Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Improved matching of therapeutic platelet concentrates for cancer patients and newborns

1. Summary of the impact (indicative maximum 100 words)

Annually in the UK ~110,000 donor platelet concentrates are used to prevent bleeding in cancer patients and ~660 newborns are born with an increased risk of bleeding because of a low platelet count caused by maternal platelet antibodies. These newborns and ~10% of the cancer patients require donor platelet transfusions matched for the platelet antibody because non-matched donor platelets are clinically less effective. University researchers have developed better methods for platelet antibody detection and typing and as a direct consequence of this research NHS Blood and Transplant (NHSBT) has from 2009 onwards been able to make platelet transfusions safer and clinically more effective, thereby reducing the number of severe, and on occasions life-threatening, bleeding episodes.

2. Underpinning research (indicative maximum 500 words)

From 1993-13 Professor Willem Ouwehand (tenured since 1989, Reader since 2004, Professor since 2010) and Dr Lorna Williamson (tenured since 1991, Reader 2005-2009) at the Cambridge University Haematology Department led, together with NHSBT service laboratories, translational research in the field of Human Platelet Antigens (HPAs). HPAs are the platelet equivalent of red blood cell groups, like ABO and D. HPA antibodies can be formed in pregnancy or after transfusion and antibody binding to donor platelets leads to their rapid removal from the circulation. Therefore patients with HPA antibodies who require transfusions should ideally receive HPA matched donor platelets, because non-matched ones are destroyed rapidly and are clinically less effective. Cancer patients with HPA antibodies and thrombocytopenic neonates born to mothers with HPA antibodies, also called Fetal-Maternal Alloimmune Thrombocytopenia (FMAIT) are the two main patient groups.

At the outset of the research NHSBT could not provide HPA matched platelets and blood for patients with HPA antibodies because the typing of donors and patients for HPA groups and the detection of HPA antibodies was laborious and tests results were not specific. Furthermore the number of FMAIT cases born per year and the best way to treat cases were not known. Therefore the objectives of the research were to i) determine the prevalence of FMAIT, ii) obtain evidence on how to treat severe cases and iii) develop more affordable laboratory tests for HPA matching of donor platelets with the recipient. The outcomes are:

i) A population study showed that 1 in ~365 mothers form HPA antibodies in pregnancy and as a consequence 1 in 1200 newborns have severe FMAIT requiring treatment by transfusion of HPA matched platelets1. With nearly 800,000 births in the UK annually ~660 severe FMAIT cases are born and if not treated bleeding may ensue, which if in the brain may cause life-long disability;

ii) The analysis of clinical outcomes of the largest FMAIT case series provided evidence that the intrauterine transfusion of HPA matched donor platelets to foetuses results in inferior outcomes if compared with more conservative treatments2; this observation has led to a reduction of the number of intrauterine procedures from >100 to <40;

iii) The laboratory research led to the following results: a) A recombinant human HPA-1a antibody was engineered and applied for rapid donor and patient typing3. A genetically modified version of the antibody has been shown in Proof-of-Concept studies in humans to be a possible effective treatment for FMAIT4, b) The genetic basis of novel HPA groups has been discovered5, and this was used together with existing knowledge, to develop affordable high-throughput DNA-based HPA typing tests for donors and patients, c) Recombinant HPA proteins for the sensitive detection of HPA antibodies were engineered6. The results of the research were disseminated through 33 peer-reviewed publications, 12 invited review articles, 7 chapters in medical textbooks and guidelines by the British Committee for Standards in Haematology and for the UK Blood Transfusion Services.

3. References to the research (indicative maximum of six references)

1. Williamson LM, Hackett G, Rennie J, Palmer CR, Maciver C, Hadfield R, Hughes D, Jobson S, **Ouwehand WH**: (1998) The natural history of fetomaternal alloimmunization to the platelet-

