

# Monitoring International Trends

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## **posted December 2017-January 2018**

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.

Some recent matters of interest appear on pages 4 to 20. Highlights are listed below:

### **Products**

- A team of Australian and US researchers discovered that, if haemophilia B patients were infused with a gene therapy called factor IX Padua (R338L), their bodies kept expressing the factor IX coagulant on their own.
- BioMarin Pharmaceutical reported it was encouraged by new data on valoctocogene roxaparovec, an investigational gene therapy for patients with severe haemophilia A.
- Spark Therapeutics described as encouraging the preliminary results from the Phase 1/11 clinical trial of its gene therapy SPK-8011 in haemophilia A.
- UniQure reported positive early results in a trial of its gene therapy for haemophilia B.
- Bioverativ presented the results of a new post-hoc longitudinal analysis demonstrating that individualised dosing with extended half-life therapy, Alprolix (eftrenonacog alfa), every 14 or more days may be an option for people with severe haemophilia B who seek the benefits of prophylactic therapy with reduced treatment burden.
- Catalyst Biosciences announced the initiation of the Phase II section of its Phase II/III trial of marzeptacog alfa (activated), a subcutaneously administered Factor VIIa therapy to treat haemophilia A and B with inhibitors.
- Prolong Pharmaceuticals has completed enrolling patients in an ongoing Phase II clinical trial of Sanguinate, to treat vaso-occlusive crises in sickle cell disease. Prolong has presented preliminary trial results suggesting that Sanguinate can return red blood cells from a sickle shape back to a round shape and restore blood flow.
- Ironwood Pharmaceuticals initiated a Phase II clinical trial of once-daily, orally administered, IW-1701, in patients with sickle cell disease. IW-1701 has been shown to improve nitric oxide signalling.
- La Jolla Pharmaceutical Company initiated a trial of synthetic human hepcidin in patients with transfusion-dependent beta thalassemia who despite chelation therapy have dangerously high cardiac iron levels.
- Novartis announced positive results from a post hoc subgroup analysis of the Phase II study, SUSTAIN on its sickle cell disease drug, crizanlizumab.
- At the American Society of Hematology 59th Annual Meeting in December it was reported that gene therapy may be able to cure severe combined immune deficiency.
- Emergent BioSolutions has initiated a phase II dose-ranging study of its human polyclonal antibody as an intravenous treatment for influenza A infection in hospitalized adults.

### **Patient Blood Management**

- UK life science company SpheriTech has been awarded a grant to develop a novel blood substitute, a haemoglobin-based oxygen carrier.

- In the US, an updated guideline for platelet transfusion in patients with cancer says that for adults undergoing hematopoietic stem-cell transplants platelet infusion may be safely delayed until the first sign of bleeding, with prophylactic infusion no longer recommended.
- A study has found that reinfusing red blood cells lost during surgery did not lead on average to a statistically significant reduction in the rates of blood transfusion amongst women undergoing caesarean section.
- A study has found that administration of post-bypass four-factor prothrombin complex concentrate decreases transfusions of both red blood cells and plasma in patients undergoing an orthotopic heart transplant who already have left ventricular assist devices.
- Research suggests that cold storage of platelets preserves their haemostatic function, which may be best for actively bleeding patients.
- A secondary analysis of the randomized controlled INFORM trial has investigated the effects on in-hospital morbidity or mortality from short- and long-term storage of red blood cells for transfusions. It found that transfusing red blood cells stored longer than 35 days did not increase risk for in-hospital death compared with fresh blood.
- A study has suggested that oral iron monotherapy has limited efficacy in the treatment of anaemia in patients with non-dialysis-dependent chronic kidney disease.
- The American College of Cardiology released new clinical guidelines for the management of acute bleeding in patients treated with oral anticoagulants.
- PhaseBio Pharmaceuticals has entered an exclusive, worldwide licence agreement with MedImmune for a Phase I-ready reversal agent for antagonist antiplatelet drug ticagrelor.

