

Monitoring International Trends

Posted October 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

Some recent matters of interest appear on pages 7 to 22. Highlights are listed below:

Safety and Patient Blood Management (begins page 7)

Appropriate transfusion; bleeding risk (p7)

- Researchers found that donor, blood component, and patient factors all affect haemoglobin levels after red blood cell transfusion.
- Hemanext outlined the potential for hypoxic red blood cells to enhance patient care.

Other (p7)

- Frequent donors give more blood but are more likely to be iron deficient.
- A study suggest that tranexamic acid could prevent death after brain injury.
- Low dose anticoagulation was found to be associated with higher bleeding and thrombotic events in frail patients with non-valvular atrial fibrillation compared with those given full dose anticoagulation.
- A study in patients with chronic kidney disease found amongst other things that anaemia increased the likelihood of hospitalization, major adverse cardiovascular events and mortality.
- Scientists have found that compounds that block a pathway called CHRM4 increase the production of red blood cells.
- Researchers have evaluated the efficacy of intravenous ferric carboxymalotose compared with physician's choice of therapy in treating chemotherapy-induced anaemia in patients with breast cancer, and found no additional benefit.
- A study showed that idarucizumab reversed the anticoagulant effect of dabigatran in most patients with life-threatening bleeding or who were facing urgent procedures, regardless of renal function.
- The antiplatelet drug Ticagrelor monotherapy was associated with a lower risk of clinically significant bleeding compared with ticagrelor plus low-dose aspirin in high-risk patients following percutaneous coronary intervention and ≥ 3 months of dual antiplatelet therapy.

Products and Treatments (begins page 8)

Treating haemophilia (p9)

- In a Phase II trial, a prophylactic for haemophilia B, dalcinonacog alfa, led to an increase of more than 12 per cent in the levels of factor IX in two patients with severe disease, with no immune reaction.
- A trial found that while uniQure gene therapies AMT-060 and AMT-061 both restored coagulation factor IX levels in a primate model of hemophilia B, AMT-061 resulted in greater coagulation activity at the same dose. AMT-061 encodes the Padua variant of the *FIX* gene.
- Research demonstrated that gene therapy using an antibody-drug conjugate conditioning regimen led to safe and sustained production of factor VIII in platelets, and prevented joint bleeding in a mouse model of haemophilia A.
- Octapharma USA introduced two new trials focussed on von Willebrand disease.

Treating beta thalassemia and sickle cell disease (p10)

- Researchers identified “a need to increase awareness among physicians about the benefits of closer monitoring and follow up of renal function in patients with thalassemia”.
- An expert group has released a new consensus on bleeding monitoring in patients with acquired haemophilia.
- Global Blood Therapeutics presented its sickle cell disease research to the Sickle Cell Disease Association of America Convention.
- Researchers proposed that additional studies looking into the underlying mechanisms of pulmonary inflammation in sickle cell disease may lead to more targeted therapies.

Treating other conditions (p11)

- In the US the shortage of immunoglobulin has meant that health care providers, hospitals, and medical systems have taken steps to optimize limited supplies, including lowering doses, delaying treatments, prioritizing based on medical need, and making use of alternative therapies where available.
- Detecting a specific variant of the F12 gene might make diagnosing certain hereditary angioedema-causing mutations quicker than using sequencing.
- Novartis' Jakavi met its primary Phase III endpoint in acute graft-versus-host disease.
- Principia Biopharma announced positive preliminary data from an ongoing Phase I/II trial of PRN1008 in immune thrombocytopenia.
- ADMA Biologics reported the data on ASCENIV in the treatment of Respiratory Syncytial Virus infection in two immunocompromised children.

Regulatory matters (begins page 12)

- The FDA approved
 - i) Amgen's Supplemental Biologics License Application for romiplostim to extend its use;
 - ii) Alexion's Ultomiris treatment for atypical haemolytic uremic syndrome;
 - iii) afamelanotide to increase pain-free light exposure in adult patients with erythropoietic protoporphyria;

- iv) the Ortho Sera suite of reagents that enable extended antigen phenotyping;
- v) rivaroxaban for the prevention of venous thromboembolism among acutely ill hospitalized patients who are at risk for blood clots but not at high risk for bleeding; and
- vi) Octapharma's Wilate as a preventive and on-demand treatment for bleeding episodes in adults and adolescents with haemophilia A.
- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency
 - i) adopted a positive trend vote on the Marketing Authorization Application from Rigel Pharmaceuticals for fostamatinib disodium hexahydrate for the treatment of chronic immune thrombocytopenia in adult patients who are refractory to other treatments;
 - ii) confirmed its negative opinion against approving Novartis' Revolade as add-on treatment in previously untreated patients at least 12 years of age with severe aplastic anemia who are not candidates for autologous stem cell transplant; and
 - iii) supported Prime designation for Emergent BioSolutions' chikungunya virus-like particle vaccine candidate.

Market structure and company news (begins page 13)

- Cerus presented further clinical data supporting the use of INTERCEPT treated blood components.
- Pennsylvania State University named CSL Behring as its 2019 Corporate Partner of the Year.
- CSL filed a lawsuit alleging that a former executive stole files containing trade secrets.
- CSL Chairman Brian McNamee reaffirmed its August guidance for full-year profit growth of between seven and ten per cent.
- Takeda has sold selected prescription and over-the-counter products to Acino.
- SK Plasma is to supply its human immunoglobulin in Brazil.
- Sobi has entered into an expanded agreement with Sanofi to exercise early opt-in for the development and commercialisation of BIVV001.
- Sobi announced a definitive agreement to acquire Dova Pharmaceuticals.
- An investor in Dova Pharmaceuticals filed a proposed class action alleging the company had not filed enough information about its proposed tie-up with Sobi.
- Akebia Therapeutics filed a complaint against the Centers for Medicare & Medicaid Services and the US Department of Health and Human Services, concerning Medicare coverage.
- Novo Nordisk has entered a gene editing deal with bluebird bio.

Specific country events (begins page 15)

- A modelling study showed that the global need for products for blood transfusions exceeds the supply, particularly in low- and middle-income countries.
- Sabah is the Malaysian state with the highest number of thalassemia patients.
- Russia's health ministry has said it fully supports the World Health Organization position against making changes to the human germline.
- Drive-thru flu-shot clinics are available in the US.
- The US Air Force has included the sickle cell trait in fitness screening questionnaires.
- Platelet BioGenesis signed a contract with the US Biomedical Advanced Research and Development Authority to develop stem cell-derived platelets.

- The US Agency for International Development awarded the University of California, Davis, a grant to train researchers in Asia and Africa in preventing animal diseases from spilling over into human populations.
- The Centers for Disease Control and Prevention has awarded funds to US states to take part in a data gathering program on sickle cell disease.
- America's Blood Centers encouraged the FDA to continue to assess the impact of the Final Guidance issued on platelet safety.
- The US Army announced that it is testing airdrops of freeze-dried plasma.
- Stephen Hahn, a radiation oncologist and chief medical executive of the MD Anderson Cancer Center, is tipped to become the next commissioner of the FDA.
- A polymer heart valve has been successfully implanted in a patient.
- In Sweden, blood donors receive a text message after donating, and another when their donation is used.
- The Singapore Red Cross website has a meter showing the level of blood supply.
- Zipline International use its fixed-wing drones in the Indian state of Telangana to deliver blood, vaccines and medicines.
- InDro Robotics has tested unmanned aerial vehicle flights in Montreal to deliver medical aid including blood products.
- In the UK, the Healthcare Safety Investigation Branch reported: "WBIT [wrong blood in tube] incidents are still frequent in the NHS despite a recognition of the risk."
- A consortium of concerned professionals is raising awareness about the need for global eradication of haemolytic disease of the foetus and newborn.

