Monitoring International Trends

Posted June 2019
The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could put financial or other pressures on the Australian sector.

Summary Report, June

Safety and Patient Blood Management (begins page 7 in the detailed report below)

Appropriate transfusion; bleeding risk

- A systematic review is exploring the availability, quality and content of clinical practice guidelines reporting on the indication for allogenic red blood cell transfusion during surgery.
- A study has reported that, for high-risk patients undergoing cardiac surgery with cardiopulmonary bypass, a restrictive approach to red blood cell transfusions leads to fewer transfusions than a liberal approach, with no increase in the risk for acute kidney injury.
- A study in over one million red blood cell recipients has reported that “the survival of patients transfused with red blood cells does not appear to be associated with whether the blood they received was donated by a man, by a woman who had been pregnant - or by one who had not”.
- A study has described the bleeding risk and blood transfusion consequences across plastic surgery procedures.
- A systematic review and meta-analysis found that there was no need to interrupt dual antiplatelet therapy before minor oral surgery.
- Researchers investigated the risk factors for blood loss in patients younger than 10, diagnosed with congenital scoliosis and hemivertebra, who underwent primary posterior hemivertebra resection. They found blood loss was determined by the preoperative total Cobb angle and the number of fused levels.
- In 2018 the US Food and Drug Administration (FDA) held a public workshop on pathogen reduction technologies for blood safety. A session-by-session report on proceedings has now been published in the journal Transfusion. The four sessions at the workshop were:
  i) BLOOD-BORNE INFECTIOUS AGENTS AND THEIR IMPACT ON BLOOD SAFETY;
  ii) IMPLEMENTATION OF PATHOGEN REDUCTION TECHNOLOGY FOR BLOOD PRODUCTS IN THE UNITED STATES;
  iii) PATHOGEN REDUCTION TECHNOLOGIES FOR WHOLE BLOOD AND RED BLOOD CELLS; and
  iv) EMERGING INNOVATIONS RELEVANT TO PATHOGEN REDUCTION TECHNOLOGY AND ALTERNATIVES.
Leukoreduction of platelet concentrate may be used to mitigate risk of acute transfusion reactions, alloimmunization, clinical refractoriness, and the very common infection cytomegalovirus. However, it does not prevent transfusion-associated graft-versus-host disease. Now a study has indicated that amotosalen–ultraviolet A pathogen reduction for platelet concentrate, without leukoreduction, gamma irradiation, or bacterial screening is feasible for support of hematopoietic stem cell transplants.

Research presented at the 2019 Euroanaesthesia congress found that receiving a blood transfusion during surgery for a common type of liver cancer (hepatocellular carcinoma) is associated with a much higher risk of cancer recurrence and premature death.

A recent meta-analysis of transfusion trials that focussed on older adults supported development of age-related transfusion thresholds. NBA funded this research under the National Blood Sector R&D Program.

Researchers report that testing in vitro platelet function using flow cytometry may accurately predict the risk of bleeding in patients with acute myeloid leukemia.

Researchers discovered that microbes in the human gut can facilitate conversion of the common blood type A to a universal donor blood type. The microbes produce two enzymes that could assist in the transformation.

Other

At a regional congress of the International Society of Blood Transfusion (ISBT) a number of presentations featured Cerus Corporation’s INTERCEPT Blood System pathogen reduction technology.

A study in enoxaparin-treated patients (40 mg/day) recovering from colorectal surgeries found that two-thirds of them received inadequate anticoagulation.

Researchers found that saline fluids frequently used to help stabilise critically ill children may trigger the blood to become more acidic, and lead to organ failure.

Products and Treatments (begins page 10 in the detailed report below)

Treating haemophilia

Sangamo Therapeutics announced the forthcoming presentation of data from the Phase I/II Alta study evaluating SB-525 gene therapy in adult patients with severe haemophilia A. Initial results will be given in an oral presentation at the XXVII Congress of the International Society on Thrombosis and Haemostasis (ISTH).

BioMarin Pharmaceutical announced that the principal investigator for the valoctocogene roxaparvovec Phase I/II study (BMN 270-201) and the Phase III study (BMN 270-301) would also present data at the ISTH Congress. The gene therapy is being trialled for severe haemophilia A.

Sobi will also be presenting data at the ISTH Congress, relating to its recombinant Factor VIII and Factor IX products, Elocta and Alprolix, in clinical settings.

The Haemophilia Drug Development Summit will be held in Boston 20-22 August. It is expected to attract treatment developers, equipment and service providers healthcare providers, research institute representatives and members of the bleeding disorders community.

Haematologist Paula James has written that haemophilia was thought to affect only men, while women were thought to be carriers of the genetic mutation that causes the condition; however her “own research has shown that around 30 to 40 per cent of
haemophilia carriers experience abnormal bleeding including heavy periods, post-partum haemorrhage and joint bleeds. Some, but not all, have low clotting factor levels." She says that while their condition is treatable, they may wait years before being tested and diagnosed, if it happens at all.