### Regulatory matters

- Shire is seeking US Food and Drug Administration (FDA) approval for a new plasma manufacturing facility which would increase the production of its Covington (Georgia) site by 30 per cent.
- The European Commission approved Shire's haemophilia A therapy Adynovi.
- Pharming Group submitted a supplemental Biologics License Application to the FDA for Ruconest [Recombinant Human C1 Esterase Inhibitor/ conestat alfa] for routine prophylaxis to prevent hereditary angioedema attacks in adult and adolescent patients.
- Grifols received FDA approval for its blood-based alpha-1 antitrypsin deficiency test.
- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended the suspension across the European Union of marketing authorizations for hydroxyethyl-starch solutions for infusion.

### Company news

- Shire has partnered with Rani Therapeutics to develop oral delivery rather than injections of peptides, proteins and therapeutic antibodies.
- Sanofi and Ablynx had entered into a definitive agreement under which Sanofi would offer to acquire all the outstanding ordinary shares in Ablynx.
- Vertex Pharmaceuticals and CRISPR Therapeutics AG will co-develop and co-commercialize gene editing treatment CTX001. An application has been submitted for a Phase I/II clinical trial in  $\beta$ -thalassaemia in Europe, and an Investigational New Drug Application will be submitted for a Phase I/II trial in sickle cell disease in the US.
- Otsuka Holdings has invested in startup Megakaryon, a venture that creates platelets out of induced pluripotent stem cells. It hopes to commercialize the technology by 2020.
- South Korea's Green Cross has been preparing for the FDA additional production-related data on its human normal immunoglobulin G for intravenous administration.

### Country news

- The US National Institutes of Health (NIH) has lifted a three-year freeze in federal funding for research projects involving pathogens that can cause pandemics.

- A Canadian study found "that persons who have immigrated to Canada from endemic Central and South American countries should be screened for Chagas disease to make sure that they are not infected, especially women of childbearing age before they get pregnant, to prevent congenital transmission in Canada".
- The Australian Red Cross Blood Service and the Department of Defence have developed technology to freeze and thaw blood without compromising its use. Medics can have blood on hand in conflict zones to help Australian personnel.

### Research not included elsewhere

- CSL Behring will proceed with a global Phase III cardiovascular morbidity and mortality trial for plasma-derived CSL112, its novel apolipoprotein A-I (apoA-I) infusion therapy.
- Researchers have discovered that sugar can encourage new blood vessel formation, which is crucial for wound healing.

### Legal matters

- Roche's haemophilia drug Hemlibra, approved in November by the FDA, has the company in a patent dispute with Shire.
- A Philadelphia court found Johnson & Johnson and Bayer AG liable for a patient's gastrointestinal haemorrhaging, which she attributed to the anticoagulant Xarelto.

### Infectious diseases

- The World Health Organization says use of Sanofi's dengue vaccine should be restricted because of concerns it increases the risk of severe disease in people who have never previously had dengue. This followed major political controversy over government-funded vaccination in the Phillipines.
- Laboratory tests in cell cultures showed a new drug known as NGI-1 can shut down flaviviruses (mosquito-borne viruses like Zika, dengue and West Nile).
- After reporting positive Phase II results on its chikungunya vaccine, Themis has raised new funds to continue with its development.
- Results from two Phase I clinical trials show an experimental Zika vaccine developed at the US National Institute of Allergy and Infectious Diseases is safe and induces an immune response in healthy adults.
- Takeda Pharmaceutical is testing its Zika vaccine candidate in a Phase I clinical trial.
- An Australian flu expert has said that the detection of the highly pathogenic form of H7N9 avian influenza in China serves as a second warning of pandemic potential.
- As of 27 January 2018, there had been a total of 1780 laboratory-confirmed cases of Middle East Respiratory Syndrome Coronavirus infection in Saudi Arabia, including 724 deaths.
- A small Phase I trial has demonstrated the safety and tolerability of a fully human polyclonal IgG antibody produced from the hyperimmune plasma of transchromosomic cattle immunized with a MERS coronavirus vaccine.
- Researchers found that the ability of the Ebola virus to copy itself and spread through hosts can be "switched off" by manipulating a host factor enzyme.
- Survivors of the world's first known Ebola outbreak still have immunity to the virus 40 years after they were infected.