Research not included elsewhere (begins page 17)

- This year's Nobel Prize in physiology or medicine was shared by three researchers for discovering how the body responds to changes in oxygen levels.
- Scientists at Scripps Research have found a compound that could reduce blood stem cells' interferon-induced transmembrane proteins for better delivery of gene therapy.
- Researchers discovered after a study in rodents that diabetes may be a major risk factor for developing respiratory infections.
- A study has found that "low and high levels of haemoglobin are associated with an increased risk of dementia, including Alzheimer's disease".
- New research suggests that a highly accurate blood test detects amyloid.
- Treatment with an oral anticoagulant slows down memory decline and the conversion to Alzheimer disease in mice.
- Scientists have used light to facilitate the formation of new blood vessels.
- The Universities of Bristol and Nottingham are being funded to lead a consortium of experts on research projects into bioengineered blood and soft tissue regeneration.
- Researchers have discovered a protection mechanism in mammals against the toxicity of free heme in the body.

Infectious diseases (begins page 19)

Mosquito-borne diseases (p19)

- A small molecule has been discovered to have the ability to block Zika virus infection in human cells (in vitro) and in mice (in vivo).
- Researchers reconstructed a gene sequence acquired by the ancestor of the malaria parasite *Plasmodium falciparum*, giving it the ability to infect human red blood cells.
- Researchers have developed a chikungunya vaccine that can be manufactured quickly and can be stored at warm temperatures.

Influenza (p20)

- The FDA has approved Xofluza as a treatment for those at high risk of developing flu-related complications.
- Some scientists believe that the first flu viruses you encounter in your life leave an indelible mark on your immune system.
- Influenza researchers have investigated whether convalescent plasma or anti-influenza hyperimmune intravenous immunoglobulin have clinical benefit.

Ebola virus disease (p20)

- A new study suggests climate change raises the risk of more Ebola outbreaks.
- The FDA accepted for priority review Merck's Biologics License Application for its investigational vaccine for Ebola Zaire virus (V920).
- The FDA approved marketing of the first rapid diagnostic test to identify Ebola virus antigens.
- The Sabin Vaccine Institute was awarded funds from the US Biomedical Advanced Research and Development Authority to advance development of vaccines against Ebola Sudan and Marburg viruses.

MERS-CoV (p21)

- By the end of September 2019, 2468 laboratory-confirmed cases of MERS, including 851 deaths had been reported globally, mostly from Saudi Arabia.

Tick-borne diseases (p21)

- US research describes a new rapid assay for Lyme disease that could lead to a practical test for use by healthcare providers.
- With an increase of tickborne disease in the US the National Institutes of Health announced a five-year plan to expand research and reduce infections.
- French company Valneva has an experimental vaccine against Lyme disease which is now in a Phase II clinical trial.
- Baxter completed a safety study on a Lyme vaccine in 2013. Takeda now owns that vaccine and is evaluating whether to take it forward.
- Using a DNA vaccine for tick-borne diseases, researchers in South Korea were able to prevent severe fever with thrombocytopenia syndrome in ferrets.

Other diseases (p22)

- Spain has had its largest ever outbreak of listeria.
- New data suggests that preventing congenital cytomegalovirus may be possible with the antiviral medication valgancyclovir, while CMV hyperimmune globulin as a preventive strategy may be less effective than hoped.
- Scientists found that a 5-minute soak in a 40 per cent solution of household bleach decontaminated stainless steel wires coated with chronic wasting disease prions.

Detailed Report

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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

- Researchers analysed retrospectively linked donor and recipient data on 38,019 single unit California transfusions in 23,194 transfusion recipients. They concluded that donor, blood component, and patient factors all affect haemoglobin levels after red blood cell transfusion¹.
- [Hemanext](#) and its research collaborators presented eight abstracts at the American Association of Blood Banks (AABB) Annual Meeting². Hemanext President and CEO Martin Cannon said: “The eight abstracts help paint a compelling picture of the potential for hypoxic RBCs to enhance patient care.”³ Hemanext’s technology offers an innovative approach to minimizing oxidative damage of stored blood.

Other

- An extended trial has confirmed that frequent donors give more blood but are more likely to be iron deficient⁴.
- [CytoSorbents Corporation](#), whose blood purification technology is used in both medical and surgical conditions, announced positive surgical outcomes⁵ ahead of the [European Association of Cardio-thoracic Surgery Annual Meeting](#)⁶.
- A study⁷ has suggested that the inexpensive anti-bleeding drug tranexamic acid could prevent death after brain injury.
- Australian researchers found⁸ that low dose anticoagulation is associated with higher bleeding and thrombotic events in frail patients with non-valvular atrial fibrillation (AF) compared with those given full dose anticoagulation. In their retrospective analysis they examined the appropriateness of direct oral anticoagulant (DOAC) prescriptions

¹ [Roubinian NH, Plimier C, Woo JP, Lee C, et al. Effect of donor, component, and recipient characteristics on hemoglobin increments following red blood cell transfusion. Blood 2019; 134\(13\): 1003-1013. 26 September 2019 <https://doi.org/10.1182/blood.2019000773>](#)

² 19 to 22 October 2019 in San Antonio, Texas

³ Amongst the abstracts were: (i) *Metabolic Predictors of 24h Post-Transfusion Recovery in End of Storage Control and Hypoxic Red Blood Cells* Abstract OA3-ST4-29, oral presentation by Angelo D’Alessandro, Assistant Professor, University of Colorado Denver School of Medicine, Biochemistry and Molecular Genetics (ii) *Long-term hypoxic storage of red blood cells results in amelioration of lesion hallmarks and Increased in vivo recovery at 24 hours post-transfusion* Abstract P-NE-17, poster presentation (iii) *Effects of hypoxic red blood cells on sickling kinetics of red blood cells from patients with sickle cell disease* Abstract P-NE-5, poster presentation

⁴ [Kaptoge S, Di Angelantonio E, Morre C, Walker M, et al. Longer-term efficiency and safety of increasing the frequency of whole blood donation \(INTERVAL\): extension study of randomized trial of 20,757 blood donors. The Lancet. Haematology, 6 \(10\), e510-e520. \[https://doi.org/10.1016/s2352-3026\\(19\\)30106-1\]\(https://doi.org/10.1016/s2352-3026\(19\)30106-1\)](#)

⁵ Kambiz Hassan et al., [CytoSorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding](#), the [Annals of Thoracic Surgery](#), July 2019, Volume 108, Issue 1, pages 45-51.

⁶ in Lisbon, 3-5 October, 2019.

⁷ The CRASH-3 trial collaborators, [Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury \(CRASH-3\): a randomised, placebo-controlled trial](#) *The Lancet*. Published online 14 October 2019 [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(19\)32233-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32233-0/fulltext)

⁸ Rowena Brook et al., “Real-World Direct Oral Anticoagulants Experience in Atrial Fibrillation: Falls Risk and Low Dose Anticoagulation are Predictive of both Bleeding and Stroke Risk”, 30 September 2019 in *Internal Medicine Journal*, <https://doi.org/10.1111/imj.14640>

in 459 patients who had commenced or continued on a blood thinner between 2013 and 2016. They found that just over a third of patients were not appropriately dosed.

- A Danish study⁹ in patients with chronic kidney disease concluded that the presence of anaemia was associated with an increased risk for incident dialysis; and that for both these patients and those already on dialysis, anaemia increased the likelihood of hospitalization, major adverse cardiovascular events and mortality.
- Scientists have reported¹⁰ a new approach for treating anaemia with medication. They found that compounds that block a pathway called CHRM4 increased the production of red blood cells. They analysed the impact of the compounds in mice with MDS¹¹ and in bone marrow samples from patients with MDS. They also administered them to elderly mice that had reduced red blood cell production because of their age. In all cases the drugs boosted increased the production of red blood cells.
- Intravenous ferric carboxymalotose (FCM) is an injectable iron product known to be effective in treating anemia and removing the need for blood transfusions. Researchers have now evaluated its efficacy compared with physician's choice of therapy in treating chemotherapy-induced anaemia in patients with breast cancer. FCM treatment was not found to provide any added benefit compared with traditional physician choice in treating chemotherapy-induced anemia¹².
- A new study¹³ showed that [idarucizumab](#) (*Praxbind*, Boehringer Ingelheim) reversed the anticoagulant effect of [dabigatran](#) (*Pradaxa*, Boehringer Ingelheim) in more than 98 per cent of patients with life-threatening bleeding or who were facing urgent procedures, regardless of renal function.
- The phase 4 TWILIGHT study found¹⁴ that the antiplatelet drug Ticagrelor (Brilinta from [AstraZeneca](#)) monotherapy was associated with a lower risk of clinically significant bleeding compared with ticagrelor plus low-dose aspirin in high-risk patients following percutaneous coronary intervention (PCI) and ≥3 months of dual antiplatelet therapy.