**Treating beta thalassemia and sickle cell disease**

- At the European Hematology Association (EHA) Congress, the latest data from the HOPE trial was introduced in an oral presentation, *Results from the Randomized Placebo-Controlled Phase 3 Hope Trial of Voxelotor in Adults and Adolescents with Sickle Cell Disease*. Results showed that Voxelotor can significantly reduce both haemolysis and anaemia in adolescents and adults with sickle cell disease.
- At the EHA Congress data were also presented from the ongoing Phase IIa HOPE-KIDS 1 trial. The poster was entitled *Cerebral Blood Flow in Adolescents with Sickle Cell Anaemia Receiving Voxelotor*. Preliminary data suggests that oxygen delivery to the brain can be sustained or improved by Voxelotor. The drug was also found to reduce cerebral blood flow and increase the levels of haemoglobin.
- HOPE trial data will be used as the basis for Global Blood Therapeutics’ planned New Drug Application for voxelotor with the US Food and Drug Administration (FDA) during the second half of 2019.
- The EHA Congress heard an oral presentation on Imara’s IMR-8687, currently being evaluated in a Phase IIa clinical trial as a disease-modifying drug for sickle cell disease.
- Editas Medicine reported to the EHA Congress results from a follow-up study to assess two different CRISPR genome editing strategies, one targeting the BCL11A erythroid enhancer (BC11Ae) and one targeting the beta-globin locus, for the treatment of sickle cell disease and beta-thalassemia.
- Cyclerion Therapeutics in June presented data on its sickle cell disease program at two meetings.
- A recent study suggests that using CRISPR-Cas9 and a corrective short DNA template could be a safe and efficient means of correcting the mutation responsible for sickle cell disease.
- Researchers have developed a rapid method of continuously monitoring sickle cell disease using a microfluidics-based electrical impedance sensor.

**Regulatory matters (begins page 13 in the detailed report below)**

- Novo Nordisk announced that the European Commission had granted marketing authorisation for Esperoct (turoctocog alfa pegol, N8-G for the treatment of adolescents (≥12 years of age) and adults with haemophilia A. It offers a 1.6-fold half-life prolongation in adults/adolescents compared with standard half-life factor VIII products.
- PATH and Sinapi Biomedical announced that the low-cost, fully assembled Ellavi uterine balloon tamponade has achieved CE marking. The current World Health Organization recommendations identify the device as an emergency intervention for postpartum haemorrhage when drug treatment fails or is unavailable.
- bluebird bio announced EU Conditional Marketing Authorization for ZYNTEGLO (autologous CD34+ cells encoding βA-T87Q-globin gene) gene therapy for patients 12 Years and older with transfusion-dependent β-Thalassemia who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. ZYNTEGLO is the first gene therapy approved for transfusion-dependent β-thalassemia.
Market structure and company news (begins page 14 in the detailed report below)

- There is speculation that uniQure, with a gene therapy for haemophilia A in Phase III trials, is a likely target for takeover.
- Cerus Corporation announced a new corporate branding campaign and the planned relocation of its corporate offices to a new facility in Concord California.
- CSL will be transitioning to its own Good Supply Practice Licence in China in 2020. This will enable CSL to own and sell products in the domestic Chinese market.

Specific country events (begins p 14 in the detailed report below)

- The Food and Agriculture Organization of the United Nations has said it believes the rising global rates of antimicrobial resistance (AMR) constitute “the most complex threat to global health”. It has launched the AMR Multi-Partner Trust Fund to accelerate the response.
- The World Federation of Haemophilia’s Annual Global Survey estimates almost 50 per cent of the world’s haemophilia sufferers live in India, where almost seventy per cent of them have inadequate information, and little (if any) access to treatment.
- The New Zealand Blood Service said that although it has 110,000 committed donors, it needs 55,000 more to keep up with plasma demands.
- The US Congress recently passed the Pandemics and All-Hazards Preparedness and Advancing Innovation Act, which will allow the Biomedical Advanced Research and Development Authority (BARDA) to strengthen the country's preparedness against a variety of global disease threats.
- Researchers found that Aboriginal and Torres Strait Islander children in far north Queensland are suffering from anaemia at a much higher rate than the general population. Their report recommends this issue be added to the “Closing the Gap” Indigenous health initiative.

Research not included elsewhere (begins page 15 in the detailed report below)

- A study has suggested that people with high iron levels are less likely to have high cholesterol. However high iron levels can have other detrimental impacts.
- Researchers found that body mass index may be directly associated with increased levels of von Willebrand factor and Factor VIII, though it confers no protection against bleeding in patients with von Willebrand disease.
- Scientists have successfully edited the genes of stem cells while still in the body.
- A study suggests that the ratio between the blood clotting protein Factor VIII and the von Willebrand factor may be a reliable biomarker of recovery and relapse in patients with acquired haemophilia A.

Infectious diseases (begins page 16 in the detailed report below)

Mosquito-borne diseases

- University of Florida scientists say that if young mosquitoes have a nitrogen-rich diet, then as adults they are less likely to transmit the Zika virus.
- The US Department of Defense awarded a grant to the Texas Biomedical Research Institute to study an experimental Zika vaccine.
- Human safety testing has been underway on a formalin inactivated Zika vaccine candidate developed at the Walter Reed Army Institute of Research.
• Scientists have trialled a new means of killing malaria-carrying mosquitoes, using a fungus enhanced by the gene of an Australian funnel web spider.

Influenza

• Researchers have found that “influenza virus coinfections probably occur more often than has been previously documented”.
• Vivaldi Biosciences announced the publication of Phase I clinical trial results for its deltaFLU vaccine for protection against potential pandemic influenza strain H5N1.
• A study has examined influenza virus transmission and revealed the type of immune responses that may be protective against influenza virus infection.
• European health officials reported a novel H1N2 infection in Denmark, a reassortment involving two seasonal flu strains: the 2009 H1N1 virus and the H3N2 virus.

Ebola virus disease

• The World Health Organization (WHO) said the outbreak of the Ebola virus in the Democratic Republic of the Congo might last another two years.
• The Uganda National Council for Science and Technology and National Drug Authority have approved the importation of three therapeutic treatments for Ebola.
• WHO said that by 16 June the case count was 2168 (death toll 1449).
• By mid-June 137,000 people had been vaccinated since August 2018: 38,000 high-risk contacts, 69,000 contacts of contacts, and over 30,000 frontline providers.
• WHO’s Ebola response in the Congo is short of funds.
• Researchers estimate that at least half of all Ebola virus disease spillover events and small outbreaks are not detected.

