

Monitoring International Trends

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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.

A selection of recent matters of interest appears below. Highlights include:

Products

- UniQure has modified its haemophilia B gene therapy AMT-060 to increase factor IX activity and will begin a pivotal trial of AMT-061 in 2018.
- Bluebird bio will present data during the 59th Annual Meeting of the American Society for Hematology highlighting Bluebird's advancement of its LentiGlobin product candidate in patients with transfusion-dependent β -thalassemia and severe sickle cell disease.
- The California Institute for Regenerative Medicine (CIRM) granted Matthew Porteus, of Stanford University, \$US 5.2 million grant. Porteus' research so far has shown that human blood cells with the mutation that causes sickle cell disease can be taken and rebuilt with gene-editing tools. In animal studies, Porteus showed that he could successfully transplant the repaired blood stem cells back into mice.
- CSL Behring presented new data for Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]), its preventive therapy for hereditary angioedema (HAE) attacks, at the American College of Allergy, Asthma & Immunology Annual Meeting in Boston. Shire presented new data from its HAE and primary immunodeficiency portfolios.

Safety and Patient Blood Management

- A study has shown that for medically evacuated US military combat casualties in Afghanistan, blood product transfusion within minutes of injury or before reaching hospital was associated with greater 24-hour and 30-day survival than delayed transfusion or no transfusion.
- In 2012, London's air ambulance began to routinely carry red blood cells to trauma sites. A retrospective study has pronounced the change in practice worthwhile.
- A study in the Johns Hopkins health system has found that moving to single-unit transfusion was an independent predictor of decreased red blood cell use, while lowering haemoglobin thresholds was not.
- Researchers reported that for males, receiving a red blood cell transfusion from a female who had ever been pregnant is associated with an increased rate of all-cause mortality.
- A recent report says that *in vitro* and clinical studies indicate that cold-stored platelets may be beneficial in treatment of critical bleeding.
- A UK study suggests some people may safely donate blood as often as every eight weeks, but that may not be a healthy choice for all.
- A US study has found that, compared with white Caucasians, Hispanic blood donors had a 25 per cent higher risk of developing absent iron stores.
- An international team has prepared a blueprint to improve routine laboratory testing among hospitalized patients. It recognizes that repeated blood draws during a hospital stay can lead to hospital-acquired anaemia.

Regulatory

- The US Food and Drug Administration (FDA):

1. designated BioMarin Pharmaceutical's gene therapy BMN 270 a Breakthrough Therapy for haemophilia A;
2. granted Pluristem Therapeutics Inc. Orphan Drug designation for its PLX-R18 cell therapy for the prevention and treatment of acute radiation syndrome;
3. accepted for consideration Prometic's Biologics License Application (BLA) for its plasminogen replacement therapy Ryplazim; and
4. received a New Drug Application from Dova Pharmaceuticals seeking approval for avatrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure.

Company news

- The US Department of Health and Human Services announced a partnership with Novartis to determine whether its product for treating thrombocytopenia - Promacta (eltrombopag) - could be used to protect people in the event of a nuclear incident.
- Kamada announced top-line results from its Phase II trial of Alpha-1 Antitrypsin (AAT) in newly diagnosed type-1 diabetes patients.

Country news

- The US Centers for Disease Control and Prevention (CDC) said that people infected with HIV whose viral load is undetectable thanks to antiretroviral therapy are at effectively no risk of transmitting the virus.
- Cerus Corporation announced that Germany's Institute for the Hospital Remuneration System will include pathogen-inactivated platelets for national reimbursement from January 1, 2018.

Research not included elsewhere

- A study has suggested that blood plasma transfusions from young healthy volunteers did not improve the cognition of Alzheimer's patients but an association was observed between the transfusions and the patients' ability to perform daily tasks.
- Researchers report that transfers of viruses from one host species to another drive the most important evolutionary changes in most viruses.

Infectious diseases

- Laboratory experiments on a new strain of the H7N9 bird flu circulating in China suggest the virus can transmit easily among animals which could trigger a global human pandemic.

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1. Products and treatments

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

Treating haemophilia

- UniQure has modified its haemophilia B gene therapy AMT-060 to increase factor IX activity to the levels achieved by Spark Therapeutics' rival product SPK-9001¹. UniQure will begin a pivotal trial in 2018 of its new candidate AMT-061 with its fast-track statuses intact. The open-label, single-dose trial begins with a six-month observational lead-in phase, so patients can provide their own baseline control data. UniQure will run a three-patient dose-confirmation study in parallel to the lead-in phase. The dose-confirmation study is due to start in the third quarter of next year.
- Interim results from the Phase III Aspire study² indicate that patients with [haemophilia A](#) showed continuous improvement in joint health for nearly three years while receiving prophylactic dosing of Bioverativ and Sobi's Eloctate³.

Treating beta thalassemia and sickle cell disease

- From Cambridge, Massachusetts, Bluebird bio announced that it would present data on its clinical and preclinical programs during the 59th Annual Meeting of the American Society for Hematology (ASH)⁴. The data would highlight amongst other

¹ Amsterdam-based uniQure has already spent two years testing its candidate AMT-060. The trial demonstrated cessation of both bleeding and replacement therapy. However, while SPK-9001 improved FIX activity by more than 60 per cent, AMT-060 struggled to reach double figures.

² The Phase III clinical trial Aspire ([NCT01454739](#)) is an extension of the Phase III A-LONG trial ([NCT01181128](#)) of [Eloctate](#) in adults and adolescents with haemophilia A.

³ J. Oldenburg, R. Kulkarni, A. Srivastava, J. N. Mahlangu, V. S. Blanchette, E. Tsao, B. Winding, J. Dumont, N. Jain. "Improved joint health in subjects with severe haemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein", *Haemophilia*, published: 30 October 2017
[DOI:10.1111/hae.13353](#)

⁴ Presentations Summary (abstracts available on the conference website): Julie Kanter, *Interim Results from a Phase 1/2 Clinical Study of LentiGlobin Gene Therapy for Severe Sickle Cell Disease* (Oral Abstract #527), December 10. John Tisdale, *Successful Plerixafor-Mediated Mobilization, Apheresis, and Lentiviral Vector Transduction of Hematopoietic Stem Cells in Patients with Severe Sickle Cell Disease* (Poster Abstract #990), December 9. Janet Kwiatowski, *Clinical Outcomes up to 3 Years Following LentiGlobin Gene Therapy for Transfusion-Dependent β -Thalassemia in the Northstar HGB-204 Study* (Oral Abstract #360), December 10. Mark C. Walters, *Results from the HGB-207 (Northstar-2) Trial: A Phase 3 Study to Evaluate Safety and Efficacy of LentiGlobin Gene Therapy for Transfusion-Dependent β -thalassemia (TDT) in Patients with non- β^0/β^0 Genotypes* (Oral Abstract #526), December 10. (This abstract contains data presented at European Hematology Association (EHA) 2017 annual meeting. Updated data to be included in ASH presentation.) Marina Cavazzana, *Longer Term Follow-up on the First Patients with Severe Hemoglobinopathies Treated with LentiGlobin Gene Therapy* (Poster Abstract #4609), December 11. (This abstract contains data

things Bluebird's advancement of its LentiGlobin product candidate in patients with transfusion-dependent β -thalassemia (TDT) and severe sickle cell disease (SCD). Dave Davidson, chief medical officer, said: "The new data in sickle cell disease suggest that the changes made to the HGB-206 protocol and to our manufacturing process are having a favorable impact on the engraftment of the gene-modified stem cells."