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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, either make new products and treatments available or may lead to new uses or changes in use for existing products.*

### Treating haemophilia

- A team of Australian and US researchers discovered that, if haemophilia B patients were infused with a gene therapy called factor IX Padua (R338L), their bodies kept expressing the factor IX coagulant on their own. All 10 men (with haemophilia B) involved in the study developed this response, according to the findings published in the *New England Journal of Medicine*<sup>1</sup>. Nine of the 10 patients had no bleeds, and eight out of 10 needed no further infusions, the researchers reported after following the men for up to 10 years<sup>2</sup>. Researchers at the Royal Prince Alfred Hospital in Sydney have called their findings a major milestone. After more than two decades of work, they had discovered "what may be a permanent cure", said co-author Professor John Rasko, a clinical haematologist and scientist at the University of Sydney. His co-researchers were led by haematology experts at the Children's Hospital of Philadelphia. Spark Therapeutics and Pfizer funded the trial. Spark is funding the commercialisation of the therapy. Professor Rasko said the research team's next focus would be targeting haemophilia A caused by a defective clotting factor VIII.

<sup>1</sup> Lindsey A. George et al., "Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant", *N Engl J Med* 2017; 377:2215-2227 [December 7, 2017](https://doi.org/10.1056/NEJMoa1708538) DOI: 10.1056/NEJMoa1708538

<sup>2</sup> The rate of bleeding the men experienced dropped dramatically from an average of 11.1 bleeds per year to 0.4. The researchers reported the treatment was safe and caused no serious side-effects.

- BioMarin Pharmaceutical reported new data on valoctocogene roxaparvovec at the American Society of Hematology (ASH) 2017 Annual Meeting in Atlanta on 11 December<sup>3</sup>, which was simultaneously published online in the *New England Journal of Medicine*, 9 December<sup>4</sup>. Valoctocogene roxaparvovec (formerly BMN 270) is an investigational gene therapy for the treatment of patients with severe haemophilia A. Patients given a single infusion showed substantially increased levels of the blood clotting factor VIII. Of the 13 patients who took part in the study, 11 achieved normal or near-normal factor VIII levels.
- BioMarin announced on 19 December that it had dosed the first patient in the global GENE8-1 Phase III study with the 6e13 vg/kg dose for valoctocogene roxaparvovec. Another Phase III study, which will enrol its first patient at the beginning of 2018, will have a 4e13 vg/kg dose (GENE8-2). Both studies will be open-label single-arm studies to evaluate the efficacy and safety of valoctocogene roxaparvovec. The primary endpoint in both studies will be based on the FVIII activity level achieved, and the secondary endpoints will measure annualized FVIII replacement therapy use rate and annualized bleed rate<sup>5</sup>.
- BioMarin has a large gene therapy manufacturing facility in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced to support clinical development activities and anticipated commercial demand. This facility could support around 2,000 patients per year. The production process was developed in accordance with International Conference on Harmonisation guidance for Pharmaceuticals for Human Use facilitating worldwide registration with health authorities.
- At the American Society of Hematology (ASH) 59<sup>th</sup> Annual Meeting in December, Spark Therapeutics discussed the Phase 1/11 clinical trial of its gene therapy SPK-8011 in haemophilia A. It reported a 100-percent reduction in annualized bleeding rate (ABR) and 98-percent reduction in annualized infusion rate (AIR) in the first four participants. None of the infused participants had so far reported a serious adverse event, including no factor VIII inhibitors and no thrombotic events.
- At the ASH meeting, UniQure reported positive results in an early-stage trial of its treatment for haemophilia B. The company said eighteen-month follow-up data from a Phase I/II trial of AMT-060 in the second-dose cohort found “substantial improvement” in disease state in all five patients, and that all those who previously needed frequent infusions were able to stop them.
- At the ASH meeting, [Swedish Orphan Biovitrum AB](#) (Sobi) [Bioverativ Inc.](#) presented in a poster session the results of a new post-hoc longitudinal analysis demonstrating

<sup>3</sup> [Abstract 603](#) *Achievement of Normal Circulating Factor VIII Activity Following Bmn 270 AAV5-FVIII Gene Transfer: Interim, Long-Term Efficacy and Safety Results from a Phase 1/2 Study in Patients with Severe Hemophilia a*. K. John Pasi, et al.