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.

⁹ Gunnar Toft et al., "Anemia and clinical outcomes in patients with non-dialysis dependent or dialysis dependent severe chronic kidney disease: a Danish population-based study", published online 5 October, [Journal of Nephrology](https://link.springer.com/article/10.1007/s40620-019-00652-9) <https://link.springer.com/article/10.1007/s40620-019-00652-9>

¹⁰ Gaurang Trivedi, Omar Abdel-Wahab, et al., [published a study](#): "Muscarinic acetylcholine receptor regulates self-renewal of early erythroid progenitors", *science Translational Medicine* 25 Sep 2019:Vol. 11, Issue 511, eaaw3781 DOI: 10.1126/scitranslmed.aaw3781

¹¹ [myelodysplastic syndrome \(MDS\)](#).

¹² Tesch H, Loibl S, Kast K, et al. *Chemotherapy (CT)-induced anaemia in patients (pts) treated with dose-dense regimen: results of the prospectively randomised anaemia substudy from the neoadjuvant GeparOcto study*. Presented at: European Society for Medical Oncology (ESMO) Congress 2019; 27 September -1 October, 2019; Barcelona, Spain. Abstract 195P.

¹³ John W. Eikelboom et al., "Dabigatran Reversal with Idarucizumab in Patients with Renal Impairment", [published 8 October 8 in the Journal of the American College of Cardiology](#). [Volume 74, Issue 14, October 2019](#) DOI: 10.1016/j.jacc.2019.07.070

¹⁴ Roxana Mehran, et al., "Ticagrelor with or without Aspirin in High-Risk Patients after PCI", 26 September 2019, the [New England Journal of Medicine](#). DOI:1056/NEJMoa1908419

Treating haemophilia

- In a single site Phase II trial in South Africa ([NCT03995784](#)), a prophylactic for haemophilia B, [dalcinonacoq alfa \(DalcA\)](#), led to an increase of more than 12 per cent in the levels of factor IX in two patients with severe disease, with no immune reaction.
 - i. Catalyst says there will be six participants overall. The company expects final study results in June 2020.
 - ii. DalcA (or CB2679d) is a recombinant factor IX which can be administered by subcutaneous injection. Patients in the Phase IIb trial will be given a single intravenous loading dose of DalcA, followed by daily subcutaneous doses for four weeks. The trial will assess the dose required to achieve steady-state FIX levels above 12 per cent. Other goals include evaluations of safety and tolerability, pharmacokinetics¹⁵ and pharmacodynamics¹⁶, and immunogenicity¹⁷.
 - iii. [Previous data](#) from a small proof-of-concept Phase I/II study ([NCT03186677](#)) was said to have shown DalcA inducing a 22 times more potent response than did BeneFIX. The [immunogenicity risk](#) of DalcA was reported to have been found to be identical to other factor IX products on the market.
 - iv. DalcA has orphan medicinal product designation in Europe to treat patients with haemophilia B, and [orphan drug designation](#) by the US Food and Drug Administration (FDA) for the same indication.
- A new study¹⁸ reports that while [uniQure](#) gene therapies AMT-060 and AMT-061 both restored coagulation factor IX levels in a primate model of hemophilia B, AMT-061 resulted in greater coagulation activity at the same dose.
 - i. AMT-060 encodes the most common version of the *FIX* gene, the ‘wild-type’ version. AMT-061 encodes the Padua variant of the *FIX* gene. Factor IX encoded by the Padua variant has a more specific activity than the wild-type version, which renders it more effective as a replacement in haemophilia B gene therapy.
 - ii. The researchers wrote: “Although the occurrence of bleeding episodes [in the Phase I/II study ([NCT02396342](#)) was reduced following AMT-060 treatment relative to pre-treatment history on high- dose prophylactic factor IX replacement therapy, it is not expected to completely prevent arthropathy (joint disease). Therefore we have improved the design of AMT-060 by introducing a single amino acid change in the encoded protein to encode the hyperactive FIX-Padua for increased FIX activity.”
 - iii. Researchers gave macaques injections of AMT-060 (at a dose equivalent to that used in human trials) or AMT-061 at varying doses. In the AMT-061-treated animals, factor IX levels were higher at higher doses, as expected.
 - iv. At the same dose, both AMT-060 and AMT-061 yielded virtually equal levels of factor IX. But factor IX activity was 6.5 times higher after AMT-061 than AMT-060.
 - v. The researchers wrote: “A gene therapy approach that results in higher FIX activity would ideally result in discontinuation of prophylaxis, reduction

¹⁵ what the body does to a drug

¹⁶ what a drug does to the body

¹⁷ the risk that a patient will produce antibodies against DalcA that will affect its efficacy

¹⁸ Elisabeth A Spronck et al., “[Enhanced Factor IX Activity Following Administration of AAV5-R338L “Padua” Factor IX versus AAV5 wildtype Human Factor IX in Non-human Primates.](#)” in [Molecular Therapy – Methods & Clinical Development. Volume 15](#), 13 December 2019, Pages 221-231

in annualized bleed rate, but also prevention of blood-induced arthropathy that is the main cause of morbidity in hemophilia.”

- vi. The researchers concluded: “These promising results of AMT-061 in non-human primates combined with the Phase I/II study clinical results of AMT-060 support a rapid transition of AMT-061 into clinical studies.” A Phase III open-label trial of AMT-061 ([NCT03569891](#)) in adults with haemophilia B is in progress in Europe and the US.
- Research¹⁹ demonstrated that gene therapy using an antibody-drug conjugate (ADC) conditioning regimen led to safe and sustained production of factor VIII (FVIII) in [platelets](#), and prevented joint bleeding in a mouse model of [haemophilia A](#).
- [Octapharma USA](#) sponsored the National Hemophilia Foundation’s (NHF) [71st Bleeding Disorders Conference](#) in Anaheim and introduced two new clinical trials focussed on von Willebrand Disease (VWD). The first study will assess the efficacy and safety of [WILATE](#) during prophylaxis in previously treated patients with VWD. The second study is a multicentre study of [WILATE](#) use in VWD for childbirth.
- A group of 36 experts has released a new consensus on bleeding monitoring in patients with acquired haemophilia. The statements²⁰ make specific recommendations on monitoring bleeding and assessing the efficacy of treatment in patients with acquired haemophilia. They cover the initial management of bleeding, and management of site-specific bleeding: urological, gastrointestinal, muscle, skin, and joint bleeds, head and neck bleeds, and intracranial and postpartum haemorrhage.

Treating beta thalassemia and sickle cell disease

- Reduced mortality in beta thalassemia has allowed previously unacknowledged complications to emerge, including renal disease. In a new paper²¹, researchers have discussed the most common pathophysiologic and clinical manifestations of renal disease in such patients. Lead author Christos Demosthenous said: “Although renal disease is a rare cause of morbidity, approximately 60 per cent of patients with thalassemia are expected to experience renal complications. Therefore there is a need to increase awareness among physicians about the benefits of closer monitoring and follow up of renal function in patients with thalassemia. Early diagnosis and appropriate intervention will prevent subsequent adverse events from emerging.”
- [Global Blood Therapeutics, Inc.](#) presented four abstracts related to its sickle cell disease (SCD) research²², in oral and poster presentations during the 47th Annual National Sickle Cell Disease Association of America (SCDAA) Convention in

¹⁹ Chunyan Gao, et al., “[Nongenotoxic antibody-drug conjugate conditioning enables safe and effective platelet gene therapy of hemophilia A mice](#),” 12 September in *Blood Advances* (2019) 3 (18): 2700-2711. <https://doi.org/10.1182/bloodadvances.2019000516>

²⁰ Andreas Tiede et al., “Clinical evaluation of bleeds and response to haemostatic treatment in patients with acquired haemophilia: A global expert consensus statement”, *Haemophilia*, 13 September 2019, <https://doi.org/10.1111/hae.13844>

²¹ Christos Demosthenous et al., “Beta-thalassemia: renal complications and mechanisms: a narrative review”, *Hematology*, 24(1):426-438 · December 2019.