- A conference on the Physiological and Pathophysiological Consequences of Sickle Cell Disease was held in Washington DC, November 6–8. Organized by the American Physiological Society, the conference explored the world's most prevalent single-gene mutation disease and new research on preventing or reversing its consequences⁵.
- Sancilio Pharmaceuticals announced positive top line results from a clinical study evaluating the efficacy and safety of Altemia, in oral soft gelatin dosage form, in sickle cell patients aged 5-17 years.⁶ The company said a clinically meaningful reduction of vaso-occlusive crises was observed in the top line results, no treatment

presented at European Hematology Association (EHA) 2017 annual meeting. Updated data to be included in ASH presentation.) Jesus Berdeja, Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: Updated results from a multicenter study of bb2121 anti-BCMA CAR T cell therapy (Oral Abstract #740), December 11. (This abstract contains data presented at European Hematology Association (EHA) 2017 annual meeting. Updated data to be included in ASH presentation.) Olivier Negre, *Preclinical Evaluation of a Novel Lentiviral Vector Driving Lineage-Specific BCL11A Knockdown γ -Globin Induced and Simultaneous Repression of β -Globin for the Potential Treatment of Sickle Cell Disease* (Poster Abstract #3557), December 11. Benjamin Boyerinas, *A novel TGF- β /interleukin receptor signal conversion platform that protects CAR/TCR T cells from TGF- β -mediated immune suppression and induces T cell supportive signaling networks* (Poster Abstract #1911), December 9. Unja Martin, *A Drug-Regulated CAR Platform (DARIC) Induces Effective and Reversible Tumor Control In Vivo Using Non-Immunosuppressive Rapamycin Dosing* (Poster Abstract #1910), December 9. Michael Magee, *Gene Editing of TRAC Locus Utilizing megaTAL Nucleases Increases Expression of Transgenic TCRs Delivered via Lentiviral Vector-Mediated Gene Transfer* (Poster Abstract #1906), December 9. James Rottman, *ROR1-directed chimeric antigen receptor T cell recognition of self-antigen is associated with acute toxicity, T cell dysfunction, and poor tumor control* (Poster Abstract #4450), December 11.

⁵ There were eight symposia- *Neural Circuits and Neurovascular Physiology*; *SCD Gene Therapy, Gene Editing, and Pharmacological Treatment*; *Cell Therapy, Small Molecules to Treat SCD*; *Renal and Vascular Physiology*; *Lung Physiology and Pathophysiology*; *Red Cell Physiology*; and *Coagulation and Thrombosis*. Individual papers included- *Oral Tetrahydrouridine and Decitabine for Non-cytotoxic Epigenetic Modification of Sickle Cell Disease: A Randomized Phase 1/2 Study* (Yogen Saunthurajah, Cleveland Clinic); *Targeting Pain at its Source in Sickle Cell Disease* (Kalpna Gupta, University of Minnesota); *Gene Therapy for Hemoglobinopathies: The Challenge to Find a Cure* (Giuliana Ferrari, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy); *Discovery of Pharmacologic Fetal Hemoglobin Inducing Agents for Sickle Cell Disease* (Betty Pace, Augusta University, Georgia); *Control of HbF Silencing: Implications for Genetic and Pharmacologic Induction of HbF for Therapy* (Stuart Orkin, Harvard University, Cambridge, Massachusetts); *CRISPR/Cas9 Enhanced Sickle Gene Correction in Human and Mouse Hematopoietic Stem Cells* (Tim Townes, University of Alabama at Birmingham); *KEAP1-NRF2 Antioxidant Response System and Sickle Cell Anemia* (Masayuki Yamamoto, Tohoku University, Japan); *RN-1, an LSD-1 Inhibitor, Induces HbF in the Baboon (*P. anubis*) and Reduces Mitochondria-containing RBC in a SCD Mouse Model* (Angela Rivers, University of Illinois, Chicago); *Sickle Cell Disease: When Endothelin Becomes a Nephrotoxic and Proinflammatory Cytokine* (Pierre-Louis Tharaux, INSERM U970, Paris, France); *Developmental Regulation of Erythroid Self-renewal* (James Palis, University of Rochester Medical Center); *Pathobiology of Sickle Red Cells: Implications for Pathophysiology of Sickle Cell Disease* (Mohandas Narla, New York Blood Center); *De-clotting Sickle Cell Disease* (Rafal Pawlinski, University of North Carolina); and *Promoting the Resolution of Inflammation in Sickle Cell Disease* (Felicity N. Gavins, Louisiana State University Health Sciences Center).

Source: <http://www.the-aps.org/mm/hp/Audiences/Public-Press/2017/68.html>

⁶<https://clinicaltrials.gov/ct2/show/NCT02973360>

related serious adverse events were observed, and the majority of patients elected to continue treatment in the open label extension study.

- A study⁷ has associated increased anaesthesia duration with significantly increased rates of surgical complications, especially the need for postoperative transfusion, among patients undergoing microvascular reconstruction of the head and neck.
- [The California Institute for Regenerative Medicine \(CIRM\)](#) granted Matthew Porteus, a Stanford University associate professor of paediatrics, \$US 5.2 million to undertake preparatory work for a clinical trial of a possible treatment for sickle cell disease. Porteus' research has shown that human blood cells with the mutation that causes sickle cell disease can be taken and re-built with gene-editing tools to repair the faulty gene. In animal studies, Porteus showed that he could also successfully transplant the repaired blood stem cells back into mice.

Other products

- Researchers have found that long-term eltrombopag is effective in restoring platelet counts and decreasing risk of bleeding in patients with chronic/persistent [immune thrombocytopenia \(ITP\)](#) lasting more than 6 months⁸.
- [CSL Behring](#) presented new data for Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]), its preventive therapy for hereditary angioedema (HAE) attacks⁹, at the 2017 American College of Allergy, Asthma & Immunology (ACAAI) Annual Scientific Meeting, October 26-30, in Boston. Among the seven presentations were new sub-analyses from [the pivotal COMPACT trial](#), including new pharmacoeconomic, pharmacokinetic, and pharmacodynamic analyses of Haegarda¹⁰.
- At the Boston ACAAI meeting just mentioned, Shire presented new data from its HAE and primary immunodeficiency (PI)¹¹ portfolios and pipeline. Presentations included:
 - i) *Longitudinal Natural History of Patients with Type I/II Hereditary Angioedema: Icatibant¹² Outcome Survey Data* (Poster Presentation 164)
 - ii) *Clinical and Demographic Characteristics of Patients with Hereditary Angioedema in the United States* (Poster Presentation 174)

⁷ Jacob S. Brady, Stuti V. Desai, Meghan M. Crippen, Jean Anderson Eloy, Yuriy Gubenko, Soly Baredes, Richard Chan Woo Park. "Association of Anesthesia Duration With Complications After Microvascular Reconstruction of the Head and Neck." *JAMA Facial Plast Surg*. Published online October 05, 2017. doi:10.1001/jamafacial.2017.1607

⁸ Wong RSM, Saleh MN, Khelif A, et al. [Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study](#) [published online October 17, 2017]. *Blood*. doi: 10.1182/blood-2017-04-748707

⁹ HAE is a rare and potentially life-threatening genetic condition. It is caused by deficient or dysfunctional C1-INH, a protein in the blood that helps to control inflammation. Inadequate amounts can lead to the accumulation of fluid in body tissues. HAE attacks can affect many parts of the body and can spread to multiple sites. Haegarda is a self-administered, plasma-derived concentrate of C1-esterase inhibitor. It is dosed on body weight and replaces deficient or dysfunctional natural C1-INH, restoring functional C1-INH levels to above 40 percent, which is proposed to reduce the risk for HAE attacks. (Longhurst H, et al. "Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor". *N Eng J Med* 2017; 376:1131-1140. DOI: 10.1056/NEJMoa1613627)

¹⁰ They included a sub-analysis of the COMPACT trial on the preventive effect of Haegarda in HAE patients who experience more than one attack per week, featured as an [oral presentation](#) (Poster #OR31). Researchers also presented data on the pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous C1-inhibitor for the prevention of HAE attacks. They outlined data from studies evaluating the reduction in use of rescue medications to treat breakthrough HAE attacks and potential cost offsets associated with the use of subcutaneous C1-inhibitor as long-term prophylaxis for HAE.