specific antigen HPA-1a (PlA1, Zwa) as determined by antenatal screening. Blood 92:2280-2287. Epub 1998/09/25. PubMed PMID: 9746765; **2.** Ghevaert C, Campbell K, Walton J, Smith GA, Allen D, **Williamson, LM Ouwehand WH**, and Ranasinghe E: (2007) Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. Transfusion 47:901-910. Epub 2007;
3. Griffin HM, **Ouwehand WH**: (1995) A human monoclonal antibody specific for the leucine-33 (P1A1, HPA-1a) form of platelet glycoprotein IIIa from a V gene phage display library. Blood 86:4430-4436. Epub 1995/12/15. PubMed PMID: 8541531;
4. Ghevaert C, Wilcox DA, Fang J, Armour KL, Clark MR, **Ouwehand WH** and **Williamson LM**: (2008) Developing recombinant HPA-1a-specific antibodies with abrogated Fcgamma receptor binding for the treatment of fetomaternal alloimmune thrombocytopenia. J Clin Invest 118, 2929-2938. Epub 2008/07/26. doi: 10.1172/JCI34708.
5. Schuh AC, Watkins NA, Nguyen Q, Harmer NJ, Lin M, Prosper JYA, Campbell K, Sutherland DR, Metcalfe P, Horsfall W, and **Ouwehand WH**: (2002) A Tyrosine703Serine Polymorphism of CD109 Defines the Gov Platelet Alloantigens. Blood 99:1692-1698. Epub 2002/02/28. PubMed PMID: 11861285.
6. Chong W, Metcalfe P, Mushens R, Lucas G, **Ouwehand WH** & Navarrete CV (2011) Detection of human platelet antigen-1a alloantibodies in cases of fetomaternal alloimmune thrombocytopenia using recombinant β3 integrin fragments coupled to fluorescently labeled beads. Transfusion, 51, 1261-1270. Epub 2010/12/21. doi: 10.1111/j.1537-2995.2010.02977.x.

4. Details of the impact (indicative maximum 750 words)

The results of the research have been successfully translated into improved patient care in the UK and also changed transfusion policy and practice internationally. The impacts are illustrated by the following examples:

i) *Postgraduate education* of medical staff and training of scientific NHS staff has changed on basis of the research findings. Particularly the use of HPA matched donor platelets for patients with HPA antibodies is now taught as 'best care' and since 2008 it is taught that intrauterine transfusion should be considered only as last resort for FMAIT cases. The research findings have been disseminated at international educational and committee meetings.

ii) *The British Committee for Standards in Haematology guidelines* for transfusion do now stipulate that the use of HPA matched donor platelets for neonates with HPA antibodies is 'best care'[7]. The policy is also adopted in the *2013 Guidelines for the Blood Services of England, Northern Ireland, Scotland and Wales* which regulate the preparation of blood and platelet products from donors and related patient services[8].

iii) Substantial improvements in *HPA antibody detection* have been achieved in the UK and internationally and the research has been instrumental for nearly all the achievements of an international platelet immunogenetics Quality Assurance (QA) scheme for 36 service labs[9,10]. The scheme has led to a) the development of World Health Organisation sensitivity and potency standards for HPA antibody detection, b) standardised reference tests for the HPA antibody detection - international WHO-approved references for the detection of HPA-1 and -5 antibodies have been developed at the NIBSC and are currently distributed worldwide to monitor the sensitivity and specificity of assays to detect HPA antibodies[11], c) consistent improvements in the proficiency of HPA antibody detection[9] and DNA-based HPA typing[10] and d) the international adaptation of the HPA nomenclature in routine clinical practice[12]. The latter is supported by a website, developed and maintained by the Cambridge researchers, together with the European Bioinformatics Institute[12]. The proficiency of the NHSBT platelet laboratory in the QA scheme ranks between 2008 and 2013 consistently in the upper decile of performance confirming that University research has brought tangible and long-lasting benefits to NHS patient care. Notwithstanding the above achievements, assays for HPA antibody detection currently used remain expensive (>£1000/sample with about 800 referrals/year). NHSBT scientists have demonstrated platform feasibility in 2009 and completed in 2013 the largest ever multi-centre validation study of recombinant HPA-1 proteins which showed that Cambridge researchers have succeeded in developing affordable HPA antibody detection tests for use in NHS service delivery[6]. Collaboration between the University, Sanger Institute and NHSBT has in 2013 resulted in the successful production of HPA-5/-15 proteins, which means that all clinically relevant HPAs, but HPA-3 have

been produced by recombinant techniques.