<sup>4</sup> Savita Rangarajan, Liron Walsh, Will Lester, David Perry, Bella Madan, Michael Laffan, Hua Yu, Christian Vettermann, Glenn F. Pierce, Wing Y. Wong, and K. John Pasi, “AAV5–Factor VIII Gene Transfer in Severe Hemophilia A”, *N Engl J Med* 2017; 377:2519-2530 [December 28, 2017](#) DOI: 10.1056/NEJMoa1708483 [Full text](#), [Editorial](#)

<sup>5</sup> The US Food and Drug Administration (FDA) granted valoctocogene roxaparvovec Breakthrough Therapy Designation, which facilitates and expedites development and review of new drugs to address unmet medical need in the treatment of a serious condition. The European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) regulatory initiative for valoctocogene roxaparvovec. BioMarin's valoctocogene roxaparvovec has also received orphan drug designation from the FDA and EMA for the treatment of severe haemophilia A. This advances the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare conditions.

<sup>6</sup> SPK-8011 is a bio-engineered adeno-associated viral (AAV) vector utilizing the AAV-LK03 capsid, also referred to as Spark200, containing a codon-optimized human factor VIII gene under the control of a liver-specific promoter. It is considered a potential one-time gene therapy for haemophilia A.

that individualised dosing with extended half-life therapy, Alprolix (eftrenonacog alfa), every 14 or more days may be a potential option for people with severe haemophilia B who seek the benefits of protection from a prophylactic therapy with reduced treatment burden. Post-hoc longitudinal analysis from B-LONG and B-YOND studies showed patients who progressed to individualised prophylactic dosing intervals of 14 days or longer maintained low annualised bleeding rates.

- On 4 January 2018, Catalyst Biosciences announced the initiation and open enrolment of the Phase II section of its Phase II/III trial of marzeptacog alfa (activated) (MarZAA), a potent, subcutaneously administered Factor VIIa therapy it is developing to treat haemophilia A and B with inhibitors. The Phase II open-label, subcutaneous efficacy trial will evaluate the ability of MarZAA to eliminate – or minimize – spontaneous bleeding episodes in patients with haemophilia A or B with inhibitors. The study has a primary endpoint of a reduction in annualized bleed rate compared with each patient’s historical annualized bleed rate as the control. MarZAA has been granted orphan drug designation by the US Food and Drug Administration (FDA) for routine prophylaxis to prevent bleeding episodes in individuals with haemophilia A or B with inhibitors.

## Treating beta thalassemia and sickle cell disease

- [Prolong Pharmaceuticals](#) has completed enrolling patients in an ongoing Phase II clinical trial<sup>7</sup> of [Sanguinate](#), to treat the very painful vaso-occlusive crises (blocking of blood vessels by abnormally shaped red blood cells) that characterise [sickle cell disease](#). Sanguinate is designed to prevent the cells from “clumping”, keeping blood flowing. Prolong presented preliminary trial results in a poster session at the ASH meeting. They suggested that Sanguinate can return red blood cells from a sickle shape back to a round shape, restoring blood flow. In a further poster presentation in Atlanta, Prolong reported that Sanguinate resolved vaso-occlusive crises in mice with sickle cell disease, improving blood flow so that tissue and organs could obtain the oxygen they needed. The FDA has designated Sanguinate an orphan drug — a status that gives companies incentives to develop therapies for rare diseases.
- [Ironwood Pharmaceuticals](#)<sup>8</sup> initiated a Phase II clinical trial<sup>9</sup> of once-daily, orally administered, IW-1701, in patients with sickle cell disease. Many of the symptoms of sickle cell disease are believed to be caused by a deficiency of nitric oxide (NO)<sup>10</sup>, an important regulator of blood flow and inflammatory processes. IW-1701 has been shown to improve NO signalling in non-clinical studies. It is being investigated for its potential to treat multiple aspects of sickle cell disease pathophysiology, including red blood cell sickling, decreased blood flow and vascular inflammation. Ironwood presented IW-1701 data at the ASH meeting<sup>11</sup>.

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<sup>7</sup> trial [NCT02411708](#)

<sup>8</sup> of Cambridge, Massachusetts

<sup>9</sup> STRONG-SCD is a multicentre, randomized, double-blind, placebo-controlled, dose-ranging Phase II clinical trial designed to assess the safety and tolerability of oral, once-daily IW-1701 in patients with sickle cell disease. Additional exploratory objectives include the evaluation of the pharmacokinetic profile of IW-1701 as well as its effects on sickle cell disease symptoms, health-related quality of life and biomarkers of pharmacodynamic activity. The trial is expected to enrol approximately 88 patients between 16 and 70 years of age. Patients will remain on their existing treatment regimens throughout the trial. After a two-week single-blind placebo run-in period, patients will be randomized to receive placebo or one of three dose levels of IW-1701 administered for approximately 12 weeks.