¹¹ PI are a group of more than 300 genetic disorders in which part of the body's immune system is missing or does not function properly.

¹² Firazyr (icatibant injection) is used to treat acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

- iii) *Post-Authorization Safety Study of Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% Treatment¹³ in Patients with Primary Immunodeficiency Diseases* (Poster Presentation 279)
- iv) *Adverse Events and Infusion Parameters of IG20Gly in Primary Immunodeficiency Patients Whose Pre-Study Treatment Was IVIG¹⁴* (Poster Presentation 281)
- v) (Investigational product; subject to Regulatory approval) *Lanadelumab¹⁵ for Prevention of Attacks in Hereditary Angioedema: Results from the Phase 3 HELP(TM) Study*, (Oral Presentation 34)
- Events sponsored by Shire at the Boston meeting were: *The Role of Sustained Kallikrein Inhibition: Driving Change in the Management of HAE; Expert Insights on Shared Decision-Making in the Treatment of Primary Immunodeficiency*; and *Approaches to HAE Patient Management*.

2. Safety and patient blood management

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

Appropriate Transfusion

- Bariatric surgery patients who received perioperative blood transfusions had an increased risk of developing infections after the procedure, researchers reported at Obesity Week 2017 in the US. Rana Higgins¹⁶ said that, overall, a person who had surgery and a perioperative blood transfusion had a 5.8-fold increased risk of developing a surgical site infection. She and her colleagues said: "Surgical site infection is an important marker of postoperative morbidity and overall quality of care. Transfusion-related immunomodulation can lead to weakened immunity in response to blood transfusion and predispose patients to surgical site infections."
- A new study suggests that perioperative blood transfusion is associated with a worse prognosis after nephrectomy for renal cell carcinoma. Yasmin Abu-Ghanem¹⁷ and colleagues reported in *Urologic Oncology*¹⁸ that in a study of 1159 renal cell carcinoma (RCC) patients undergoing nephrectomy¹⁹, receiving a perioperative blood transfusion was associated with a 2.1-, 2.4-, 2.5-, and 2.2-fold increased risk of tumour recurrence, metastatic progression, RCC-related death, and all-cause mortality, respectively. The authors concluded: "Although these findings require further validation, continued efforts to minimize the use of blood products in patients with RCC are essential".
- A study has shown that for medically evacuated US military combat casualties in Afghanistan, blood product transfusion within minutes of injury or before reaching hospital was associated with greater 24-hour and 30-day survival than delayed

¹³ Hyqvia contains human immune globulin and recombinant human hyaluronidase which helps more of the immune globulin to be absorbed into the body to fight infection.

¹⁴ Cuvitru [Immune Globulin Subcutaneous (Human), 20% Solution] is made from human plasma and administered subcutaneously, often by self- infusion.

¹⁵ Investigational product; subject to regulatory approval

¹⁶ of the Medical College of Wisconsin in Milwaukee

¹⁷ of Sheba Medical Center in Tel Hashomer, Israel

¹⁸ Abu-Ghanem Y, Zilberman DE, Dotan Z, et al. [Perioperative blood transfusion adversely affects prognosis after nephrectomy for renal cell carcinoma](#). *Urol Oncol* 2017; published online ahead of print. doi: 10.1016/j.urolonc.2017.09.006

¹⁹ 52 per cent partial and 48 per cent radical

transfusion or no transfusion²⁰. The study was led by doctors at the Joint Trauma System at Fort Sam Houston in San Antonio²¹.

- In 2012, London's air ambulance became the first UK civilian pre-hospital service to routinely carry red blood cells to trauma sites. A retrospective trauma database study²² has compared pre-implementation and post-implementation experience of bleeding trauma patients transported directly to one major trauma centre. It concluded that pre-hospital trauma transfusion practice is feasible and associated with overall reduced consumption of red blood cells, platelets and fresh frozen plasma.
- Dr Steven M. Frank is professor of anaesthesiology and critical care, and director of the blood management program at Johns Hopkins School of Medicine, in Baltimore. To identify the optimal methods of reducing unnecessary red blood cell transfusions, Dr Frank and his colleagues examined data from three community hospitals in the Johns Hopkins health system before and after initiation of a patient blood management program. The first element in the program was to promote a haemoglobin threshold of 7 or 8 g/dL instead of the standard of 9 or 10 g/dL previously in use. The second element was a campaign called “Why give 2 when 1 will do?”, encouraging single-unit red blood cell transfusions in patients who were haemodynamically stable and not actively bleeding. As Dr Frank reported at the 2017 annual meeting of the International Anesthesia Research Society (abstract 1292), researchers found that the single-unit transfusion was an independent predictor of decreased red blood cell use, while haemoglobin thresholds were not.
- Researchers reported²³ that for males, receiving a red blood cell transfusion from a female who had ever been pregnant is associated with an increased rate of all-cause mortality. They studied the correlation between mortality and exposure to transfusions from females who had been pregnant, compared with transfusions from females who had never been pregnant. It was a retrospective cohort study involving over 31,000 first-time transfusion recipients. All-cause mortality rates for male recipients of red blood cell transfusions from a female donor who had been pregnant versus a male donor were 101 versus 80 deaths per 1,000 person-years. Mortality rates were 78 versus 80 deaths per 1,000 person-years for male recipients of transfusion from a never-pregnant female donor versus a male donor. Such a

²⁰ The study examined the fate of 502 troops evacuated from the battlefield in Afghanistan from 2012 to 2015. Most had been in an explosion; some had been shot. All of them had lost a limb at or above the elbow or knee, or were in shock with extremely low blood pressure resulting from massive bleeding. Eighty-five of the 447 troops who were not transfused on their medevac — waiting an average of 30 minutes from the time the helicopter lifted off until arriving at the hospital — died within 24 hours. Seventeen more died within 30 days, the study found, for a 23 percent mortality rate. Fifty-five troops were transfused on their medevac, within about seven minutes of take-off, only three of whom died that day. Three more died within 30 days, for an 11 percent mortality rate. The study's researchers matched the injuries by severity and type and controlled for age, injury year, transport team, tourniquet use and time until rescue. The median total evacuation time was 47 minutes for troops in the study. The study suggested that even earlier blood transfusion — at the point of injury — could save more lives.