<https://tandfonline.com/doi/pdf/10.1080/16078454.2019.1599096>

²² *Treatment of Moderate to Severe Anemia in Sickle Cell Disease: Results from a 2018 U.S. Patient Chart Analysis*, Robin Howard, Vice President, Commercial Planning, GBT; *Evaluation of Variables Affecting the Care of Patients with Sickle Cell Disease by U.S. Location*, Julie Kanter, Associate Professor, University of Alabama at Birmingham; *Beyond Pain: The Symptoms and Impacts of Sickle Cell Disease on Children and Their Caregivers*, Clark Brown, Clinical Director, Children’s Healthcare of Atlanta; and *Results from the Randomized Placebo-controlled Phase 3 HOPE Trial of Voxelotor in Adults and Adolescents with Sickle Cell Disease*, Carolyn Hoppe, Senior Medical Director, GBT

Baltimore²³. GBT also hosted a symposium, “Sickle Cell Disease and Brain Health.” This focussed on how SCD affects neurocognition and the function of the brain over a patient’s lifetime.

- US-based researchers have shown²⁴ how low-cost, non-invasive diffuse correlation spectroscopy (DCS) can improve the assessment of cerebral blood flow in children with sickle cell disease.
- In a pilot, cross sectional study, both systemic and airway inflammatory markers were compared in patients with sickle cell disease (SCD) with and without asthma or obstructive airway symptoms. The researchers propose that additional studies looking into the underlying mechanisms of pulmonary inflammation in SCD may help researchers to develop more targeted therapies for these patients²⁵.

Treating other conditions

- A news item on 29 September said that an FDA report²⁶ had confirmed that an increased demand for Ig products has led to a shortage of Ig intravenous (IVIg) and Ig subcutaneous (ScIg) in the United States, which has affected hospitals and clinics across the country. In response health care providers, hospitals, and medical systems have taken steps to optimize limited supplies of Ig for patients, including lowering doses, delaying treatments, prioritizing based on medical need, and making use of alternative therapies where available. However IVIg may be the only therapy for specific genetic, life threatening conditions that disable the body’s infection-fighting function. The intravenous form is licensed by the FDA for primary immunodeficiencies, Kawasaki disease, preventative care after bone marrow transplants, and chronic inflammatory demyelinating polyneuropathy. However the use of IVIg has expanded to include a wider variety of illnesses. [The Plasma Protein Therapeutics Association](#) reports that there was a 66 per cent increase in distribution of the treatment between 2012 and 2018 across North America and Europe. This increased distribution has contributed to the shortage. Dana Lynch, from CSL Behring, said: “CSL Behring has had no manufacturing issues or supply disruptions related to Hizentra or Privigen and expects to supply the market significantly to help meet growing demand; however, we cannot fill the entire gap created by shortages of other manufacturers’ products.”
- A study²⁷ has shown that a genetic technique called [allelic discrimination](#) — which detects a specific variant of the [F12 gene](#) — might make diagnosing certain [hereditary angioedema](#)-causing mutations quicker and cheaper than using sequencing.
- Novartis announced that Jakavi (ruxolitinib) met its primary endpoint in a Phase III study of acute graft-versus-host disease²⁸.

²³ October 9-12, 2019.

²⁴ Seung Yup Lee et al., “Noninvasive optical assessment of resting-state cerebral blood flow in children with sickle cell disease” [Neurophotonics](#) 10.1117/1.NPh.6.3.035006.

²⁵ Aliva De, Sabhyata Agrawal et al., ["Airway Inflammation and Lung Function in Sickle Cell Disease"](#), *Pediatric Allergy, Immunology, and Pulmonology*, Published Online:17 Sep 2019 <https://doi.org/10.1089/ped.2019.1014>

²⁶ See FDA [letter](#) released in August

²⁷ Marina M Dias, [A cost-effective algorithm for diagnosis of hereditary angioedema with normal C1 inhibitor: applying molecular approach to clinical practice](#),” in *The Journal of Allergy and Clinical Immunology: In Practice*. <https://doi.org/10.1016/j.jaip.2019.06.041>

²⁸ REACH2 trial results confirmed that Jakavi improves the overall response rate at 28 days vs. best available therapy in steroid-refractory acute graft-versus-host disease. This is a serious and common complication of stem cell transplants. In its acute form it has a one-year death rate of well over 50 per cent.

- Principia Biopharma announced positive preliminary data from an ongoing Phase I/II trial of its investigational drug, PRN1008, in a treatment-resistant and refractory patient population (median of five prior therapies) with immune thrombocytopenia (ITP). Further updated data from the trial will be presented at the American Society of Hematology (ASH) Annual Meeting in December.
- ADMA Biologics offered a poster presentation²⁹ at IDWeek 2019, in Washington, D.C. This reported the data obtained from the compassionate use of ASCENIV (formerly RI-002) in the treatment of Respiratory Syncytial Virus (RSV) infection in two immunocompromised children at the Mayo Clinic, Rochester, MN.

3. Regulatory

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

- The US Food and Drug Administration (FDA) approved Amgen's Supplemental Biologics License Application (sBLA) for romiplostim (Nplate) to include new data in its US prescribing information showing sustained platelet responses in adults with immune thrombocytopenia (ITP)³⁰. The update extends treatment with romiplostim to newly diagnosed and persistent adult ITP patients who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. In December 2018, the FDA had approved a previous sBLA for Nplate in the treatment of paediatric patients with ITP.
- Alexion Pharmaceuticals said the FDA had [approved](#) its Ultomiris³¹ treatment for atypical haemolytic uremic syndrome (aHUS)³². Ultomiris was already approved in the US (and some other countries) to treat adults with paroxysmal nocturnal hemoglobinuria.
- The FDA approved Scenesse (afamelanotide) to increase pain-free light exposure in adult patients with a history of phototoxic reactions (damage to skin) from erythropoietic protoporphyria³³.
- Ortho Clinical Diagnostics said the FDA had cleared its Ortho Sera suite of reagents that enable extended antigen phenotyping. The product was approved for use with the Ortho Vision analyser.
- The FDA approved rivaroxaban³⁴ for the prevention of venous thromboembolism among acutely ill hospitalized patients who are at risk for blood clots but not at high risk for bleeding.
- The FDA approved Octapharma's [Wilate](#) as a preventive and on-demand treatment for bleeding episodes in adults and adolescents with haemophilia A. Wilate is an injectable treatment that contains human plasma-derived von Willebrand Factor

²⁹ *Treatment of RSV Lower Respiratory Tract Infection in Two Immunocompromised Children with Polyclonal Immunoglobulin Containing Standardized Levels of Neutralizing Anti-RSV Antibody.* Presentation and Poster Board Number: 2630

³⁰ ITP is a rare, serious autoimmune disease characterized by low platelet counts.

³¹ ravulizumab-cwvz

³² A very rare disease that can progressively injure vital organs, especially the kidneys, through damage to blood vessels and through blood clots.

³³ Erythropoietic protoporphyria results from mutations causing impaired activity of ferrochelatase, an enzyme involved in production of heme, a component of haemoglobin. The decrease in ferrochelatase activity causes an accumulation of protoporphyrin IX (PPIX) in the body. Light reaching the skin can react with PPIX causing intense skin pain, redness and thickening. Scenesse (afamelanotide) is an implant inserted under the skin. It is a melanocortin-1 receptor (MC1-R) agonist, increasing the production of eumelanin in the skin independent of exposure to sunlight or artificial light.