MERS-CoV

• WHO reported MERS-CoV cases during May 2019, all in Saudi Arabia.
• Researchers from The University of Texas Medical Branch at Galveston, and from Saudi Arabia and Canada, say they have developed a potent and safe vaccine against MERS.

Other diseases

• A newly identified virus (“Alongshan virus”) is infecting people in China, with ticks thought to be the vector.
• A Phase I clinical study is investigating Hookipa Pharma’s HB-10, which is believed to help prevent cytomegalovirus infection after kidney transplant.
• NSW and Victorian poultry farms have been affected by salmonella and the need to recall eggs from the retail market, along with quarantine, culling and disinfection.
• An unvaccinated horse was found with Hendra virus disease near Scone, NSW.
• Globally, as many as 1 million new cases of sexually transmitted diseases are reported daily.
• African swine fever is ravaging Asia’s pig industry.
• Scientists found how the hepatitis C virus "ghosts" the human immune system and remains undiagnosed in many people.
• Emergent BioSolutions has been awarded a contract for the continued delivery of Vaccinia Immune Globulin Intravenous product to the US Strategic National Stockpile.
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1. Safety and patient blood management

We follow current issues in patient safety and achieving favourable patient outcomes.

**Appropriate Transfusion; Bleeding Risk**

- A systematic review is exploring the availability, quality and content of clinical practice guidelines reporting on the indication for allogenic red blood cell transfusion during surgery.
- A study has reported that, for high-risk patients undergoing cardiac surgery with cardiopulmonary bypass, a restrictive approach to red blood cell transfusions leads to fewer transfusions than a liberal approach, with no increase in the risk for acute kidney injury.
- A study in over one million red blood cell recipients has reported that “the survival of patients who got transfused with red blood cells does not appear to be associated with whether the blood they received was donated by a man, by a woman who had been pregnant - or by one who had not”, according to Dr Simone Glynn, chief of the Blood Epidemiology and Clinical Therapeutics Branch of the US National Heart, Lung, and Blood Institute. “That's important to know,” she said.
- A study published in the journal of the American Society of Plastic Surgeons has described the bleeding risk and blood transfusion consequences across plastic surgery procedures and named those procedures where higher rates of bleeding are routinely expected.
- A systematic review and meta-analysis (16 studies) of bleeding in minor oral surgery in patients on dual antiplatelet therapy (DAPT), single antiplatelet therapy (SAPT), or no antiplatelet therapy (no APT) found that the perioperative bleeding risk was significantly higher for DAPT than for SAPT, but not higher vs no APT. However, the clinical observation was that all reported bleeding could be controlled by local haemostatic measures. The researchers concluded that there was no need to interrupt DAPT before minor oral surgery.

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• Researchers investigated the risk factors for blood loss in patients younger than 10, diagnosed with congenital scoliosis and hemivertebra, who underwent primary posterior hemivertebra resection. They found no correlation of preoperative platelet count and preoperative coagulation function with blood loss in the patients. This loss was determined by the preoperative total Cobb angle and the number of fused levels. Further research would be necessary to determine the possible role of blood management in reducing blood loss and transfusion in patients undergoing hemivertebra resection.

• In 2018 the US Food and Drug Administration (FDA) held a public workshop on pathogen reduction technologies for blood safety. A session-by-session report on proceedings has now been published in the journal Transfusion. The program at the workshop follows.

  i) SESSION 1: BLOOD-BORNE INFECTIOUS AGENTS AND THEIR IMPACT ON BLOOD SAFETY: Risk to the blood safety from infectious agents; Pathogen reduction: an overview of policy issues; Current status of pathogen-reduced platelets in the United States; Pathogen reduction technology for plasma in the United States

  ii) SESSION 2: IMPLEMENTATION OF PATHOGEN REDUCTION TECHNOLOGY FOR BLOOD PRODUCTS IN THE UNITED STATES: Experience implementing pathogen reduction technology; Implementation in a hospital-based blood centre and acceptance by hospital staff; Impact of pathogen reduction technology on platelet quality, count, and clinical implications; Using solvent/detergent-treated pooled plasma (Octaplas): implementation at University of Minnesota; Health economic considerations for pathogen reduction technology

  iii) SESSION 3. PATHOGEN REDUCTION TECHNOLOGIES FOR WHOLE BLOOD AND RED BLOOD CELLS: Optimal pathogen reduction system for blood safety: is it a dream; Clinical experience with pathogen reduction for red blood cells: completing the triad; State of PRT for whole blood; Pathogen reduction technologies for red blood cell products: impact on biochemical and viability variables in humans

  iv) SESSION 4: EMERGING INNOVATIONS RELEVANT TO PATHOGEN REDUCTION TECHNOLOGY AND ALTERNATIVES: A nucleic acid–binding photosensitizer with flexible structure for pathogen inactivation in red blood cell suspensions; Blue light inactivation of pathogens in platelet and plasma: a pilot study; Pathogen reduction in blood products: refrigerate and use pathogen reduction technology; Concluding remarks. Insights for future research and development

• Leukoreduction of platelet concentrate may be used to mitigate risk of acute transfusion reactions, alloimmunization, clinical refractoriness, and the very common infection cytomegalovirus. However, it does not prevent transfusion-associated graft-versus-host disease. Now a study has indicated that amotosalen–ultraviolet A pathogen reduction for platelet concentrate, without leukoreduction, gamma irradiation, or bacterial screening is feasible for support of hematopoietic stem cell transplants.

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8 The Cobb angle measures the extent of bending disorders of the vertebral column.
Research presented at the 2019 Euroanaesthesia congress\textsuperscript{11} found that receiving a blood transfusion during surgery for a common type of liver cancer (hepatocellular carcinoma) is associated with a much higher risk of cancer recurrence and premature death\textsuperscript{12}. The increased risk was significant even when only a small amount of blood was transfused. Transfusion of 1 to 4 units of blood heightened the risk of cancer recurrence by 23 per cent and death by 55 per cent (compared with matched controls).