<sup>10</sup> Sickled red blood cells are more susceptible to haemolysis (rupturing). Upon red blood cell rupturing, nitric oxide (NO) is depleted due to arginase release and haemoglobin scavenging. NO is an important regulator of blood flow, and the resulting deficiency of NO is believed to contribute to disease mechanisms and symptoms of sickle cell disease.

<sup>11</sup> In an oral presentation entitled “The Clinical-Stage sGC Stimulator IW-1701 Prevents Increase of Plasma Biomarkers of Intravascular Inflammation and Suppresses Leukocyte-Endothelial Interactions in TNF $\alpha$ -Treated Mice,” non-clinical data were presented demonstrating that, in these models, pre-

- [La Jolla Pharmaceutical Company](#) announced the initiation of a clinical study of LJPC-401 (synthetic human hepcidin) in patients with transfusion-dependent beta thalassemia who, despite chelation therapy, have cardiac iron levels above normal, which puts them at risk of heart failure and sudden death.
- At the American Society of Hematology 59<sup>th</sup> Annual Meeting in December (the ASH meeting):
  - i) Italfarmaco Group of Milan announced the positive results from two clinical trials evaluating its proprietary histone deacetylase (HDAC) inhibitor givinostat in polycythemia vera patients<sup>12</sup>. In an oral presentation, the company discussed positive safety and efficacy data from a two-part study in which over 80 per cent of patients responded to the treatment. These results were supported by a poster presentation of a four-year evaluation of givinostat's effect in patients. The company will now proceed with a pivotal Phase III trial.
  - ii) Editas Medicine<sup>13</sup> in a poster presentation announced results from experiments to demonstrate expanded CRISPR genome editing strategies in hematopoietic stem cells for the treatment of haematologic diseases such as sickle cell disease and beta-thalassemia. "These data together support multiple approaches to creating a superior therapy for the treatment of sickle cell disease and beta-thalassemia," said Charles Albright, the company's Chief Scientific Officer. "Combined with our previously reported data showing the upregulation of fetal hemoglobin, we are continuing to advance our program to develop best-in-class, durable therapies for patients with hemoglobinopathies."
  - iii) [Intellia Therapeutics](#) discussed<sup>14</sup> how it had used gene editing to replace an oxygen-carrying component in blood that is defective in sickle cell disease. This involved editing the *BCL11A* gene in a mouse model to produce an effective version of haemoglobin.
  - iv) Global Blood Therapeutics (GBT) presented six studies supporting Voxelotor (previously known as GBT440) in sickle cell disease<sup>15</sup>.
  - v) Bluebird bio presented data suggesting its Lentiglobin gene therapy could be a significant treatment in severe sickle cell disease.
  - vi) preclinical efficacy data of Oryzon Genomics' investigational drug ORY-3001, as a potential treatment for sickle cell disease, was presented.<sup>16</sup>
  - vii) Epizyme announced new preclinical data from its G9a program for sickle cell disease<sup>17</sup>. The company also announced that its drug development candidate,

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treatment with IW-1701 inhibited the intravascular inflammation typically caused by TNF $\alpha$ , and that the effect of IW-1701 on inflammation was enhanced when co-administered with hydroxyurea, the current standard of care for sickle cell disease. In addition, Ironwood presented data from a randomized, placebo-controlled Phase Ib multiple ascending dose study of IW-1701 tablets in healthy subjects. Data from these studies support the continued clinical evaluation of IW-1701 in sickle cell disease.

<sup>12</sup> Polycythemia Vera is characterized by an increased number of red blood cells, white blood cells and platelets, which significantly raises the risk for thromboembolic and haemorrhagic complications.

<sup>13</sup> Of Cambridge, Massachusetts, [www.editasmedicine.com](http://www.editasmedicine.com).

<sup>14</sup> In a presentation entitled "[CRISPR/Cas9 Gene-Edited Hematopoietic Stem Cell Therapy for Sickle Cell Disease](#)."