³⁴ [rivaroxaban \(Xarelto, Janssen\)](#) is a direct oral anticoagulant

(VWF) and coagulation factor VIII (FVIII). In 2009, the FDA [approved](#) Wilate as an on-demand treatment to control spontaneous bleeding episodes in children and adults with [von Willebrand Disease](#) (VWD) — a disorder characterised by lacking or having faulty VWF in the blood — and to manage peri-operative bleeding.

- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has adopted a positive trend vote on the Marketing Authorization Application from Rigel Pharmaceuticals for fostamatinib disodium hexahydrate (fostamatinib) for the treatment of chronic immune thrombocytopenia in adult patients who are refractory to other treatments. The CHMP intends to hold a final vote on the recommendation at their November meeting. Fostamatinib is commercially available in the US.
- The European Medicines Agency's advisory committee CHMP has [confirmed](#) the negative opinion it issued in June against approving Novartis' Revolade (eltrombopag) as add-on treatment in previously untreated patients at least 12 years of age with severe aplastic anemia who are not candidates for autologous stem cell transplant. CHMP explained it considered that the clinical study supporting the application was inadequate to show a treatment effect in these patients since there was no direct comparison between Revolade plus immunosuppressive therapy and immunosuppressive therapy on its own. At present, Revolade is approved in the EU for adults with severe aplastic anemia, patients at least one year old with primary immune thrombocytopenia and HCV-positive adults with thrombocytopenia.
- CHMP supported Prime designation for Emergent BioSolutions' chikungunya virus-like particle (VLP) vaccine candidate, CHIKV VLP. The company expects to initiate a pivotal trial in 2020. PRIME Designation allows for frequent and timely interactions with the EMA to facilitate accelerated evaluation and approval.

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.

- The AABB Annual Meeting took place in San Antonio, Texas, from 19 October to 22 October. Dr. Richard Benjamin, Cerus' Chief Medical Officer, said: "We are looking forward to the AABB meeting and sharing with the transfusion medicine community the latest clinical data supporting the use of INTERCEPT treated blood components. Between Cerus and our scientific collaborators, we will have 23 abstracts³⁵, including 6 oral presentations related to INTERCEPT. We think the Swiss experience, supporting the use of INTERCEPT treated platelets with a 7-day shelf-life in routine use in allogeneic stem cell transplant recipients over more than 5 years, and data showing the absence of septic transfusions with pathogen-reduced platelets compared to culture-screened platelets that used a secondary rapid test on day 5,

³⁵ A full list of Cerus related abstracts can be viewed at <https://intercept-usa.com/aabb2019>. Highlights include: *Pathogen Reduced Platelets Reduce Septic Transfusion Reactions Compared to Conventional Platelets – Despite Point of Release Testing; Achieving 100% Pathogen Reduced Platelet Component Inventory with Production Optimization and Variable Dosing; and Five Years of Routine Experience Using Amotosalen/UVA-Treated Platelets with Storage up to 7 Days* Information on Cerus' industry workshop can be viewed at: https://intercept-usa.com/images/AABB2019/Cerus_AABB_Workshop_Postcard_email.pdf.
Cerus Corporation Industry Workshop: Are you ready for FDA's Bacterial Contamination Guidance?

will be of particular interest at the conference given the final FDA guidance document³⁶.”

- Pennsylvania State University named [CSL Behring](#) as its 2019 Corporate Partner of the Year. The award recognizes CSL Behring’s, including philanthropic commitments to expand biotechnology research and deliver industry-relevant student experiences, seminars and other student engagement activities, and an active recruiting presence at Penn State.
- CSL reportedly filed a lawsuit on 7 October in the US District Court of Pennsylvania alleging that a former executive stole files containing trade secrets before he left for a job at a rival company.
- CSL Chairman Brian McNamee told the annual general meeting that the company reaffirmed its August guidance for full-year profit growth of between seven and ten per cent. He said CSL expects a continuation of strong demand for plasma and recombinant therapies, and a shift in product mix should yield a slight increase in margin.
- Following its acquisition of Shire and the need to reduce its portfolio, Takeda has sold selected prescription and over-the-counter products to Acino covering its Near East, Middle East and African interests.
- SK Plasma (South Korea) is to supply its human immunoglobulin, LIV-Gamma, in Brazil. It is the last of eight suppliers. The company plans to manufacture the product at its new plant located in Andong Bio Industrial Complex in North Gyeongsang Province. SK Plasma has been expanding its influence in South American markets, including Peru, Dominica, and Paraguay, since 2016.
- [Swedish Orphan Biovitrum AB](#) (Sobi) has entered into an expanded agreement with Sanofi to exercise early opt-in for the development and commercialisation of BIVV001, an investigational extended half-life factor VIII therapy with the potential to provide extended protection from bleeds with once-weekly dosing for people with haemophilia A. Sobi will make a payment to Sanofi of \$US 50 million and will become a development partner in this programme. A BIVV001 phase III pivotal trial is expected to start later this year³⁷. In the collaboration agreement with Sanofi, Sobi holds the commercial rights for joint haemophilia programmes for Europe, North Africa, certain countries in the Middle East, and Russia. In connection with the expansion of the collaboration agreement, a new supply contract with Sanofi until 2027 regarding Elocta and Alprolix has been agreed, with the potential for expansion to include BIVV001.
- Swedish Orphan Biovitrum (Sobi) announced a definitive agreement to acquire Dova Pharmaceuticals by means of a tender offer. The acquisition of Dova provides Sobi with Doptelet (avatrombopag)³⁸. The arrangement will enhance Sobi’s product portfolio in haematology and expand Sobi’s commercial presence in the US. Sobi

³⁶ the recently published final FDA guidance document on mitigating the risk of bacterial contamination in transfused platelet components.

³⁷ Data from the BIVV001 phase I/IIa study was presented at the 27th congress of the International Society on Thrombosis and Haemostasis (ISTH), in July 2019. BIVV001 was granted orphan drug designation by the FDA in August 2017 and by the European Commission in June 2019.

³⁸ Dova Pharmaceuticals was founded in 2016 to commercialise Doptelet, a second generation small-molecule thrombopoietin receptor agonist used in the treatment of thrombocytopenia by increasing platelet count. In May 2018, Doptelet was approved by the FDA for the treatment of thrombocytopenia in adult patients with Chronic Liver Disease who are scheduled to undergo a procedure, and in June 2019 for Chronic Immune Thrombocytopenia in adult patients who have had an insufficient response to a prior treatment. Doptelet was approved by the European Medicines Agency (EMA) for Chronic Liver Disease in June 2019, and a European filing for the Chronic Immune Thrombocytopenia indication is expected in 2020. Dova is also conducting a Phase III trial in Chemotherapy-Induced Thrombocytopenia which is a common side effect of chemotherapy that results in a low number of platelets. At present, there are no approved drugs to treat this condition.

expects to grow Doptelet across its indications by expanding patient access outside the US.

- An investor in Dova Pharmaceuticals filed a proposed class action in Delaware federal court alleging the company had violated securities laws by not filing enough information about its proposed \$US 915 million tie-up with Sobi.
- Akebia Therapeutics filed a [complaint](#) in federal district court against the Centers for Medicare & Medicaid Services (CMS) and the US Department of Health and Human Services (HHS). It challenges a CMS decision in September 2018 that rescinded Medicare Part D coverage of Auryxia (ferric citrate), Akebia's FDA-approved drug, when used for the treatment of iron deficiency anemia (IDA) in adult patients with chronic kidney disease (CKD) not on dialysis (the IDA Indication). The lawsuit also seeks to reverse the CMS decision imposing a requirement for prior authorization for Auryxia when used to control serum phosphorus levels in adult patients with CKD on dialysis (the Hyperphosphatemia Indication). Auryxia was approved by the FDA on 5 September, 2014 for the hyperphosphatemia Indication and approved by the FDA on 6 November, 2017 for the IDA Indication.
- Novo Nordisk has entered a gene editing deal with [bluebird bio](#). Novo Nordisk gains access to bluebird bio's MegaTal gene editing technology, which can be delivered by viral and non-viral vectors, for initially three years. Daniel Brunicardi Timmermann, corporate VP of Novo Nordisk's Biopharm Transformational Research Unit, said: "We are delighted today to announce a research partnership between bluebird bio and Novo Nordisk with the aim of delivering the next generation of gene therapy for hemophilia A based on genome editing."