A recent meta-analysis\textsuperscript{13} of transfusion trials that focussed on older adults supported development of age-related transfusion thresholds.

Researchers report\textsuperscript{14} that testing \textit{in vitro} platelet function using flow cytometry may accurately predict the risk of bleeding in patients with acute myeloid leukemia.

Researchers led by Stephen Withers, a chemical biologist at the University of British Columbia discovered\textsuperscript{15} that microbes in the human gut can facilitate conversion of the common blood type A to a universal donor blood type. The microbes produce two enzymes that could assist in the transformation. News of this development was made public at a meeting of the American Chemical Society in August 2018, but an updated version has now been published in \textit{Nature Microbiology}.

\textbf{Other}

At the 29\textsuperscript{th} regional congress of the International Society of Blood Transfusion (ISBT)\textsuperscript{16} a number of presentations\textsuperscript{17} featured Cerus Corporation’s INTERCEPT Blood System pathogen reduction technology. Cerus also hosted a satellite symposium, \textit{Safeguarding the Blood Supply Against (Re)emerging Pathogens and Balancing Blood Safety and Economics.} Dr Richard Benjamin, the company’s chief medical officer, said: “The data being presented at this year’s ISBT will highlight topics including the operational benefits associated with INTERCEPT treated 7-day platelets compared to conventional 5-day platelets, the design of a Phase I clinical trial in Africa evaluating INTERCEPT in whole blood transfusions, and the

\textsuperscript{11} the annual meeting of the European Society of Anaesthesiology in Vienna, 1-3 June.
\textsuperscript{12} https://www.eurekalert.org/pub_releases/2019-06/eso-btd053019.php
\textsuperscript{15} Peter Rahfeld, Stephen G Withers et al., “An enzymatic pathway in the human gut microbiome that converts A to universal O type blood” published 10 June in \textit{Nature Microbiology}.
\textsuperscript{16} Basel, Switzerland, 22-26 June
\textsuperscript{17} Titles
2. \textit{Efficient Inactivation of Brucella Clinical Isolates in Human Platelet Concentrates in 100\% Plasma with Amotosalen and Ultraviolet A Light Treatment, F Alseraye, O Alsaweed, F Albloui et al.}
3. \textit{Therapeutic Response to Amotosalen/UVA-Treated Platelets With Up to 7 Days Storage During 5 Years of Routine Practice, L Infanti, A Holbro, J Passweg et al.}
4. \textit{How to Prepare the Madrid Region for a Potential Outbreak of Emergent Pathogens without Increasing Overall Production Cost? A Arruga, I Lucea, A Richart et al.}
5. \textit{Influence of the Use of 7-Day Platelets Pathogen Inactivated with Amotosalen/UVA on the Discards Due to Expiry in the Hemotherapy Area of Castilla La Mancha (Spain), AL Pajares Herraiz, C Coello de Portugal, MD Morales et al.}
assessment of INTERCEPT’s efficacy in reducing the load of viral and bacterial pathogens.”

- A study\textsuperscript{18} in enoxaparin-treated patients (40 mg/day) recovering from colorectal surgeries found that two-thirds of them received inadequate anticoagulation.
- Researchers from Imperial College London found\textsuperscript{19} that saline fluids frequently used to help stabilise critically ill children may trigger the blood to become more acidic, and lead to organ failure. They recommended that hospitals replace saline fluids with a buffered solution that helps prevent the blood becoming too acidic\textsuperscript{20}.
- Researchers\textsuperscript{21} have developed a device — known as BlooDe — to study the plugging capacity of platelets. The device can detect deficient platelet-related haemostasis in a patient effectively and in advance of an invasive procedure. It artificially reproduces blood circulation and holes in the vessel walls, and it can test patient’s platelets with sufficient accuracy in under an hour using only a few millilitres of blood. The researchers are now upgrading some of its parts and starting to scale up in preparation for industrial production.

2. Products and treatments

Here the NBA follows the progress in research and clinical trials that may, within a reasonable timeframe, either make new products and treatments available or may lead to new uses or changes in use for existing products.

Treating haemophilia

- On 21 June, Sangamo Therapeutics announced the forthcoming presentation of data from the Phase I/II Alta study evaluating SB-525 gene therapy in adult patients with severe haemophilia A. The therapy is being developed in collaboration with Pfizer. Initial results will be given in an oral presentation at the XXVII Congress of the International Society on Thrombosis and Haemostasis (ISTH)\textsuperscript{22}. Barbara Konkle\textsuperscript{23} will present the paper, titled "Initial results of the Alta study, a phase 1/2, open label, adaptive, dose-ranging study to assess the safety and tolerability of SB-525 gene therapy in adult subjects with severe haemophilia A".\textsuperscript{24} The abstract is available \href{https://www.isth.org/meetings/2019/congress/abstracts-of-oral-presentations/abstracts/00637.pdf}{here} on the ISTH website. The FDA has granted Orphan Drug and Fast Track


\textsuperscript{20} They studied a cohort of over 3000 children with malaria or sepsis in Africa, but they say the findings could apply to all critically ill children and adults.

\textsuperscript{21} from the University of Geneva (UNIGE), the University of Franche-Comté (UFC) and the Etablissement français du Sang (Bourgogne Franche Comté) in partnership with the University Hospitals of Geneva (HUG) and the CHU of Dijon and Besançon

\textsuperscript{22} Melbourne, 6 to 10 July 2019.

\textsuperscript{23} Of Bloodworks Northwest, Professor of Medicine, University of Washington, and Principal Investigator of the Alta study

\textsuperscript{24} She will expand on the interim results Sangamo and Pfizer released on 2 April, and will include follow-up data on the first eight patients in the study including Factor VIII levels, bleeding rates, Factor VIII replacement therapy usage, and safety. She will also include early data from the first two patients dosed in the 3e13 vg/kg expansion cohort.
designations to SB-525, which also received Orphan Medicinal Product designation from the European Medicines Agency.