iv) *HPA typing*: Up until the late nineties in the UK almost no blood donors had been typed for the clinically relevant HPA groups. Patients with HPA antibodies therefore received non-matched and clinically inferior donor platelets. Tests for high throughput and affordable HPA-1-15 genotyping and HPA-1a phenotyping[4] were developed and clinically validated in the Cambridge research laboratory and these have been used over the 2008-13 period by NHSBT to HPA type 90,000 donors. This effort has resulted in a) the routine provision of HPA-matched platelets for cancer patients with HPA antibodies (per year 300-400 HLA/HPA matched concentrates are provided), b) Since 2008 "off the shelf universally matched" HPA-1a/-5b negative donor platelets for the treatment of neonates with low platelet counts to reduce the risk of bleeding[13], because Cambridge research showed that >90% of FMAIT cases are caused by HPA-1a/-5b antibodies[2]. As a direct result of the Cambridge research these superior transfusion products have become available across the country. The NHSBT platelet laboratory receives per year ~800 FMAIT referrals and the majority of cases with counts <20x10^9/L will have been transfused with the novel therapy of universally HPA matched donor platelets, which was previously unavailable. The University received a £150,000 down payment for a license of the recombinant HPA-1a antibody to the diagnostic company DiaMed for use in other countries. All together translational research has resulted during the 2008-13 period in sustained improvements in patient care by better diagnosis and treatment of FMAIT and improved HPA matching of transfusion products. This has reduced the use of costly concentrates because matched platelets survive longer and are clinically superior to random ones. As a direct consequence of the research the risk of life-threatening bleeding has been reduced and patients experience fewer side effects and in addition a reduced exposure to donor products also diminishes the risk of serious hazards of transfusion, e.g. death by bacteria or HIV, HepB/C transmission.

5. Sources to corroborate the impact (indicative maximum of 10 references)

7. British Committee for Standard in Haematology: (2004) Transfusion guidelines for neonates and older children, Brit J Haemat, 124, 433-453. doi:10.1111/j.1365-2141.2004.04815.x

8. National Blood Service: (2013) Guidelines for the blood transfusion services in the UK, The UK Stationary Office, 8th Edition, ISBN 9780117081673, Chapter 18: Platelets, paragraphs 18.1-18.4 http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB&Section=25&pageid=7942

9. Clinical study in collaboration with the Regional Blood Transfusion Centre (Oxford); Allen DL, Chapman J, Phillips PK, Ouwehand WH: (1994) Sensitivity of the platelet immunofluorescence test (PIFT) and the MAIPA assay for the detection of platelet-reactive alloantibodies: a report on two U.K. National Platelet Workshop exercises. Transfus Med 4:157-164. Epub 1994/06/01. PubMed PMID: 7921052.

10. Clinical study in collaboration with the National Institute for Biological Standards and Control (NIBSC) and National Blood Service (Newcastle, Cambridge); Metcalfe P, Cavanagh G, Hurd C, Ouwehand WH: (1999) HPA genotyping by PCR-SSP: report of 4 exercises. Vox Sang 77:40-43. Epub 1999/09/04. doi: vox77040 [pii].

11. WHO/NIBSC documents.
http://www.who.int/biologicals/BS%202079%20HPA-1a.pdf
http://www.nibsc.org/Science/Diagnostics/Transfusion_-_Transplantation/Platelets/Standardisation.aspx
http://apps.who.int/iris/bitstream/10665/69955/1/WHO_BS_05.2011_eng.pdf

12. Clinical study in collaboration with the NIBSC; Metcalfe P, Watkins NA, Ouwehand WH, Kaplan C, Newman P, Kekomaki R, Haas M de, Aster R, Shibata Y, Smith J, Kiefel V, Santoso S: (2003) Nomenclature of Human Platelet Antigens (HPA). Vox Sang 85:240-245. Epub 2003/10/01. doi: 331 [pii] and associated website can be found at http://www.ebi.ac.uk/ipd/hpa/ (most recent access date July, 2013).

13. Clinical study in collaboration with the National Blood Service (Cambridge); Ranasinghe E, Walton JD, Hurd CM, Saul L, Smith G, Campbell K, Ouwehand WH: (2001) Provision of platelet support for fetuses and neonates affected by severe fetomaternal alloimmune thrombocytopenia. Br J Haem 113:40-42. Epub 2001/05/01. PubMed PMID: 11328278.