5. Specific country events

- A modelling study reported in *The Lancet Haematology*³⁹ showed that the global need for products for blood transfusions exceeds the supply of blood products, particularly in low- and middle-income countries. Researchers reported 1.12 ratio of blood product need to supply. Denmark had the greatest supply of blood products at 14,704 units per 100,000 people, and South Sudan had the least supply, with 46 units per 100,000 people. Blood supply was insufficient to meet needs in every country in central, eastern, and western sub-Saharan Africa, Asia, and south Asia, but in no countries in Australasia, southern Latin America, and western Europe.
- Malaysia has acknowledged that Sabah is the State with the highest number of thalassemia patients, about 80 per cent of all patients in the country,
- Russia's health ministry has said it fully supports the [World Health Organization position](#) against making changes to the human germline. This is despite reported comments from Moscow scientist Denis Rebrikov that he wants to use the genome-editing technology CRISPR to alter embryos.
- Drive-thru flu-shot clinics are available in the US.
- The US Air Force is now asking personnel about the sickle cell trait as part of their [fitness screening questionnaires](#) in response to some [physical fitness training-related deaths](#) earlier this year.
- In the US, Platelet BioGenesis signed a \$US 56 million contract with the [Biomedical Advanced Research and Development Authority](#) (BARDA)⁴⁰, to develop and

³⁹ Roberts N, James S, Delaney M, Fitzmaurice C. [The global need and availability of blood products: a modelling study](#) [published online October 17, 2019]. *Lancet Haematol*. doi:10.1016/S2352-3026(19)30217-0

⁴⁰ an agency of the US government's Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response

establish donor-independent (stem cell-derived) platelets as a medical countermeasure for treating victims of a nuclear or radiological event.

- The [US Agency for International Development](#) awarded the University of California, Davis, an \$US 85 million grant over five years to train academic researchers in Asia and Africa in preventing animal diseases from spilling over into human populations.
- The [Centers for Disease Control and Prevention](#) (CDC) has so far awarded funds to nine US states to take part in a data gathering program on sickle cell disease and how it affects daily life.
- America's Blood Centers (ABC) encouraged⁴¹ the US Food and Drug Administration (FDA) to continue to assess the impact of the Final Guidance⁴² issued on [Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion Guidance for Industry](#). The organisation said that an extended implementation period was allowed but operational complexities remained.
- The US Army announced that it is testing airdrops of freeze-dried plasma as a way of getting it closer to the battlefield to help improve the survival rate for wounded soldiers. Soldiers from the [Fort Bragg](#), North Carolina.-based 432nd Blood Support Detachment jumped out of a [CH-47 Chinook](#) with the product packed in their ruck sacks. This delivery method was deemed infeasible with other blood products. Around 40 per cent of combat deaths are caused by haemorrhaging. Col. Roberto E. Marin, material systems branch chief with the Army Medical Department Board, said: "Tourniquets helped in enhancing survivability for our warfighters. But it's blood that keeps them alive." Freeze-dried plasma takes 1-6 minutes to rehydrate⁴³. Pennsylvania-based Teleflex Inc. has partnered with the military to try to gain FDA approval for a freeze-dried plasma product, EZPlaz, by 2020. It comes in ready-to-use bags, stored in a protective, hard-plastic sheath alongside a bag of sterile water that's used to rehydrate the blood component for injection.
- Stephen Hahn, a radiation oncologist and chief medical executive of the MD Anderson Cancer Center, is tipped to become the next commissioner of the FDA.
- A polymer heart valve, designed in Australia, has been successfully implanted in a patient. The Tria heart valve was created through a joint project between CSIRO and medical device manufacturer Foldax, of Utah. The valve uses a proprietary CSIRO polymer which carries no risk of calcification, clotting, or damage to red blood cells.
- In Sweden, blood donors receive a thank you text message just after donating, but then when their blood has been used to help another person, they are informed.
- The Singapore Red Cross website has a meter which shows the [latest levels of blood supply](#) available in Singapore. The [Red Cross also gives out medals](#) annually to donors who have attained donation milestones. The Champion Blood Donor Recognition Ceremony by SRC on World Blood Donor Day.
- Californian company Zipline International, will soon have its fixed-wing drones flying throughout the Indian state of Telangana. The state government has adopted a new framework on delivery of blood, vaccines and medicines to cut transport time and increase supply chain efficiency.

⁴¹ <http://www.prnewswire.com/news-releases/americas-blood-centers-urges-fda-to-continue-to-evaluate-impact-of-new-final-guidance-on-platelet-availability-300930314.html>

⁴² The guidance document can be viewed at the following URL.
<https://www.fda.gov/media/123448/download>

⁴³ European allies used freeze-dried plasma to treat US Special Forces casualties in Afghanistan. Special operations troops have been supplied with the French product since 2012. The FDA granted the Defense Department permission in 2018 to use freeze-dried plasma produced by France's Centre de Transfusion Sanguine des Armees to treat uncontrolled haemorrhaging from combat wounds.

- The Ghanaian Government was in talks with Zipline to start delivering the malaria vaccine to remote locations via drones, a service it already provides for other products, including intravenous antibiotics, blood platelets and snake antivenom.
- InDro Robotics, a global leader in drone technology, has tested unmanned aerial vehicle (UAV) flights in downtown Montreal to deliver medical aid in a simulated emergency, including blood products to trauma patients in circumstances where roads may be closed and traffic gridlocked. Defibrillators too are time critical.
- In the UK, the Healthcare Safety Investigation Branch (HSIB) reported: “WBIT [wrong blood in tube] incidents are still frequent in the NHS despite a recognition of the risk.” Last year there were close to 800 incidents in which patients narrowly avoided a “catastrophic outcome” after blood-transfusion test results were either labelled or collected incorrectly. The number of potentially lethal errors has more than doubled since 2010.
- WIRhE is a consortium of physicians, scientists, epidemiologists, midwives, global health advocates and industrial partners committed to raising awareness about the need for global eradication of haemolytic disease of the foetus and newborn due to anti-Rh(D) antibodies. WIRhE is supporting a series of pilot projects in underserved settings to help families now and to demonstrate proof-of-principle approaches that can be scaled up to serve large populations in the future.

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.

- This year’s Nobel Prize in physiology or medicine was shared by three researchers for discovering how the body responds to changes in oxygen levels. William Kaelin Jr⁴⁴, Sir Peter Ratcliffe⁴⁵ and Gregg Semenza⁴⁶, worked out how cells sense falling oxygen levels and respond by making new blood cells and vessels. While their research on hypoxia described the fundamental physiological process that enables animals to thrive at high altitudes, understanding the mechanism has given researchers new openings to treatments for anaemia, cancer, heart disease and other conditions.
- Scientists at Scripps Research have found that a resveratrol-based compound could reduce blood stem cells’ interferon-induced transmembrane proteins for better delivery of gene therapy⁴⁷.
- A group of researchers⁴⁸ set out to identify any particular risk factors associated with succumbing to Middle East respiratory syndrome coronavirus (MERS-CoV). They discovered after an extensive study in rodents that diabetes may be a major risk factor for developing respiratory infections⁴⁹.

⁴⁴ Of the Dana-Farber Cancer Institute and Harvard University in Massachusetts

⁴⁵ University of Oxford and the Francis Crick Institute in London

⁴⁶ Of Johns Hopkins University in Baltimore, Maryland

⁴⁷ Stosh Ozog, Bruce E Torbett et al., “ Resveratrol trimer enhances gene delivery to hematopoietic stem cells by reducing antiviral restriction at endosomes”, *Blood* (2019) 134 (16): 1298-1311.