²¹ Stacy A Shackelford, Deborah J Del Junco, Nicole Powell-Dunford, Edward L Mazuchowski, Jeffrey T Howard, Russ S Kotwal, Jennifer Gurney, Frank K Butler, Kirby Gross, Zsolt T Stockinger, “Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival”, *JAMA: the Journal of the American Medical Association* 2017 October 24, 318 (16): 1581-1591). [DOI: 10.1001/jama.2017.15097](https://doi.org/10.1001/jama.2017.15097)

²² M.Rehn et al.,” Pre-hospital transfusion of red blood cells in civilian trauma patients”, *Transfusion Medicine*, 24 October 2017, DOI: 10.1111/tme.12483

²³ online October 17 in the *Journal of the American Medical Association*. Caram-Deelder C, Kreuger AL, Evers D, et al. “Association of blood transfusion from female donors with and without a history of pregnancy with mortality among male and female transfusion recipients”. *JAMA*. 2017 Oct 17;318(15):1471-1478. [doi: 10.1001/jama.2017.14825](https://doi.org/10.1001/jama.2017.14825)

disparity was not found for female recipients of red blood cell transfusions, where mortality rates were 74 versus 62 per 1,000 person-years for a female donor who had been pregnant versus a male donor; and very similar for transfusions from a never-pregnant female donor versus a male donor. The authors commented: "Further research is needed to replicate these findings, determine their clinical significance, and identify the underlying mechanism".

- A recent report says that *in vitro* and clinical studies indicate that cold-stored platelets may be beneficial in treatment of critical bleeding.²⁴

Recognising and treating anaemia

- A UK study²⁵ suggests some people may safely donate blood as often as every eight weeks, but that may not be a healthy choice for all. Currently in the UK, experts recommend that blood donors wait 12 to 16 weeks before giving again. In the US blood donations are permitted at eight-week intervals. In France and Germany, men can donate every eight weeks, and women every 12.
 - i) The UK trial involved more than 45,000 blood donors. Donors were randomly assigned to donation intervals. Men donated every 12, 10 or eight weeks over two years; women gave every 16, 14 or 12 weeks. "Frequent" was defined as every eight weeks for men and every 12 weeks for women, over two years. A quarter of frequent donors developed iron deficiency by the two-year mark. Some donors complained of symptoms like fatigue, dizziness and trouble breathing, but no correlation was found between those symptoms and depleted iron stores.
 - ii) "The shorter interval between donations is probably not ideal," said Dr. Edward Murphy, a researcher with the Blood Systems Research Institute, in San Francisco, who co-authored an editorial published with the study²⁶. He explained that as blood donors give about a pint of blood each time, that depletes them of about 200 to 250 milligrams of iron, and it takes the average donor about six months to recover those iron stores unless supplements are given. That window shrinks to around 90 days if a donor takes a standard daily iron pill, according to Murphy.
- Keryx Biopharmaceuticals presented data on Auryxia (ferric citrate) at the 2017 American Society of Nephrology (ASN) Annual Meeting²⁷ in New Orleans. The presentations were based on post-hoc analysis of the Phase III study of ferric citrate in adults with iron deficiency anaemia and non-dialysis dependent chronic kidney disease (NDD-CKD). Geoffrey Block spoke of the effect of ferric citrate on fibroblast growth factor (FGF23), a phosphate-regulating hormone that is associated with chronic kidney disease progression²⁸. A poster presentation demonstrated the effect of ferric citrate on serum phosphorus in patients with normal and elevated baseline phosphorus levels²⁹.

²⁴ T.O. Apolseth, A. P. Cap, P. C. Spinella, T. Hervig, G. Strandenes, "Cold stored platelets in treatment of bleeding", *ISBT Science Series*, Volume 12, issue 4, November 2017, pp 488-495. DOI: 10.1111/vox.12380

²⁵ John Danesh et al., "Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors", *The Lancet*, online 20 September 2017. DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)31928-1](http://dx.doi.org/10.1016/S0140-6736(17)31928-1)

²⁶ Edward Murphy, also professor in residence, laboratory medicine, University of California, September 20, 2017, *The Lancet*, online

²⁷ held October 31 - November 5, 2017

²⁸ "Ferric Citrate Reduced FGF23 in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) and Iron Deficiency Anemia (IDA) Irrespective of the Change in Serum Phosphate (P)" Oral presentation [#TH-OR038](#).

²⁹ "Ferric Citrate Lowered Serum Phosphate Only When Elevated in Patients with Non-Dialysis Dependent (NDD) CKD and Iron Deficiency Anemia (IDA)" [Poster # TH-PO514](#).

- The AABB Annual Meeting in San Diego was advised of the results of a US study³⁰ which examined longitudinally US blood donor records to see if factors other than age, sex, and donation frequency put donors at risk of low iron levels. The study enrolled 8,439 white Caucasian blood donors along with 1,605 African-American, 1,616 Asian, and 1,023 Hispanic donors. Nineteen per cent of all donors had absent iron stores (AIS). While expected patterns were observed with age, sex and donation frequency, ethnicity showed up as an important risk factor for low iron levels. African Americans and Asians appeared to have a 20 per cent lower risk of AIS, compared with white Caucasians, but Hispanic donors had a 25 per cent higher risk of AIS. Daily iron supplements and hormone therapy reduced the risk of AIS in females. Hormone use in males, however, increased their risk for AIS. The study concluded that a “one-size-fits-all approach” may not be best way to ensure all blood donors have adequate iron stores.

Other

- Between 2000 and 2015, from \$US 602.4 million to \$US 2.1 billion annually in international development assistance was provided for blood safety programs worldwide, mostly as part of the global response to the human immunodeficiency virus/ acquired immunodeficiency syndrome epidemic. The US President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis, and Malaria were responsible for the majority of blood safety funding, which peaked in 2010 and had dropped off by 2015.
- Two recent studies on the impact of anticoagulants were reported online 3 October in the *Journal of the American Medical Association*. One found that nonvalvular atrial fibrillation (AF) patients who take non-vitamin K oral anticoagulants (known as novel anticoagulants or NOACS) along with certain other medications are at increased risk for major bleeding³¹, while the other found that antithrombotic medications are significantly associated with increased rates of haematuria³²-related complications in older adults³³.
- A study reported³⁴ that new anti-clotting drugs – such as Xarelto, Pradaxa and Eliquis -- aren't linked with a higher risk of bleeding than warfarin. Lead researcher Min Jun, senior research fellow at the University of New South Wales, said: "Given the advantages associated with these new drugs not requiring frequent monitoring, our results suggest that they may be considered as a treatment option for patients with VTE (venous thromboembolism) who are candidates for receiving oral anticoagulant therapy". Jun and his colleagues considered nearly 60,000 patients in the US and Canada with VTE who were prescribed warfarin or one of the newer drugs between January 2009 and March 2016. The risk of major bleeding was similar for both the newer anticoagulants and warfarin, the researchers found, with no difference in the risk of death. Jun said the findings didn't change when patients were followed for up to six months. He did, however, sound a note of caution: since the study was an observational one, the results could be due to other unmeasured factors. He noted: "Further studies are needed to better understand the longer-term safety of these drugs among VTE patients as well as their safety among advanced chronic kidney

³⁰ Spencer BR, Guo Y, Cable RG et al. for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Abstract # PG-A03A. "Iron status and novel risk factors for iron depletion in a diverse donor population". *Transfusion* 2017; 57 Supplement S3; 4A-5A.

³¹ Chang S, Chou I, Yeh Y, et al. "Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation." *JAMA*. 2017;318(13). [doi:10.1001/jama.2017.13883](https://doi.org/10.1001/jama.2017.13883)

³² Haematuria refers to the presence of red blood cells in the urine,

³³ Wallis CJD, Juvet T, Lee Y, et al. "Association between use of antithrombotic medication and hematuria-related complications." *JAMA*. 2017;318(13). [doi:10.1001/jama.2017.13890](https://doi.org/10.1001/jama.2017.13890)

³⁴ online October 17 in *BMJ*.

disease patients, in whom the risk of major bleeding is greater compared with other patient groups."