- BioMarin Pharmaceutical announced on 26 June that Professor John Pasi, principal investigator for the valoctocogene roxaparvovec Phase I/II study (BMN 270-201) and the Phase III study (BMN 270-301) would also present data at the ISTH Congress. The investigational gene therapy is being trialled for severe haemophilia A.
- Sobi will also be presenting data at the ISTH Congress, relating to its recombinant Factor VIII and Factor IX products, Elocta and Alprolix, in clinical settings.
- A study has suggested that in patients with severe haemophilia A from all age groups, treatment with Esperoct led to stabilization and/or improvement of health-related quality of life.
- The Hemophilia Drug Development Summit will be held in Boston 20-22 August. It is expected to attract treatment developers, equipment and healthcare providers, research institute representatives and members of the bleeding disorders community.
- Paula James, a haematologist at Queen’s University in Canada, has written that haemophilia was thought to affect only men, while women were thought to be carriers of the genetic mutation that causes the condition; however her “own research has shown that around 30 to 40 per cent of haemophilia carriers experience abnormal bleeding including heavy periods, post-partum haemorrhage and joint bleeds. Some, but not all, have low clotting factor levels.” She says that while their condition is

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25 from Barts and the London School of Medicine and Dentistry
26 The presentation in a late-breaking abstract session is titled First-in-human Evidence of Durable Therapeutic Efficacy and Safety of AAV Gene Therapy Over Three-years with Valoctocogene Roxaparvovec for Severe Haemophilia A (BMN 270-201 Study)
27 Sobi Posters (all abstracts can be found on the official ISTH website)
  - A Survey of Physicians’ Treatment Switching Practice in Long-term Prophylaxis for People with Haemophilia B in five European Countries: Poster # PB0208
  - Improved Haemostasis and Joint Health over Time in a Subset of Patients who Did Not Reach Optimal Haemostatic Control in the First Year of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) Therapy: Poster # PB0234. Joint with Sanofi Genzyme
  - A Survey of Physicians’ Treatment Switching Practice in Long-term Prophylaxis for People with Haemophilia A in Five European Countries: Poster # PB0692. Joint with Sanofi Genzyme
  - Long-term Outcomes after Switch from On-demand Treatment to Prophylaxis with rFVIIIFc: Longitudinal Subgroup Analysis of the A-LONG and ASPIRE Study Population: Poster # PB1410. Joint with Sanofi Genzyme
29 turoctocog alfa pegol — Novo Nordisk’s recombinant extended half-life factor VIII
30 Topics to be addressed include research and development, patient engagement, and payer challenges of gene therapies; development progression of novel subcutaneous prophylaxis strategies for inhibitor-positive patients; optimization of clinical development strategies; strategies to overcome the knowledge gap in the diagnosis and treatment of Von Willebrand disease; understanding of the needs of patients and insight from clinicians. Speakers include the chief medical officer of Catalyst Biosciences; the chief scientific officers of uniQure and LogicBio; the head of research of rare blood disorders at Sangamo Therapeutics; and the senior vice president of program development of the National Hemophilia Foundation. Workshop A will address immune reactions in next-generation factor replacement prophylaxis and will be led by the vice president of translational research at Catalyst Biosciences and the global head, life cycle management of rare blood disorders at Sanofi Genzyme. Workshop B will address new payer and reimbursement strategies to improve patient access to gene therapies and will be led by the senior vice president of external affairs at the National Hemophilia Foundation, the director of external affairs at the National Hemophilia Foundation, and the CEO and founder of Enlightenment Bioconsult.
31 The Conversation.
treatable, they may wait years before being tested and diagnosed, if it happens at all. She says organizations like the World Federation of Hemophilia are endeavouring to improve awareness that women can also have haemophilia.

**Treating beta thalassemia and sickle cell disease**

- At the 24th European Hematology Association (EHA) Congress, in Amsterdam, the latest data from the HOPE trial was introduced in an oral presentation, *Results from the Randomized Placebo-Controlled Phase 3 Hope Trial of Voxelotor in Adults and Adolescents with Sickle Cell Disease*. This 24-week data from the Phase III HOPE trial were also published. Results showed that Voxelotor, from Global Blood Therapeutics, can significantly reduce both haemolysis — the destruction of red blood cells — and anaemia in adolescents and adults with sickle cell disease (SCD). The drug was also found to increase markedly the amount of haemoglobin.

- At the EHA Congress data were also presented from the ongoing Phase IIa HOPE-KIDS 1 trial. The poster was entitled *Cerebral Blood Flow in Adolescents with Sickle Cell Anaemia Receiving Voxelotor*. Preliminary data suggests that oxygen delivery to the brain can be sustained or improved be Voxelotor. Again the drug was found to reduce cerebral blood flow and increase the levels of haemoglobin.

- HOPE trial data will be used as the basis for GBT’s planned New Drug Application for voxelotor with the US Food and Drug Administration (FDA) during the second half of 2019. The FDA granted Voxelotor, formerly GBT440, breakthrough therapy designation in January 2018. It already had fast track, orphan drug, and rare paediatric disease designations as a potential sickle cell treatment. The European Medicines Agency also has included Volexotor in its Priority Medicines (PRIME) program.

- The EHA Congress heard an oral presentation on Imara’s IMR-8687, an orally administered, selective phosphodiesterase 9 (PDE9) inhibitor currently being evaluated in a Phase IIa clinical trial as a disease-modifying drug for sickle cell disease.