Published 17 October 2019 <https://doi.org/10.1182/blood.2019000040>

⁴⁸ from the Schools of Medicine at the University of Maryland and Johns Hopkins University

⁴⁹ Kirsten A Kulcsar et al., “Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection”, [Journal of Clinical Investigation Insights](#). Published 24 September 2019.

- A study⁵⁰ has found that “low and high levels of hemoglobin are associated with an increased risk of dementia, including AD⁵¹, which may relate to differences in white matter integrity and cerebral perfusion”.
- New research suggests that a highly accurate blood test detects amyloid, a key biomarker of [Alzheimer's disease](#) (AD), potentially eliminating the need for a lumbar puncture. Investigator Suzanne Schindler⁵², told *Medscape Medical News* that the study shows “that plasma A β 42/A β 40 accurately identifies individuals with brain [amyloidosis](#), whether they are cognitively normal or cognitively impaired.” Findings were presented at the 144th Annual Meeting of the American Neurological Association, adding to those the researchers had recently [published online](#) in *Neurology*⁵³.
- Russian and Finnish scientists published⁵⁴ the results of a joint study on the interaction of red blood cells for drug delivery, using recent advances in medical nanotechnology.
- Treatment with an oral anticoagulant delays memory decline and the conversion to [Alzheimer disease](#) (AD) in mice⁵⁵. Long-term anticoagulation therapy with [dabigatran](#) (Pradaxa from Boehringer Ingelheim) inhibited [thrombin](#) and abnormal deposition of fibrin in a mouse model of AD. After receiving dabigatran for 1 year, the mice had no memory loss, and there was no reduction in cerebral circulation. Dabigatran also reduced typical AD symptoms, including cerebral inflammation, blood vessel injury, and amyloid protein plaques.
- Scientists have developed a device that, by illuminating blood with red light while simultaneously exchanging carbon monoxide for oxygen, can quickly eliminate the toxin from rats⁵⁶.
- At the [American Society for Bone and Mineral Research \(ASBMR\) 2019 Annual Meeting](#) in Orlando, Florida, researchers presented data⁵⁷ showing that red blood cell distribution width (RDW) shows strong accuracy as a predictor of [hip fracture](#).
- Scientists at [Istituto Italiano di Tecnologia \(IIT\)](#) in Milan used light to facilitate the formation of new blood vessels, showing that it is possible to impact the fate of tissue cells by using visible light together with photo-sensitive and biocompatible materials⁵⁸.

⁵⁰ Frank J Wolters et al., “Hemoglobin and anemia in relation to dementia risk and accompanying changes on brain MRI”, *Neurology* 27 August 2019; 93 (9)

<https://doi.org/10.1212/WNL.0000000000008003>

⁵¹ Alzheimer's Disease

⁵² assistant professor of neurology, Washington University School of Medicine, St Louis, Missouri

⁵³ Suzanne E Schindler et al., ‘High-precision plasma β -amyloid 42/40 predicts current and future brain amyloidosis’. *Neurology* October 22, 2019; 93 (17) DOI:

<https://doi.org/10.1212/WNL.0000000000008081>

⁵⁴ Tatiana Avsievich et al., “Mutual interaction of red blood cells influenced by nanoparticles”, *Scientific Reports* volume 9, Article number: 5147 (2019) <https://www.nature.com/articles/s41598-019-41643-x>

⁵⁵ Marta Cortes-Cantell et al., “Long-Term Dabigatran Treatment Delays Alzheimer's Disease Pathogenesis in the TgCRND8 Mouse Model”, [published online](#) 7 October, *Journal of the American College of Cardiology*, DOI: 10.1016/j.jacc.2019.07.081

⁵⁶ L. Zazzeron et al., “Phototherapy and extracorporeal membrane oxygenation facilitate removal of carbon monoxide in rats,” October 9, *Science Translational Medicine* 11:eaau4217, 2019. DOI: 10.1126/scitranslmed.aau4217

⁵⁷ First author Kyoung Min Kim, , of the San Francisco Coordinating Center, California Pacific Medical Center Research Institute, presented the findings from the Osteoporotic Fractures in Men (MrOS) study. Presented 21 September, 2019. Abstract 1069.

⁵⁸ F.Lodola, et al., “Conjugated polymers optically regulate the fate of endothelial colony-forming cells”, 27 September 2019 [Science Advances](#). Vol. 5, no. 9, eaav4620

DOI: 10.1126/sciadv.aav4620

- The Universities of Bristol and Nottingham are being funded⁵⁹ to lead a consortium of experts on research projects into bioengineered blood and soft tissue regeneration. The research is designed to save lives and improve their quality for injured military personnel. The funding will enable the University of Bristol to continue its research to engineer a multi-compatible blood type, with an improved storage profile. This could transform the logistics of transporting and storing blood supplies on the front line. In longer term civilian use, first responders like paramedics could also benefit from the portability of a blood supply that is suitable for all. The University of Nottingham will continue to research a novel approach to preserve and regenerate soft tissue after blast and ballistic trauma through transient gene therapy. Preserving living tissue after injury is critically important.
- Iqbal Hamza, professor in Animal and Avian Sciences at the University of Maryland, and colleagues have discovered a protection mechanism in mammals against the toxicity of free heme in the body -- the production of hemozoin, a crystallized form of heme. The production of hemozoin was previously thought only to be possible by blood-feeding organisms like malarial parasites, but finding this protective phenomenon in mammals opens up new lines of enquiry into how heme tolerance occurs in humans and how this can be used to treat not only malaria and other parasitic infections, and also haemolytic diseases like sickle cell disease.⁶⁰

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

- A small molecule has been discovered to have the ability to block Zika virus infection in human cells (in vitro) and in mice (in vivo)⁶¹. It may also inhibit human infections by other flaviviruses.
- Researchers⁶² reconstructed a 50,000-year-old gene sequence acquired by the ancestor of the malaria parasite *Plasmodium falciparum*, giving it the ability to infect human red blood cells⁶³.

⁵⁹ The funding is awarded at Phase 2 of the Defence and Security Accelerator (DASA) Regenerative Medicine themed competition which is facilitated and managed by the Defence Science and Technology Laboratory (Dstl) on behalf of the MOD, in partnership with the Academic Department of Military Surgery and Trauma (ADMST).

⁶⁰ Rini H Pek, Iqbal Hamza. 'Hemozoin produced by mammals confers heme tolerance.' *eLife*, 2019; 8 DOI: [10.7554/eLife.49503](https://doi.org/10.7554/eLife.49503)

⁶¹ Alicia Martinez-Lopez, "Glycosylated diphyllin as a broad-spectrum antiviral agent against Zika virus", *EBioMedicine*, Volume 47, September 2019, Pages 269-283.

<https://doi.org/10.1016/j.ebiom.2019.08.060>

⁶² From the Wellcome Sanger Institute and the University of Montpellier

⁶³ Francis Galaway et al., [Resurrection of the ancestral RH5 invasion ligand provides a molecular explanation for the origin of *P. falciparum* malaria in humans](https://doi.org/10.1371/journal.pbio.3000490) 15 October, *PLOS Biology*, <https://doi.org/10.1371/journal.pbio.3000490>

- Researchers from the [University of Bristol](#), the [French National Centre for Scientific Research](#) (CNRS), France and technology company [Oracle](#) have developed a chikungunya vaccine that can be manufactured quickly and can be stored at warm temperatures. It elicited a powerful immune response in animal models⁶⁴.