- An international team including physicians from Johns Hopkins has prepared a blueprint to improve routine laboratory testing among hospitalized patients³⁶. It recognizes that repeated blood draws during a hospital stay can lead to hospital-acquired anaemia and that diagnosing the anaemia can lead to additional tests, interventions, and costs; while studies have shown that decreasing blood draws for testing does not result in missed diagnoses or increase the number of readmissions to the hospital, and the cost savings are significant. The blueprint recommendations include standardizing best practices, establishing targets for test reductions and reprogramming electronic test-ordering systems to restrict the number of "pre-ordered" tests.

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) designated BioMarin Pharmaceutical's gene therapy valoctocogene roxaparvovec (BMN 270) a Breakthrough Therapy³⁷ for haemophilia A.
- The Saudi Food & Drug Authority approved Swedish Orphan Biovitrum's Alprolix (eftrenonacog alfa) for the treatment of haemophilia B.
- Cerus Corporation announced on October 5 that Rhode Island Blood Center had received approval from the FDA for their Biologics License Application (BLA) requesting allowance for interstate distribution of platelets that have been pathogen-reduced with the INTERCEPT Blood System. Seven other blood centres submitted similar BLAs³⁸.
- The FDA granted [Pluristem Therapeutics Inc.](#) Orphan Drug³⁹ designation for its PLX-R18 cell therapy for the prevention and treatment of acute radiation syndrome (ARS)⁴⁰. The product is designed to treat bone marrow that is unable to produce enough blood cells due to a variety of causes including ARS, some cancers or cancer treatments, or immune-mediated bone marrow failure. Pluristem [recently reported](#) positive data from non-human primates studies of PLX-R18 cells as a treatment for ARS, conducted by the National Institute of Allergy and Infectious Diseases (NIAID). This demonstrated improvement in survival rates and the enhancement of recovery across white blood cells, red blood cells, and platelets. PLX-R18 cells are also being [studied](#) by the US Department of Defense's Armed Forces Radiobiology Research Institute (AFRRI) to examine the effectiveness of the cells as a treatment for ARS prior to, and within the first 24 hours of exposure to radiation. Fukushima Medical University in Japan is studying Pluristem PLX-R18 for the treatment of ARS and as an adjunct to radiotherapy in cancer patients.

³⁶ [Kevin P. Eaton, Kathryn Levy, Christine Soong](#), et al., "Evidence-Based Guidelines to Eliminate Repetitive Laboratory Testing", JAMA Intern Med. Published online October 16, 2017. doi:10.1001/jamainternmed.2017.5152

³⁷ Breakthrough Therapy status conveys more intensive FDA guidance on development, the involvement of more senior agency personnel and a rolling review of the marketing application.

³⁸ The Biologics License Application is the means by which blood centers request FDA permission to introduce a biologic product into interstate commerce. While some US blood centers may distribute primarily in state, many blood centers have extensive interstate distribution.

³⁹ Orphan Drug designation brings with it close guidance by the FDA which may accelerate marketing approval, orphan drug grants, tax credits, and 7-year market exclusivity upon marketing approval.

⁴⁰ ARS follows exposure to high levels of radiation, as in the case of a nuclear accident or attack, and can cause death.

- Prometic Life Sciences received a priority review status⁴¹ from Health Canada with respect to its new drug submission for its plasminogen replacement therapy, Ryplazim, for the treatment of patients with plasminogen deficiency. The FDA accepted for consideration Prometic's Biologics License Application (BLA) for Ryplazim, having granted a priority review status and set a Prescription Drug User Fee Act (PDUFA) action date for April 14 2018. The FDA had previously granted Ryplazim Fast Track, Orphan Drug and Rare Paediatric Disease designations. Prometic had already reported data from its pivotal Phase II/III trial, which showed that Ryplazim treatment consistently replaced and maintained the plasminogen concentration at an appropriate level and that it resolved all lesions in all patients treated.
- Dova Pharmaceuticals submitted a New Drug Application (NDA) to the FDA seeking approval for avatrombopag for the treatment of thrombocytopenia (low blood platelets) in patients with chronic liver disease who are scheduled to undergo a procedure. Dova acquired avatrombopag from Eisai in March 2016. The drug is an orally administered, second-generation thrombopoietin receptor agonist.

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 US Department of Health and Human Services' ([HHS](#)) Office of the Assistant Secretary for Preparedness and Response ([ASPR](#)) announced a partnership with Novartis Pharmaceuticals Corporation of East Hanover, New Jersey, to determine whether a product for treating patients suffering from thrombocytopenia - Promacta (eltrombopag) - could be used to protect people in the event of a nuclear incident. Thrombocytopenia, which is a drop in circulating blood platelets, can occur when radiation causes myelosuppression, a decrease in bone marrow activity⁴². The four-year contract, worth \$US 24 million, is with the Biomedical Advanced Research and Development Authority (BARDA)⁴³. The drug currently is already in use to treat low blood platelet counts due to chronic immune thrombocytopenia, an autoimmune disorder where the body targets its own platelets for destruction; it acts on bone marrow progenitors to increase platelet production.
- Pennsylvania State University is to receive \$US 4.92 million from CSL Behring over the next six years to create the multidisciplinary Centre of Excellence in Biotechnology, and to revitalize the Shared Fermentation Facility.
- Dimension Therapeutics has terminated earlier plans to be acquired by Regenxbio for \$US 85 million after accepting a \$US 151 million offer from Ultragenyx Pharmaceutical. Regenxbio will receive the \$US 2.85 million termination fee called for under their acquisition agreement, [announced on August 25](#). Ultragenyx will

⁴¹ In Canada, Priority Review status assigns eligible submissions a shortened review target of 180 days, in comparison to 300 days for non-priority.

⁴² Radiation injures organs, including the bone marrow, gastrointestinal tract, brain, and lungs, and can cause neutropenia, which is a drop in white blood cells, and thrombocytopenia. This decrease in circulating platelets from following irradiation may lead to hemorrhage and organ failure.

⁴³ [BARDA](#) adopts a comprehensive, integrated portfolio approach to the advanced research and development, innovation, acquisition, and manufacturing of vaccines, drugs, therapeutics, diagnostic tools, and non-pharmaceutical products for public health emergency threats. These threats include radiological and nuclear agents, chemical and biological terrorism threats, pandemic influenza, and emerging infectious diseases.