<sup>15</sup> Preliminary results from one Phase IIa study suggested that treatment with voxelotor appeared associated with considerable improvement in haemoglobin and reduced clinical measures of haemolysis among adolescents with sickle cell disease.

<sup>16</sup> "Oral Administration of the LSD1 Inhibitor OG-S1335 Increases Fetal Hemoglobin in Humanized Transgenic Sickle Cell Disease Mice and in Baboons", presented by Professor Donald Lavelle from the Department of Medicine, University of Illinois at Chicago. A summary of the data is available at: <https://ash.confex.com/ash/2017/webprogram/Paper99635.html>

<sup>17</sup> The oral presentation provided details on Epizyme's tool compound that supports further study of G9a inhibition and the reactivation of foetal haemoglobin (abstract #537): *Reawakening of Human Fetal Hemoglobin and an Epigenetic Path to the Clinic for Sickle Cell Disease and Beta-Thalassemia*:

EZM8266, a G9a inhibitor, will begin enabling studies in 2018 to enable an Investigational New Drug Application to the US Food and Drug Administration (FDA).

- Novartis announced positive results from a post hoc subgroup analysis of the Phase II study, SUSTAIN on its sickle cell disease drug, crizanlizumab. The year-long multicentre, multinational, randomized, placebo-controlled, double-blind study evaluated the drug's safety and efficacy with or without concomitant use of hydroxyurea therapy. Crizanlizumab was found to defer the time to first sickle cell pain crisis in patients compared with placebo in key subgroups of adult patients. The results were published in *The New England Journal of Medicine*.

## Other products

- At the American Society of Hematology 59<sup>th</sup> Annual Meeting in December (the ASH meeting):
  - i) Dova Pharmaceuticals presented data on avatrombopag in patients with chronic liver disease (CLD) and immune thrombocytopenic purpura (ITP)<sup>18</sup>. Avatrombopag is a second generation orally administered thrombopoietin receptor agonist developed for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure. Dova has submitted a New Drug Application avatrombopag to the FDA.
  - ii) Principia Biopharma, of San Francisco, which has initiated a clinical trial for PRN1008 in patients with Immune Thrombocytopenia Purpura<sup>19</sup> (ITP), presented preclinical data. The studies showed that PRN1008 did not adversely affect platelet aggregation in blood from both healthy volunteers and ITP patients. Additionally, results in an animal model of ITP showed that animals treated with PRN1008 had significantly higher platelet counts than control animals (p<0.05).
  - iii) a late-breaking report was received on a randomized Phase III study of Ablynx's caplacizumab, which was found to reduce time to platelet count response and to result in faster resolution of acquired [thrombotic thrombocytopenic purpura \(TTP\)](#) than placebo.
  - iv) it was reported that gene therapy may be able to cure severe combined immunodeficiency (SCID), sometimes known as "bubble boy disease". Six out of seven infants treated using a newly crafted gene-based therapy already are out of the hospital and leading normal childhoods at home with family<sup>20</sup>.

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*Identification of an Orally-Available, Potent, and Selective Euchromatic Histone Lysine Methyltransferase 1 and 2 (EHMT1/2) Inhibitor.*

<sup>18</sup> *Avatrombopag, a Novel Oral Thrombopoietin Receptor Agonist, Demonstrates Superiority to Placebo for the Treatment of Chronic Immune Thrombocytopenic Purpura in a Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial* (oral presentation); *Superiority of Avatrombopag to Placebo in Increasing Platelet Counts in Patients with Chronic Liver Disease-Associated Thrombocytopenia Undergoing Scheduled Procedures: Results from 2, Phase 3 Randomized Studies* (oral presentation); *Avatrombopag, a Novel Thrombopoietin Receptor Agonist, Increases Platelet Counts without Increasing Platelet Activation in Patients with Thrombocytopenia Due to Chronic Liver Disease* (oral presentation); *Platelet Function in Thrombocytopenic Patients with Chronic Liver Disease* (poster); and *Disorders of Platelet Number or Function* (poster)

<sup>19</sup> ITP is an autoimmune disorder characterized by a decreased number of circulating platelets, which play a key role in clot formation.