Influenza

- The FDA has approved Xofluza ([baloxavir marboxil](#)) as a treatment for those at high risk of developing flu-related complications. It was approved in 2018 for the treatment of acute, uncomplicated flu in otherwise healthy people.
- One effect researchers consider with influenza — known as [imprinting](#) — is based on the idea that the first flu viruses you encounter in your life leave an indelible mark on your immune system⁶⁵. If your first infection was caused by an H3N2 virus, you'll always produce more antibodies to H3 viruses when you are vaccinated than you will to the other influenza A viruses, such as H1N1, and vice-versa. Daniel Jernigan, director of the Influenza Division in the US Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases, has commented that the data on who gets sickest each flu season are making the pattern "very clear". Since the 2009 flu pandemic, caused by a new H1N1 virus, different age groups are being hospitalized with severe flu infections in H1N1 years. The elderly (who are often assumed to be hardest hit by the flu season) did not fare too badly in the H1N1 pandemic — their immune systems recognizing it as a distant relative of a flu virus they'd encountered earlier. It was people who were born in the late 1950s and the 1960s, and had their first infections with other viruses, who found H1N1 viruses the biggest threat for them.
- In influenza patients, do convalescent plasma or anti-influenza hyperimmune intravenous immunoglobulin (hIVIG) have clinical benefit? Researchers set out to evaluate the safety and efficacy of hIVIG in a randomised controlled trial⁶⁶. They concluded: "on the basis of our results and the two plasma trials, hIVIG and plasma are not recommended for patients hospitalised with influenza A. By contrast, the beneficial clinical and viral load results of hIVIG consistently seen in patients with influenza B warrant further investigation at both the laboratory and clinical levels".

Ebola virus disease

- A new study⁶⁷ suggests climate change raises the risk of more Ebola outbreaks.
- Merck⁶⁸ announced in mid-September that the FDA had accepted for priority review the company's Biologics License Application (BLA) for its investigational vaccine for Ebola Zaire virus (V920). The target action date is 14 March, 2020. The FDA granted

⁶⁴ Charles Vragliau et al., "Synthetic self-assembling ADDomer platform for highly efficient vaccination by genetically encoded multiepitope display" 25 September 2019, [Science Advances](#). Vol. 5, no. 9, eaaw2853 <https://advances.sciencemag.org/content/5/9/eaaw2853.full>

⁶⁵ Alicia P Budd et al., "Birth Cohort Effects in Influenza Surveillance Data: Evidence That First Influenza Infection Affects Later Influenza-Associated Illness" *The Journal of Infectious Diseases*, Volume 220, Issue 5, 1 September 2019, Pages 820–829, <https://doi.org/10.1093/infdis/jiz201>

⁶⁶ Richard T Davey Jr et al., "Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial", *The Lancet Respiratory Medicine* [Volume 7, ISSUE 11](#), P951-963, November 01, 2019 [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(19\)30253-X/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30253-X/fulltext)

⁶⁷ David W Redding, "Impacts of environmental and socio-economic factors on emergence and epidemic potential of Ebola in Africa", published 15 October 2019, [Nature Communications](#) volume 10, Article number: 4531 (2019)

⁶⁸ MSD outside the US and Canada

Breakthrough Therapy Designation to V920 in July 2016. In March 2019, the European Medicines Agency (EMA) accepted the Marketing Authorization Application (MAA) for V920 for review. Submissions have also been made to the World Health Organization (WHO) to achieve prequalification status and to health authority representatives of the African Vaccine Regulatory Forum (AVAREF).

- The FDA has approved marketing of the first rapid diagnostic test⁶⁹ to identify Ebola virus antigens, in specific body fluids from living and deceased individuals.
- The Sabin Vaccine Institute was awarded \$US 20.5 million with options for an additional \$US 107.5 million from the Biomedical Advanced Research and Development Authority (BARDA) within the U S Department of Health and Human Services. The full program is expected to advance development of clinical-stage monovalent vaccines against Ebola Sudan and Marburg viruses through Phase II clinical trials⁷⁰.

MERS-CoV

- By the end of September 2019, a total of 2468 laboratory-confirmed cases of MERS, including 851 associated deaths had been reported globally; the majority of these cases were reported from Saudi Arabia (2077 cases, including 773 related deaths) since July 2012.

Tick-borne diseases

- US research⁷¹, supported by the National Institute of Allergy and Infectious Diseases (NIAID)⁷², describes a new rapid assay for Lyme disease⁷³ that could lead to a practical test for use by healthcare providers. The assay uses several biomarkers to detect Lyme disease infection. It is more sensitive than current laboratory-based tests when diagnosing Lyme disease early after possible infection.
- With an increase of nearly 10,000 cases of tickborne disease in the US from 2016 to 2017 -- mostly lyme disease -- the National Institutes of Health announced a five-year plan to expand research and reduce infections.
- French company Valneva has an experimental vaccine against Lyme disease which is now in a Phase II clinical trial. A trial in the US will determine the final dose and vaccination schedule. The company should have the initial data by the middle of 2020. The next step will be to launch two efficacy trials including about 8,000 people each, one in Europe and one in the US. The company could seek regulatory approval in about five years. Valneva has been seeking a partner to help develop and commercialize the vaccine. GlaxoSmithKline had been supporting the research and development, but in June the two companies [terminated their partnership](#). The Valneva vaccine protects against the six most common strains in the northern hemisphere, including those in Europe.
- Baxter completed a safety study on a Lyme vaccine [in 2013](#), but despite promising results, did not launch a follow-up. Takeda now owns that vaccine and is evaluating whether to take it forward.

⁶⁹ The OraQuick Ebola Rapid Antigen Test (OraSure Technologies)

⁷⁰ [Ebola Sudan and Marburg program](#). (Sabin institute)

⁷¹ Arumugam *et al.* [A multiplexed serologic test for diagnosis of Lyme disease for point-of-care use](#). *Journal of Clinical Microbiology*. DOI: 10.1128/JCM.01142-19 (2019).

⁷² part of the National Institutes of Health

⁷³ Lyme disease results from infection with *Borrelia burgdorferi*, a spiral-shaped bacterium transmitted by deer ticks.

- Using a DNA vaccine for tick-borne diseases, researchers in South Korea were able to prevent severe fever with thrombocytopenia syndrome (SFTS) in ferrets⁷⁴.

Other diseases

- Spain has had its largest ever outbreak of listeria, linked to packaged pork products produced in Andalusia.
- At ID Week in Washington DC⁷⁵, one of the topics of interest was foetal cytomegalovirus (CMV)⁷⁶. Brenna Hughes⁷⁷ presented data from a multicentre randomized trial which suggested that using CMV hyperimmune globulin as a preventive strategy may be less effective than hoped⁷⁸. Keren Shahar-Nissan⁷⁹ presented findings from a randomized, double-blind, placebo-controlled trial which suggested the antiviral medication valacyclovir could be used for the prevention of congenital cytomegalovirus⁸⁰.
- Scientists at the US National Institutes of Health found that a 5-minute soak in a 40 per cent solution of household bleach decontaminated stainless steel wires coated with chronic wasting disease (CWD) prions⁸¹.

⁷⁴ [Kwak et al. \(2019\) Development of a SFTSV DNA Vaccine That Confers Complete Protection Against Lethal Infection in Ferrets](#). Published in *Nature Communications*

⁷⁵ 2-6 October 2019. Organized by the Infectious Diseases Society of America (IDSA)

⁷⁶ Some children [prenatally exposed to the virus](#) suffer neurologic impairment and hearing loss and experience

⁷⁷ associate professor of obstetrics and gynaecology at Duke University, speaking on behalf of the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Maternal-Fetal Medicine Units Network

⁷⁸ Abstract LB17. For a previous study by others see [Revello MG, et al. *N Eng J Med*. 2014;doi:10.1056/NEJMoa1310214](#).

⁷⁹ a paediatric emergency medicine fellow at Schneider Children's Medical Center of Israel and a paediatric specialist in the Sackler Faculty of Medicine at Tel Aviv University

⁸⁰ The study found that valacyclovir reduced the rate of foetal CMV infection by 71 per cent in babies born to mothers with evidence of early primary CMV infection. Abstract LB 20.

⁸¹ K Williams *et al.* [Inactivation of chronic wasting disease prions using sodium hypochlorite](#). *PLOS One* DOI: 10.1371/journal.pone.0223659 (2019).