- assume Dimension's licence from Regenxbio for novel adeno-associated virus (AAV), or NAV, technology in seven inherited disease fields, including haemophilia A.
- ADMA Biologics develops, produces and markets plasma-based biologics for the treatment of Primary Immune Deficiency Disease and for prophylaxis and therapy of certain infectious immunological diseases. It recently completed the acquisition of Biotest Pharmaceuticals Corporation's Therapy Business Unit. On November 3, Adam Grossman, President and CEO of ADMA, said: "We continue to make progress with business integration, improving operating efficiencies, and remedying our outstanding US Food and Drug Administration compliance issues⁴⁴. Importantly, we remain on schedule to be FDA inspection-ready by year-end 2017. We have continued commercial production for Nabi-HB, an FDA-approved hyperimmune globulin for the treatment of Hepatitis B, during the third quarter of 2017, and further advanced our optimization program for our immunoglobulin manufacturing process, which is the process used for both Bivigam, an FDA-approved immune globulin intravenous for the treatment of primary humoral immunodeficiency, and RI-002 our lead IGIV product candidate intended for immunodeficient patients. We are pleased with our operational progress, as we achieved year-over-year revenue growth of approximately 61 per cent⁴⁵ in the third quarter."
 - For Swedish Orphan Biovitrum (SOBI) total revenues increased 37 per cent over revenues in the corresponding quarter of 2016. Haemophilia A drug Elocta (rFVIII Fc; recombinant factor VIII Fc fusion protein) registered sales of 417 million Swedish kronor, compared with just 73 million kronor a year earlier, and haemophilia B treatment Alprolix (rFIX Fc) sales were 98 million kronor, versus 17 million kronor. The growth primarily derived from the UK, Italy, France and Germany. The top five European Union markets represented more than 75 per cent of sales in the quarter.
 - Kamada announced top-line results from its Phase II trial⁴⁶ of Alpha-1 Antitrypsin (AAT) in newly diagnosed type-1 diabetes patients. Peter Gottlieb, Professor of Pediatrics and Professor of Medicine, Barbara Davis Center for Diabetes, University of Colorado School of Medicine, commented: "Given this study was not powered to show efficacy, the results are very encouraging. These findings suggest that administration of AAT could be an effective treatment option for newly diagnosed type- 1 diabetes patients who are 12-18 years old. The results of this subgroup are intriguing and warrant further studies in a larger population."

5. Specific country events

- Of concern in the US is the parasite *Babesia microti*, which has been linked to four deaths following blood transfusions. The parasite, initially acquired through tick bites, can be passed on in donated blood. The American Red Cross conducted a two-year study⁴⁷ in the New England states and found 29 cases where *Babesia* was transmitted through infected donors. Of 89,153 blood donations screened by the American Red Cross, 335 were positive for *Babesia*.
- The US Centers for Disease Control and Prevention (CDC) issued a "[Dear Colleague](#)" letter saying that people infected with HIV whose viral load is

⁴⁴ The CEO said ADMA had established a timeline and engaged experts to assist with the remediation of the FDA warning letter and compliance issues for the Boca Raton, Florida manufacturing facility it acquired from Biotest.

⁴⁵ ADMA reported total revenues of \$US 4.7 million for the third quarter ended September 30, 2017, as compared with \$US 2.9 million for the third quarter ended September 30, 2016. Growth was primarily attributable to sales of Nabi-HB. ADMA acquired commercial rights to Nabi-HB from Biotest.

⁴⁶ Details about this study are available at <https://www.clinicaltrials.gov/ct2/show/NCT02005848?term=AAT&cond=Type+1+Diabetes&rank=2>

⁴⁷ See Erin D Moritz et al, "Screening for *Babesia microti* in the U.S. Blood Supply", *N Engl J Med* 2016; 375:2236-2245 [December 8, 2016](#) DOI: 10.1056/NEJMoa1600897

undetectable thanks to antiretroviral therapy are at effectively no risk of transmitting the virus. The letter brings the CDC in line some with other public health organizations around the world⁴⁸..

- Cerus Corporation announced that Germany's Institute for the Hospital Remuneration System⁴⁹ will include pathogen-inactivated platelets for national reimbursement from January 1, 2018. This will cover both platelet collection methods currently in use in Germany, apheresis and whole blood derived buffy coat platelets. The national reimbursement codes for pathogen-inactivated platelets allow German hospitals to recoup the costs of INTERCEPT platelets at a premium price over untreated platelet units. The German market is the largest in Europe. Reimbursement is expected to improve access to increased shelf life for platelets. In 2008, the German National Blood Advisory Committee⁵⁰ recommended to the Ministry of Health that the shelf life of conventional platelet components should be shortened to four days to reduce the incidence of septic transfusion reactions from bacterial contamination. Only pathogen-inactivated platelets, such as those treated with the INTERCEPT Blood System, may be stored for five days, without additional interventions to reduce the risk of sepsis. The option to extend shelf life from four to five days is estimated to reduce platelet wastage rates by as much as 15-20 per cent.
- In the UK, an inquiry into contaminated blood products in the 1970s and 1980s will come under the responsibility of the Cabinet Office after victims and families "expressed strong views" over the potential involvement of the Department of Health.

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.

- A matter of continuing speculation is whether transfusing blood from young people into older people can reduce the effects of aging, and in particular whether it can slow the progress of Alzheimer's disease. Now a study reported at the Tenth Clinical Trials on Alzheimer's Disease meeting in Boston⁵¹ has suggested that blood plasma transfusions from young healthy volunteers did not improve the ability of Alzheimer's patients to comprehend their surroundings, that is, cognition was unchanged. However, an association was observed between the transfusions and the patients' ability to perform daily tasks such as dressing and meal preparation⁵².

⁴⁸ The letter to health professionals was signed by Eugene McCray, the director of the CDC's Division of HIV/AIDS Prevention, and Jonathan Mermin, director of the CDC's National Center for HIV/AIDS, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Prevention.

⁴⁹ Institut für das Entgeltsystem im Krankenhaus, or InEK

⁵⁰ Arbeitskreis Blut, or AK Blut

⁵¹ On 4 November 2017

⁵² The results are based on only 18 people. "This is a really very small trial and the results should not be over-interpreted," said Tony Wyss-Coray, a neurologist at Stanford University who led the trial which was conducted by his start-up company Alkahest, which is based in San Carlos, California. He and his colleagues studied people aged between 54 and 86 with mild to moderate Alzheimer's disease. The subjects were given weekly infusions for a month, either a saline placebo or plasma from blood donors aged 18–30. This human trial post-dated 'parabiosis' experiments, in which the blood systems of two rodents were surgically joined. Wyss-Coray plans to conduct a second, larger trial using plasma from which many proteins and other molecules have been removed.

- Protalex announced that preclinical data, showing its lead drug candidate PRTX-100 increases blood platelet counts in a mouse model of immune thrombocytopenia (ITP), had been published in the *British Journal of Haematology*⁵³.
- The FDA awarded [Dr. Kenneth Ataga](#)⁵⁴ a \$US 2 million grant over five years to support a prospective study in [sickle cell anaemia](#) to identify biomarkers of specific cellular function changes in [chronic kidney disease \(CKD\)](#)⁵⁵.
- [Edward Holmes](#), professor of biology at the University of Sydney, and his research team have discovered⁵⁶ that transfers of viruses from one host species to another drive the most important evolutionary changes in most viruses: [cross-species transmission has been more important and more frequent than anyone realized](#). Co-divergence (where viruses have stuck with their hosts, mutating to make minor adjustments every time the host branched into a new species) has been less common than was assumed and has mostly caused incremental changes. The discovery that viruses move between species with unexpected frequency may have alarming implications for the threat from emerging infectious diseases.
- Researchers at the University of Southampton in the UK have found that the human body's key immune cells can recognise many different viruses through a single receptor, which could change the way viruses are targeted by vaccines. Salim Khakoo said that, while animal studies/clinical trials will be needed to test the findings, "it is very exciting to discover that other viruses similar to Hepatitis C, such as Zika virus, dengue virus, yellow fever virus, Japanese encephalitis virus and in fact all flaviviruses, contain a region within their NS3 helicase proteins that is recognised by exactly the same KIR2DS2 receptor. We believe that by targeting this NS3 helicase region, we could make a new type of vaccine based upon natural killer cells, which can be used to help protect people from these infections."
- In the UK, researchers at the University of Birmingham have developed gold nanoparticles that can be tracked as they travel along with blood through the narrowest arteries and veins. They synthesized iridium-coated gold nanoparticles, which are much smaller (less than 100 nanometers) than red blood cells, that luminesce within the visible spectrum and can be followed using optical techniques. Since the nanoparticles have long lives they can be tracked for extended time periods⁵⁷.
- Research suggests⁵⁸ that administration of low-dose intravenous immunoglobulin (IVIg) is no more effective than placebo in complex regional pain syndrome (CRPS).
- A team of researchers from the University of Nebraska-Lincoln, MIT, and Harvard Medical School have developed a 'smart bandage' built with electrically conductive fibres coated in a specialized gel. The bandage could quickly administer treatment to