<sup>20</sup> Lead researcher Dr. Ewelina Mamcarz, an assistant member of the faculty in the Bone Marrow Transplant Department at St. Jude Children's Research Hospital in Memphis, Tennessee, said: "They left the hospital after four to six weeks and we're following these babies on an outpatient basis. The last infant is barely six weeks past treatment, and his immune system is still in the process of constructing itself." The therapy focuses on the most common type of the disease. It affects only boys because it is caused by a genetic defect found on the male X chromosome. Boys born with X-SCID cannot produce any of the immune cells that defend the body against infection: T-cells, B-cells



- A Phase II clinical trial, [COBALT](#), assessing Akari Therapeutics' Coversin in patients with paroxysmal nocturnal hemoglobinuria (PNH) [met the primary endpoint](#). Two Phase III studies will evaluate the 45 mg/day dose: CAPSTONE will assess Coversin in treatment-naïve PNH patients and ASSET will include patients that will switch from Alexion Pharmaceuticals' Soliris (eculizumab).
- Scientists from the Universities of Bristol, Cambridge, and Oxford reported in March 2017<sup>21</sup> on how they had isolated and manipulated stem cells to produce red blood cells. Their goal is to produce red cells for patients with complex blood types, as there is a lack of suitable donors. Over time, they see lab-grown blood could transform medical care by supplying much-needed blood around the world regardless the blood type. However, their immortal cells will not be the source of the synthetic red cells which are about to be tested in human trials in England. That will need further work. French researchers have already transfused lab-grown red blood cells — which grew from stem cells — into a human, with successful results.
- Emergent BioSolutions has initiated a phase II dose-ranging study to evaluate its investigational immune globulin. The study will evaluate the safety, pharmacokinetics and clinical benefit of FLU-IGIV, Emergent's human polyclonal antibody, as an intravenous treatment for influenza A infection in adult hospitalized patients. The phase II study was designed to evaluate FLU-IGIV in combination with the standard of care, including a minimum five-day administration of an anti-viral drug. It will be conducted on approximately 75 patients across 50 sites within the US. The anti-influenza drug was developed on Emergent's established hyperimmune platform. Emergent already has a polyclonal antibody therapeutic licensed by the FDA. Anthrasil was developed for the treatment of inhalational anthrax. Emergent has been awarded a contract for Anthrasil by Canada's Department of National Defence. Emergent is developing a next-generation anthrax vaccine candidate, NuThrax for post-exposure prophylaxis of anthrax.

## 2. Safety and patient blood management

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

### Appropriate Transfusion

- UK life science company SpheriTech<sup>22</sup> has been awarded a grant from Innovate UK for a research project to develop a novel blood substitute, a haemoglobin-based oxygen carrier (HBOC) to be intravenously administered to deliver oxygen to the body's tissues. It can then be excreted from the body rather than accumulate in various tissues, and is said to be non-toxic, non-immunogenic, non-antigenic and non-carcinogenic.
- In the US, an updated guideline for platelet transfusion in patients with cancer says that for adults undergoing hematopoietic stem-cell transplants (HSCT) platelet infusion may be safely delayed until the first sign of bleeding, with prophylactic infusion no longer recommended. The change reflects recent evidence from multiple

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and natural killer (NK) cells. Without treatment, these babies typically die by age 2. Those who receive a stem cell transplant usually die by age 10.

<sup>21</sup> Kongtana Trakarnsanga, Rebecca E. Griffiths, Marieangela C. Wilson, Allison Blair, Timothy J. Satchwell, Marjolein Meinders, Nicola Cogan, Sabine Kupzig, Ryo Kurita, Yukio Nakamura, Ashley M. Toye, David J. Anstee, Jan Frayne, "An immortalized adult human erythroid line facilitates sustainable and scalable generation of functional red cells", *Nature Communications* volume 8, Article number: 14750 (2017), doi:10.1038/ncomms14750. In an interview, Jan Frayne, a lead author and biochemist at the University of Bristol, said: "When we kept (the cells) continually dividing for a year, we were quite excited".

<sup>22</sup> based at The Heath Business and Technical Park in Runcorn

published sources, reviewed by a panel convened by the American Society of Clinical Oncology (ASCO)<sup>23</sup>.