- Editas Medicine reported to the EHA Congress results from a follow-up study to assess two different CRISPR genome editing strategies, one targeting the *BCL11A* erythroid enhancer (*BC11Ae*) and one targeting the beta-globin locus, for the treatment of sickle cell disease and beta-thalassemia. Charles Albright, Chief Scientific Officer, said: “We are encouraged by these pre-clinical results demonstrating cells edited at the beta-globin locus repopulated all lineages of the blood system including, importantly, the red blood cell precursors and the high percentage of foetal haemoglobin expression. Editing at this site continues to meet our preclinical goals for making a medicine including robust, long-term induction of foetal haemoglobin and maintenance of normal hematopoietic stem/progenitor cell function. Our program is on track towards the clinic, and we have started our IND-enabling activities as we look to develop a best-in-class medicine for the treatment of sickle cell disease and beta-thalassemia.”

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32 The continuing, double-blind HOPE trial (NCT03036813) is evaluating the effectiveness and safety of once-daily treatment with voxelotor in sickle cell patients ages 12 to 65.
34 NCT02850406
35 By Biree Andemariam, Associate Professor and Director of the New England Sickle Cell Institute at University of Connecticut Health
Researchers\textsuperscript{36} have developed a rapid method of continuously monitoring sickle cell disease using a microfluidics-based electrical impedance sensor\textsuperscript{37}. This technology characterizes the cell sickling and unsickling processes in sickle blood without the use of microscopic imaging or biochemical markers.

Cyclerion Therapeutics in June presented data on its sickle cell disease program at two meetings\textsuperscript{38}. Cyclerion is developing soluble guanylate cyclase (sGC) stimulators for the treatment of serious and orphan diseases.

A recent study\textsuperscript{39} suggests that using CRISPR-Cas9 and a corrective short DNA template could be a safe and efficient means of correcting the mutation responsible for sickle cell disease.

3. Regulatory

The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.

- On 20 June Novo Nordisk announced that the European Commission had granted marketing authorisation for Esperoct (turoctocog alfa pegol, N8-G for the treatment of adolescents (≥12 years of age) and adults with haemophilia A. The authorisation covers all 28 European Union member states. Esperoct is an extended half-life factor VIII molecule for replacement therapy in haemophilia A patients. It offers a 1.6-fold half-life prolongation in adults/adolescents compared with standard half-life factor VIII products.
- At the Women Deliver 2019 Conference in Vancouver in June, PATH and Sinapi Biomedical announced that the low-cost, fully assembled Ellavi uterine balloon tamponade (UBT)\textsuperscript{40} has achieved CE marking\textsuperscript{41}. The current World Health Organization (WHO) recommendations identify the UBT as an emergency intervention for postpartum haemorrhage when drug treatment fails or is unavailable.

\textsuperscript{36} from Florida Atlantic University’s College of Engineering and Computer Science


\textsuperscript{38} At the 13th Annual Sickle Cell Disease Research and Educational Symposium – June 7-9, 2019, Fort Lauderdale, Cyclerion presented an overview of olinciguat, its investigational treatment for sickle cell disease, and an update on the ongoing Phase 2 STRONG SCD study during the Investigational New Drug, Therapeutic, and Device Symposium. At the 24th European Hematology Association (EHA) Congress – June 13-16, 2019, Amsterdam, Cyclerion there were two poster presentations:

- the results of a series of sickle cell disease patient and clinician interviews and a literature review conducted to understand the symptoms that patients consider to be most important and relevant to their daily experience, as well as an assessment of existing patient-reported outcome (PRO) tools to evaluate how well each tool measures these symptoms. Abstract #PF731: A Strategy for the Measurement of Sickle Cell Disease Symptoms from the Patient Perspective
- preclinical research demonstrating that olinciguat was associated with improved blood flow and reduced inflammatory response caused by interactions between leukocytes and endothelial cells in a sickle cell disease model. Abstract #PS1521: The Soluble Guanylate Cyclase Stimulator Olinciguat Attenuates Leukocyte/Endothelial Cell Interactions In Berkeley SCD Mice (Presenter: Huihui Li, Cell Biology Postdoctoral Fellow, Albert Einstein College of Medicine)

\textsuperscript{39} So Hyun Park, “Highly efficient editing of the β-globin gene in patient-derived hematopoietic stem and progenitor cells to treat sickle cell disease”, Published 31 May 2019, Nucleic Acids Research, gkz475, https://doi.org/10.1093/nar/gkz475

\textsuperscript{40} http://ellavi.com/

\textsuperscript{41} Meets European regulatory requirements
bluebird bio announced EU Conditional Marketing Authorization for ZYNTEGLO (autologous CD34+ cells encoding βA-T87Q-globin gene) gene therapy for patients 12 Years and older with transfusion-dependent β-Thalassemia who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. ZYNTEGLO is the first gene therapy approved for transfusion-dependent β-thalassemia. (TDT) Germany’s Apceth Biopharma has been awarded the contract to produce bluebird Bio’s recently EU-approved Zynteglo.

4. Market structure and company news

The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.

- There is speculation that uniQure, with a gene therapy for haemophilia A in Phase III trials, is a likely target for takeover, possibly by Novo Nordisk, Pfizer or Sanofi.
- On 3 June, Cerus Corporation announced a new corporate branding campaign and the planned relocation of its corporate offices to a new facility in Concord California. This will co-locate all non-field based, US employees.
- In February 2019 CSL announced it would be transitioning to its own Good Supply Practice (GSP) License in China in 2020. This licence enables CSL to own and sell products in the domestic Chinese market. CSL has been exporting albumin to China for more than 30 years and is the largest supplier of imported human albumin. In 2018 CSL’s albumin sales into China were over $US 500 million. Until now, it has been distributed by a third party.