⁵³ Rick Kapur et al., "A highly purified form of Staphylococcal protein A alleviates murine immune thrombocytopenia." 19 October 2017. DOI: 10.1111/bjh.14985

⁵⁴ Of the University of North Carolina

⁵⁵ The award was part of the FDA's larger [Orphan Products Grants Program](#), which awarded six grants together worth \$US 6.3 million for studies in rare diseases, defined as illnesses affecting no more than 200,000 Americans. To increase the number of grants awarded, the National Center for Advancing Translational Sciences (NCATS), a unit of the National Institutes of Health, contributed additional funding through its Therapeutics for Rare and Neglected Diseases program.

⁵⁶ Jemma L. Geoghegan, Sebastián Duchêne, and Edward C Holmes, "Comparative analysis estimates the relative frequencies of co-divergence and cross-species transmission within viral families" *PLOS Pathogens*, <https://doi.org/10.1371/journal.ppat.1006215>

⁵⁷ Nicola J Rogers, et al., "[Tailoring iridium luminescence and gold nanoparticle size for imaging of microvascular blood flow](#)", *Nanomedicine*, vol.12 no. 22, published online 29 September 2017, <https://doi.org/10.2217/nnm-2017-0211>

⁵⁸ A Goebel et al., "Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome: A Randomized Trial", *Ann Intern Med.* 2017 Oct 3;167(7):476-483. [doi: 10.7326/M17-0509](https://doi.org/10.7326/M17-0509). Epub 2017 Sep 12.

chronic wounds or battlefield injuries. The bandage can be individually loaded with medications including antibiotics, tissue regenerating growth factors, and painkillers. A smartphone or other wireless device activates a microcontroller on the bandage which transmits through a selected fibre to heat up the component and the hydrogel, releasing the medication. Ali Tamayol, co-author of the study report⁵⁹ and assistant professor of mechanical and materials engineering at the University of Nebraska, said: "You can release multiple drugs with different release profiles. That's a big advantage in comparison with other systems. What we did here was come up with a strategy for building a bandage from the bottom up".

- Research in mice⁶⁰ suggests that the spleen's marginal zone (MZ) B-cells respond to blood coagulation factor VIII and demonstrate potential to become the target of future therapies to reduce FVIII inhibitors in [haemophilia A](#).
- Katerina Akassoglou and her research team at the Gladstone Institutes found that when the blood clotting protein fibrinogen leaks into the central nervous system, it stops brain cells from producing myelin and, as a result, prevents repair⁶¹.
- A person with sickle cell disease produces abnormally shaped, stiff red blood cells that can build up and block blood vessels, causing pain and sometimes death. Although the disease is named after its characteristic crescent-shaped red cells, it also results in other shapes, such as oval or elongated red blood cells. The shapes found in a specific patient can indicate the severity of their disease. To automate the process of identifying [red blood cell](#) shape, Mengjia Xu of Northeastern University, China, and colleagues developed a computational framework that employs a machine-learning tool known as a deep [convolutional neural network](#) (CNN)⁶².
- Research from Weill Cornell Medicine showed that transplanting young blood vessel cells into older mice can make their aged stem cells take on the characteristics of young stem cells, leading to healthier blood systems.⁶³
- In an attempt to match the minute scale of human blood vessels⁶⁴, Professor Leonid Ionov and his team at the University of Bayreuth, Germany, have concluded that 4D bioprinting is the way forward⁶⁵. They say their approach "paves new avenues for the creation of tailored cell-laden shape-morphing architectures for tissue engineering and regenerative medicine applications."
- Hemoglobin Oxygen Therapeutics LLC (HBO₂ Therapeutics) announced the first human organ transplant of a previously rejected liver, reconditioned *ex-situ* with

⁵⁹ published in the journal *Advanced Functional Materials*.

⁶⁰ The study's senior author was Sean R. Stowell, from the Center for Transfusion Medicine and Cellular Therapies, [Department of Pathology and Laboratory Medicine at Emory University School of Medicine](#) in Atlanta, Georgia. "[Marginal zone B cells are critical to factor VIII inhibitor formation in mice with hemophilia A](#)," appeared in the journal *Blood*.

⁶¹ Mark A. Petersen, Jae Kyu Ryu, Kae-Jiun Chang, Ainhoa Etxeberria, Sophia Bardehle, Andrew S. Mendiola, Wanjiru Kamau-Devers, Stephen P.J. Fancy, Andrea Thor, Eric A. Bushong, Bernat Baeza-Raja, Catriona A. Syme, Michael D. Wu, Pamela E. Rios Coronado, Anke Meyer-Franke, Stephanie Yahn, Lauriane Pous, Jae K. Lee, Christian Schachtrup, Hans Lassmann, Eric J. Huang, May H. Han, Martina Absinta, Daniel S. Reich, Mark H. Ellisman, David H. Rowitch, Jonah R. Chan, Katerina Akassoglou. "Fibrinogen Activates BMP Signaling in Oligodendrocyte Progenitor Cells and Inhibits Remyelination after Vascular Damage". *Neuron*, 2017; DOI: [10.1016/j.neuron.2017.10.008](#)

⁶² Xu M, Papageorgiou DP, Abidi SZ, Dao M, Zhao H, Karniadakis GE (2017) "A deep convolutional neural network for classification of red blood cells in sickle cell anemia". *PLoS Comput Biol* 13(10): e1005746. [doi.org/10.1371/journal.pcbi.1005746](#)

⁶³ The study was published online October 16 and appeared in the November issue of *The Journal of Clinical Investigation*, senior author Jason Butler.

⁶⁴ the diameter of the smallest blood vessels in the human body is around 5 microns

⁶⁵ Alina Kirillova, Ridge Maxson, Georgi Stoychev, Cheryl T. Gomillion and Leonid Ionov, "[4D Biofabrication Using Shape-Morphing Hydrogels](#)", *Advanced Materials*, first published 12 October 2017. DOI: 10.1002/adma.201703443

Hemopure before transplantation⁶⁶. The surgery was performed in the Netherlands by Professor Robert J. Porte, Chief of HPB Surgery and Liver Transplantation at University Medical Center Groningen. The transplant was part of a pilot study. The donor liver was perfused with a cold Hemopure oxygenated solution, before being gradually warmed up to a temperature of 37 degrees to bring it 'back to life'. The donor liver regained its normal colour and acidity and began producing bile. It was tested for several hours outside the body before transplantation. Dr. Porte commented that in addition to this being the first successful transplantation of a normo-thermally perfused liver in the Netherlands, this was also the first ever-clinical application of a haemoglobin-based solution for ex situ warm machine perfusion of a human donor liver. Dr Porte went on to add: "This is an important step forward in the implementation of machine perfusion technology in Transplantation Medicine, which can help us to increase the number of organs for transplantation. It indicates we can preserve and test human organs at body temperature without the need for human blood products."

