a complete loss of donor chimerism was reported on day 34.	**True**
5.	Anti-HLA antibody positivity was defined as mean fluorescence intensity >500.	**False**
6.	To determine the presence of the CTL clone-specific TCR rearrangement, semi-nested PCR was performed using TCR Vβ-specific primer sets.	**True**
7.	Antibodies against the antigen encoded by HLA-C*01:02 were not detected at the time of graft rejection.	**True**
8.	Antibodies against the antigen encoded by HLA-DPB1*09:01 were detected at the time of graft rejection.	**False**
9.	IFN-γ production of CTL#1 was significantly increased when stimulated by transfectants expressing HLA-B*54:01.	**True**
10.	The authors conclude that the patient had HLA-B*54:01 specific antibodies and CTL#1 before transplantation which were directed against the mismatched donor HLA-B*54:01 molecule.	**True**
11.	The mean fluorescence intensity for antibody to HLA-B*54:01 was lower after transplantation as compared with before transplantation.	**True**
12.	The CTL recognising HLA-B*54:01 expanded approximately 2000 times after transplantation.	**False**
13.	According to the authors, whether or not DSAs can directly cause graft rejection is unknown.	**True**
14.	According to the authors, this study clearly showed that allele-level DSA had direct cytolytic activity and impaired colony growth by unrelated BMMNC in vitro.	**True**
15.	According to the authors, the mechanism by which alloreactive antibodies and T cells are produced has been clearly elucidated.	**False**
16.	This study looked at both IgG and IgM class DSA.	**False**
17.	Naïve T cells do not produce IFN-γ within the first 24 hours of antigen stimulation.	**True**
18.	According to the authors, the presence of DSAs not only means a deleterious effect on donor cells, but also reflects the presence of CTLs that target the corresponding HLA molecules.	**True**
19.	In this study the group could not determine whether humoral or cellular immunity would be a dominant barrier to engraftment.	**True**
20.	According to the authors only cellular immune responses are responsible for graft rejection following cord blood transplantation.	**False**

Scoring
CPD points will be awarded as follows:
0-10 correct 0 points | 11 – 14 correct 1 point | 15 – 19 correct 2 points | 20 correct 3 points

Call for Case Studies

This notice is an update on the process for submission of case studies for publication in the Newsletter.

The purpose of publishing case studies in the Newsletter is to highlight interesting cases from individual H&I laboratories that the community as a whole would benefit from in terms of training and education or to generate discussion. We all stand to learn from each others' experiences.

There is no template for the submission. As a guide, it should be approximately 1000 words in length and at least at the level appropriate for inclusion in a portfolio for the Association of Clinical Scientists. Cases should include only a brief description of laboratory tests and focus primarily on the interpretation of results in the clinical context and their impact on patient management. Essentially, the more unusual and informative it is the better. Key learning points should be identified in order to highlight the educational value of the case.

Cases equals prizes!

As a replacement for the CPD prizes previously awarded for achievements in Journal Based Learning, the BSHI Education Board will now award a £25 book token for each case selected for publication in the Newsletter.

Submission process

Please send your submission to the BSHI Secretary, Dave Turner (secretary@bshi.org.uk). Cases will then be reviewed by at least two members of the Education Board to assess suitability for publication. No more than one case study will be published in each Newsletter but if there is more than one suitable case submitted for one edition then cases may be held in reserve for publication in subsequent editions.

Chair, BSHI Education Board

BSHI Diploma Viva dates 2016

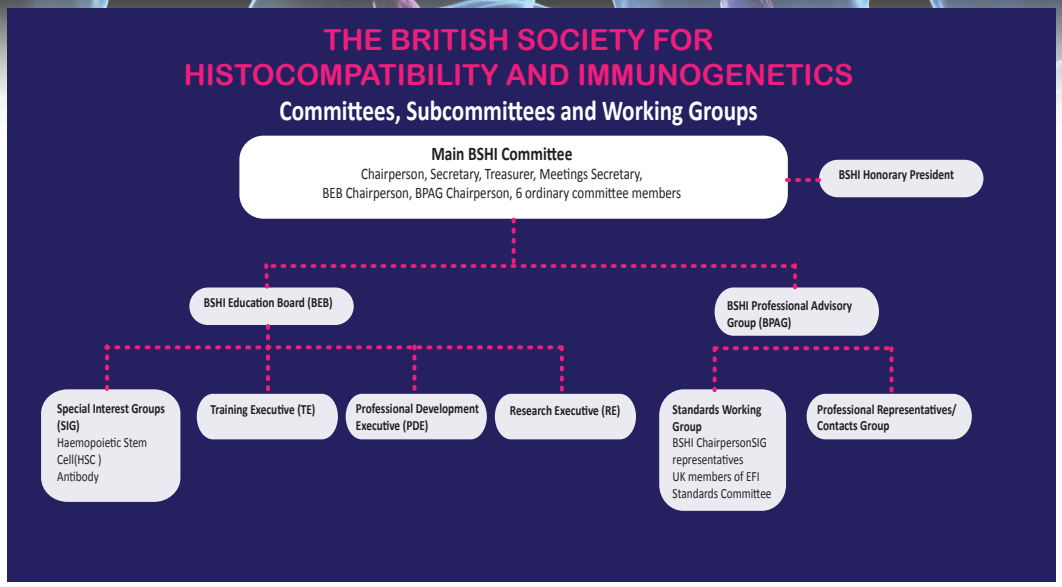
Work Submission Deadline	Application for viva deadline	Viva Week
25th January 2016	28th March 2016	Week Commencing 25th April 2016
14th July 2016	5th September 2016	Week Commencing 3rd October 2016

BSHI On-line Journal Access

BSHI provides members with full-text access to the following journals:

American Journal of Transplantation
Bone Marrow Transplantation
Current Opinion in Organ Transplantation
International Journal of Immunogenetics
Transplantation

Instructions on how to access these journals is on the Members' Section of the BSHI website:
www.bshi.org.uk/



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Ordinary Member	Zareen Goburdhun	21/11/2013	Zareen.Goburdhun@nhsbt.nhs.uk

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