5. Specific country events

- The Food and Agriculture Organization (FAO) of the United Nations (UN) has said it believes the rising global rates of antimicrobial resistance (AMR) constitute “the most complex threat to global health”. It has launched the AMR Multi-Partner Trust Fund to accelerate the response. The founding contribution is $US 5 million from the Netherlands. The concept of the fund is supported by two other UN agencies, the World Organization for Animal Health, and the World Health Organization. The Trust Fund has a five-year scope and the initial funding appeal is for $US 70 million.
- The World Federation of Haemophilia’s Annual Global Survey estimates almost 50 per cent of the world’s haemophilia sufferers live in India, where almost seventy per cent of them have inadequate information, and little (if any) access to treatment. The Haemophilia Federation (India) (HFI) is working with the Indian Government’s Ministry of Health and Family Welfare on a national Haemophilia Care drive. Reports suggest that HFI has identified only 22,000 people with haemophilia but believes the figure should be around 1.3 million.
- In the week leading up to World Blood Donor Day on 14 June the New Zealand Blood Service said that although it has 110,000 committed donors, it needs 55,000 more to keep up with plasma demands.

43 UniQure weighs sale after hemophilia gene therapy turnaround: report
• The US Congress recently passed the Pandemics and All-Hazards Preparedness and Advancing Innovation Act, or PAHPAI, which will allow the Biomedical Advanced Research and Development Authority (BARDA) to strengthen the country's preparedness against a variety of global disease threats. Although the agency is expected to receive a modest increase from the House of Representatives’ proposed fiscal year 2020 appropriation, Jamie Bay Nishi, director of the Global Health Technologies Coalition called on Congress for more money: “BARDA’s reinforced authority to pursue Strategic Initiatives against naturally occurring threats can provide a significant contribution to our nation’s defences. But this authority is of limited value without sufficient funding. We urge Congress to provide BARDA with a budget that is aligned with its mandate — and its unique capacity to deliver new tools to fight back against intensifying threats like Ebola; unexpected emergencies like Zika; and smouldering problems, like the steady, ominous rise in drug-resistant infections, and the near certainty of a future fight against a deadly strain of pandemic influenza.”
• Researchers have found that Aboriginal and Torres Strait Islander children in far north Queensland are suffering from anaemia at a much higher rate than the general population. Their report recommends the issue of childhood anaemia in Indigenous children be added to the targets of the “Closing the Gap” Indigenous health initiative.

6. Research not included elsewhere

A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

• An international study has suggested that people with high iron levels are less likely to have high cholesterol. The authors cautioned that high iron levels can have other detrimental impacts.
• Researchers found that body mass index may be associated with increased levels of von Willebrand factor (VWF) and Factor VIII (FVIII), though it confers no protection against bleeding in patients with von Willebrand disease (VWD).
• Research led by Harvard scientists has successfully edited the genes of stem cells while still in the body.
• New immunosuppressants have reduced the need for splenectomy in thrombotic thrombocytopenic purpura (TTP). However, surgery may be appropriate in some refractory TTP cases associated with increased ADAMTS13 antigen clearance.

46 Dipender Gill et al., “Associations of genetically determined iron status across the phenome: A mendelian randomization study”, PLOS Medicine, 20 June 2019. https://doi.org/10.1371/journal.pmed.1002833
49 BMI, the weight in kilograms divided by height in meters squared
• A study suggests that the ratio between the blood clotting protein factor VIII (FVIII) and the von Willebrand factor (VWF) may be a reliable biomarker of recovery and relapse in patients with acquired hemophilia A.

7. Infectious diseases

The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).

Mosquito-borne diseases

• University of Florida scientists say that if young mosquitoes have a nitrogen-rich diet, then as adults they are less likely to transmit the Zika virus.
• As part the Congressionally Directed Medical Research Program, the US Department of Defense is awarding Texas Biomedical Research Institute $US 2 million over the next three years to study a promising experimental Zika vaccine.
• Human safety testing has been underway on a formalin inactivated Zika Virus Vaccine (ZPIV) candidate developed at the Walter Reed Army Institute of Research. Three Phase I, placebo-controlled, double-blind clinical trials of the ZPIV vaccine candidate with aluminium hydroxide adjuvant reported positive results.
• Scientists from the University of Maryland have developed a new means of killing malaria-carrying mosquitoes. The fungus enhanced by the gene of an Australian funnel web spider has been trialled in Burkina Faso.
• Research has identified targets of natural human antibody responses found on the surface of red blood cells infected with malaria parasites. The scientists believe that a vaccine could be developed which would boost this natural response and provide an efficient way to block the spread of malaria. Professor Matt Marti, from the University of Glasgow's Institute of Infection, Immunity and Inflammation, said: “This is a significant development in our need to find a plausible target for a malaria vaccine against the human blood stage forms of the parasite. Targeting antigens that are present both on asexual and gametocyte stages may reduce disease and transmission in one hit.”

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54 These trials are NCT02963909, NCT02952833, and NCT02937233.
55 Led from the University of Glasgow in collaboration with Radboud University Medical Centre, The Netherlands and Harvard University. The researchers studied plasma samples from over 500 infected people from Cameroon, Burkina Faso, the Gambia and Malawi.
• Another report\textsuperscript{57} is also concerned with \textit{antibodies} preventing the malaria parasite entering red blood cells. Simon Draper, Professor of Vaccinology and Translational Medicine at the Nuffield Department of Medicine, University of Oxford, said: “The malaria parasite has a protein called RH5, which must bind to a human protein on red blood cells called basigin in order to infect them. In this study, we were able to demonstrate which human antibodies effectively block RH5 from binding with basigin, thus preventing the parasite from spreading through the blood.”

\textbf{Influenza}

• Researchers have found\textsuperscript{58} that “influenza virus coinfections probably occur more often than has been previously documented” and that “the clinical implication of coinfections with distinct influenza viruses in the respiratory tract is not well understood”\textsuperscript{59}.