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

- Oxitec plans to build a centralized facility in Oxfordshire with the capacity to produce one billion genetically modified mosquito eggs every week. Oxitec's non-biting male mosquitoes have been genetically modified to pass on a self-limiting gene to their offspring so that they do not survive to maturity, reducing wild populations of *Aedes aegypti* mosquitoes, which spread diseases like chikungunya, dengue, yellow fever and Zika.
- Mouse trials for a live-attenuated Zika vaccine developed by the University of Texas Medical Branch and Brazil's Evandro Chagas Institute showed that a single dose in pregnant mice prevented transmission to their offspring. In male mice a single dose prevented testicular damage.
- From a small, case-control study based in Puerto Rico has come a report of confirming a correlation between Zika infection and the subsequent development of Guillain-Barre syndrome, which can cause muscle weakness and sometimes paralysis⁶⁷. Similar findings followed the 2013 Zika outbreak in French Polynesia.

⁶⁶ Hemoglobin Oxygen Therapeutics LLC, headquartered in Souderton Pennsylvania, manufactures the oxygen carrying solutions Hemopure (hemoglobin glutamer - 250 (bovine) and Oxyglobin (hemoglobin glutamer - 200 (bovine), for human and veterinary use respectively. Hemopure is not approved by the FDA and classified as an investigational product in the US. Oxyglobin is FDA approved (NADA 141-067) for veterinary use to treat anemia in dogs. See www.hbo2therapeutics.com

⁶⁷ Emilio Dirlikov, Nicole A. Medina, Chelsea G. Major, Jorge L. Munoz-Jordan, Carlos A. Luciano, Brenda Rivera-Garcia, Tyler M. Sharp. "Acute Zika Virus Infection as a Risk Factor for Guillain-Barré Syndrome in Puerto Rico". *JAMA*. 2017;318(15):1498–1500. doi:10.1001/jama.2017.11483

- David Watkins, a professor of pathology with the University of Miami Miller School of Medicine reported that a blend of three potent antibodies completely prevented Zika infection in a group of four lab monkeys, and that regular injections of these antibodies potentially could provide vital protection to pregnant women either living in or traveling to areas where Zika is endemic⁶⁸. He said: "I would say if you were to give a woman in the first trimester an injection and then another injection at the middle of the second trimester, that would suffice" to protect her unborn child from Zika throughout the pregnancy". Amesh Adalja, a senior associate at the Johns Hopkins Center for Health Security, said: "If further studies -- including ones done in humans - - replicate these findings, a preventative antibody cocktail could be constructed and used to temporarily protect those traveling to Zika-prone areas."⁶⁹
- Scientists have discovered five new malaria vaccine targets that lead to reduction in the parasite's ability to enter the red blood cells⁷⁰. Future malaria vaccines may be most effective if they target multiple parasite factors.

Influenza

- UK researchers have examined a number of psychological and behavioural factors that affect how well vaccinations work⁷¹. Professor Kavita Vedhara, from the University of Nottingham's Division of Primary Care, said: "Vaccinations are an incredibly effective way of reducing the likelihood of catching infectious diseases. But their Achilles heel is that their ability to protect against disease is affected by how well an individual's immune system works. So people with less effective immune systems, such as the elderly, may find vaccines don't work as well for them as they do in the young. We have known for many years that a number of psychological and behavioural factors such as stress, physical activity and diet influence how well the immune system functions and these factors have also been shown to influence how well vaccines protect against disease." The research team measured negative mood, positive mood, physical activity, diet and sleep three times a week over a six-week period in a group of 138 older people due to have their flu jab. Then they examined how well the injection was working by measuring the amount of influenza antibody in the blood at four weeks and sixteen weeks after the vaccination. Of all of the factors measured, only positive mood over the six-week observational period predicted how well the jab worked – with good mood associated with higher levels of antibody. When the researchers looked at influences on the day of vaccination itself, they found an even greater effect on how well it worked, accounting for between eight and fourteen per cent of the variability in antibody levels.
- Defective genetic material in flu viruses may activate the immune system in infected patients, and new research suggests that lower levels of these molecules could increase flu severity⁷².

⁶⁸ Diogo M. Magnani, et al., "Neutralizing human monoclonal antibodies prevent Zika virus infection in macaques", *Science Translational Medicine*, 04 Oct 2017: Vol. 9, Issue 410, eaan8184 DOI: 10.1126/scitranslmed.aan8184

⁶⁹ This is not a Zika vaccine, where the immune system produces its own antibody against a pathogen. Rather, it is "passive immunotherapy," where people receive pre-made antibodies that provide immediate direct protection.

⁷⁰ Leyla Y. Bustamante et al., "Synergistic malaria vaccine combinations identified by systematic antigen screening," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1702944114

⁷¹ Kieran Ayling, Kavita Vedhara et al., "Positive mood on the day of influenza vaccination predicts vaccine effectiveness: A prospective observational cohort study", *Brain, Behavior, and Immunity*, Volume 67, January 2018, Pages 314-323

⁷² Vasilijevic J, Zamarreño N, Oliveros JC, Rodriguez-Frandsen A, Gómez G, Rodriguez G, et al. (2017) "Reduced accumulation of defective viral genomes contributes to severe outcome in influenza virus infected patients." *PLoS Pathog*13(10): e1006650. <https://doi.org/10.1371/journal.ppat.1006650>

Avian influenza

Because of the capacity of influenza viruses for re-assortment, the spread of influenza strains in animals and birds is of interest as one or more strain may eventually develop the potential to cause a pandemic in humans. There are also strains which, while primarily infecting and being transmitted by animals or birds, nevertheless can infect humans, and the concern there is that human-to-human transmission might develop.

- The US National Institutes of Health awarded \$US 5.8 million over five years, for development of a next-generation H7N9 vaccine, to EpiVax, based in Providence, Rhode Island, and scientists from the University of Massachusetts Medical School, Protein Sciences, and the University of Georgia.
- Researchers have reported that laboratory experiments on a new strain of the H7N9 bird flu circulating in China suggest the virus can transmit easily among animals and can cause lethal disease, raising alarm that the virus has the potential to trigger a global human pandemic⁷³.

Other diseases: occurrence, diagnosis, prevention and treatment

- At 29 November there had been in Saudi Arabia a total of 1747 laboratory-confirmed cases of MERS-CoV infection, including 706 deaths.
- China has approved a domestically developed Ebola vaccine, developed by its Academy of Military Medical Sciences and CanSino Biologics Inc. China is the third country to develop a vaccine against Ebola following the [United States](#) and [Russia](#). The vaccine is based on the 2014 mutant gene type and is in the form of freeze-dried powder, which can remain stable for at least two weeks in temperatures of up to 37 degrees Celsius and is suitable for the climate in West Africa. It has undergone clinical trials in Sierra Leone.
- in Central Australia an outbreak of meningococcal disease has mainly affected indigenous children. Northern Territory health authorities have mounted a large-scale immunisation campaign in the affected regions.

⁷³ Masaki Imai, Yoshihiro Kawaoka, et al. "A Highly Pathogenic Avian H7N9 Influenza Virus Isolated from A Human Is Lethal in Some Ferrets Infected via Respiratory Droplets", *Cell Host & Microbe*, Volume 22 , Issue 5 , pp 615 - 626.e8, 8 November 2017 DOI: <http://dx.doi.org/10.1016/j.chom.2017.09.008>