• Vivaldi Biosciences announced the publication in the journal \textit{Vaccine} on 19 June of Phase I clinical trial results for its deltaFLU vaccine for protection against potential pandemic influenza strain H5N1. The company said the results compare favourably with manufacturers’ data for the two H5N1 vaccines licensed by the FDA\textsuperscript{60}. Vivaldi’s production system is not egg-based, with its consequent speed being an advantage in the case of a pandemic.

• British scientists have used gene-editing to stop bird flu spreading in chicken cells grown in a laboratory\textsuperscript{61}.

• A study\textsuperscript{62} supported by the US National Institutes of Health has examined influenza virus transmission in Nicaraguan households and revealed the type of immune responses that may be protective against influenza virus infection. Research focussed on antibodies produced against the “stem” of the mushroom-shaped influenza virus surface protein, hemagglutinin. This stem is less variable than the head, the region currently targeted by changing seasonal influenza vaccines and by standard laboratory tests for a person’s immune response to a specific flu strain.

• European health officials reported a novel H1N2 infection in Denmark, a reassortment involving two seasonal flu strains: the 2009 H1N1 virus and H3N2. A genetic analysis of the novel H1N2 virus found that it has a hemagglutinin gene from the 2009 H1N1 virus and a neuraminidase gene from H3N2. No evidence of coinfection was found. The latest novel H1N2 case marks Europe’s third in just over a year; earlier cases were detected in March 2018 in the Netherlands and in February 2019 in Sweden.


\textsuperscript{59} https://www.healio.com/infectious-disease/influenza/news/online/%7B122193da-ff54-4a7b-948f-35650e9eae7%7D/flu-virus-coinfection-occurs-more-often-than-previously-thought

\textsuperscript{60} https://brookshires.precisionvaccinations.com/vivaldi-biosciences-deltaflu-nasal-vaccine-candidate-protects-humans-against-influenza-h5n1


Ebola virus disease

- Early in June, the World Health Organization (WHO) said the outbreak of the Ebola virus in the Democratic Republic of the Congo might last another two years. WHO estimated that about a quarter of Ebola infections in the eastern Congo were not being detected, or not detected till it was too late.
- In mid-June, Uganda’s Health Minister reported that clearance had been given by the Uganda National Council for Science and Technology and National Drug Authority for importation of three therapeutic treatments for Ebola: Mapp Biopharmaceutical’s ZMapp, Regeneron Pharmaceuticals’ REGN-EB3 and Gilead Sciences’ Remdesivir. The announcement followed the death in Uganda of infected travellers from the Congo.
- A clinical trial of those three products is being attempted in three treatment centres in the Congo, along with a fourth product Mab114.
- On 18 June, a WHO situation report on the Congo outbreak to 16 June said the case count was 2168 and the death toll 1449.
- Reports on 23 June said the WHO’s Ebola response in the Congo was short of funds, and member states were implored to meet the funding shortfall.
- Researchers have estimated that at least half of all Ebola virus disease spillover events and small outbreaks are not detected. They said their “findings highlight the importance of primary health care and local case management to detect and contain undetected early stage outbreaks at source”.

MERS-CoV

- WHO reported MERS-CoV cases during May 2019, all located in Saudi Arabia. Their epidemiological characteristics were similar to others during the period from 2013 to 2019. The 50–59 years age group continues to be at the highest risk. In total, 2,442 laboratory-confirmed MERS cases, including 842 associated deaths, have been reported worldwide since April 2012. Saudi Arabia accounted for 2,051 cases, including 765 deaths.

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63 https://thehill.com/policy/healthcare/447481-ebola-outbreak-may-last-up-to-2-years-who-says
65 https://af.reuters.com/article/topNews/idAFKCN1TJ264-OZATP
66 https://www.npr.org/sections/goatsandsoda/2019/06/21/734477699/will-1-of-these-4-experimental-treatments-cure-ebola
67 This is a monoclonal antibody based on antibodies from the blood of an Ebola survivor from Kikwit in 1995. It was initially trialled in monkeys, and then the safety and pharmacokinetics were studied in healthy adults. https://clinicaltrials.gov/ct2/show/NCT03478891
68 https://apps.who.int/iris/bitstream/handle/10665/325405/SITREP_EVD_DRC_20190618-eng.pdf?ua=1
Researchers from The University of Texas Medical Branch at Galveston, and from Saudi Arabia and Canada say they have developed a potent and safe vaccine against MERS.\(^7\)1

Other diseases

- A newly identified virus ("Alongshan virus") is infecting people in China, with ticks thought to be the vector.\(^7\)2
- Up to 40 sites round the world will participate in a Phase I clinical study of an investigational vaccine to prevent cytomegalovirus (CMV). Hookipa Pharma’s HB-101 is believed to help prevent CMV infection after kidney transplant by forming antibodies and stimulating immune cells against CMV. The study will enrol 150 transplant patients over approximately 18 months. A vaccine that developed protective antibodies prior to transplant would reduce the need for prophylaxis post-transplant as well as decrease adverse events.
- By 19 June, eleven NSW and Victorian poultry properties so far this year had been affected by salmonella and the necessity for egg recalls from the retail market, along with quarantine, culling and disinfection.
- In early June, an unvaccinated horse was found with Hendra virus disease near Scone, NSW. It was destroyed.
- According to data from WHO, as many as 1 million new cases of sexually transmitted diseases are reported daily. More than 376 million new cases of chlamydia, gonorrhoea, trichomoniasis, and syphilis are reported globally each year in men and women between the ages of 15 and 49.
- African swine fever, a highly contagious disease, is ravaging Asia’s pig industry. The current outbreak began in China in August 2018. It kills nearly all animals it infects.
- Scientists from Trinity College Dublin found how the hepatitis C virus "ghosts" the human immune system and remains undiagnosed in many people.\(^7\)3
- Emergent BioSolutions has been awarded a contract of approximately $US 535 million over a 10-year period for the continued delivery of Vaccinia Immune Globulin Intravenous product to the US Strategic National Stockpile.

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