- Over two decades ago, a study demonstrated that revision cardiac surgery had a 75 per cent greater transfusion requirement than first-time cardiac surgery. Nadia Blakemore Hensley<sup>24</sup> offered updated estimates at the International Anesthesia Research Society 2017 annual meeting<sup>25</sup>. She said the earlier study was conducted before restrictive transfusion triggers and blood conservation measures were implemented<sup>26</sup>. She told the meeting that with current practice with coronary artery bypass (CAB) surgeries, the mean transfusion requirements for redo patients were two- to fourfold greater than the non-redo CAB patients. For non-CAB surgeries, however, the mean transfusion requirements for redo cases were two times greater. She commented: “Knowing that revision cases have a dramatic increase in blood utilization should allow anaesthesiologists to be better prepared for either emergency bleeding or haemorrhaging upon opening the chest, or more diffuse microvascular bleeding that’s harder for surgeons to control. But these patients should also be targeted ahead of surgery, when there is time to increase haemoglobin with erythropoietin or iron supplementation, or by correcting coagulopathies.”
- A study by Khalid Khan from Queen Mary University (London) and colleagues<sup>27</sup> has found that reinfusing red blood cells lost during surgery (cell salvage) did not lead on average to a statistically significant reduction in the rates of blood transfusion needed by all women undergoing caesarean section.
- A study<sup>28</sup> has found that administration of post-bypass four-factor prothrombin complex concentrate (PCC) decreases transfusions of both red blood cells and plasma in patients undergoing an orthotopic heart transplant who have existing left ventricular assist devices (LVADs). The use of the concentrate did not result in shorter lengths of stay in the ICU or hospital. It was not associated with thrombotic complications.
- Platelets are transfused to help stop severe bleeding, or else prophylactically for oncology and haematology patients. Since the mid-1980s in the US, platelets have been stored at room-temperature with constant agitation. Research suggests that cold storage of platelets preserves their haemostatic function, which may be best for actively bleeding patients. In 2013, doctors at the Mayo Clinic requested permission from the AABB and the FDA to store platelets at 1-6°C for the benefit of actively bleeding patients. In 2015, the Mayo Clinic was granted permission to store platelets at 1-6°C without agitation for no more than 3 days for patients with severe bleeding. A recent report<sup>29</sup> said the Mayo Clinic had transfused a total of 21 of 119 units stored

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<sup>23</sup> Charkes A Schiffer et al., “Platelet Transfusion for Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update”, DOI: 10.1200/JCO.2017.76.1734 *Journal of Clinical Oncology* - published online before print November 28, 2017

<sup>24</sup> assistant professor of anaesthesiology and critical care medicine at the Johns Hopkins University School of Medicine

<sup>25</sup> abstract 1879

<sup>26</sup> See for example Ludhmila A. Hajjar et al., “Transfusion Requirements After Cardiac Surgery: The TRACS Randomized Controlled Trial”, *JAMA*. 2010; 304(14):1559-1567. doi: 10.1001/jama.2010.1446; and Gavin J Murphy et al., “Liberal or Restrictive Transfusion after Cardiac Surgery”, *N Engl J Med* 2015; 372:997-1008 [March 12, 2015](https://doi.org/10.1056/NEJMoa1403612) DOI: 10.1056/NEJMoa1403612

<sup>27</sup> Khan KS, Moore PAS, Wilson MJ, Hooper R, Allard S, Wrench I, et al. (2017) “Cell salvage and donor blood transfusion during caesarean section: A pragmatic, multicentre randomised controlled trial (SALVO)”. *PLoS Med* 14(12): e1002471. <https://doi.org/10.1371/journal.pmed.1002471>

<sup>28</sup> Grace S. Kao, associate professor of medicine at Tufts University School of Medicine, in Boston, reported at the 2017 annual meeting of the Society of Cardiovascular Anesthesiologists (abstract SCA97)

<sup>29</sup> Stubbs, JR, Tran SA, Emery RL, et al. “Cold platelets for trauma-associated bleeding: regulatory approval, accreditation approval, and practice implementation—just the “tip of the iceberg.” *Transfusion* 2017; published online doi:10.1111/trf.14303

at 1-6°C, with the rest discarded due to storage time and formation of clots in the current plasma-rich storage solution. The report suggested that pathogen-reduction combined with a platelet additive solution for storage may help improve shelf life for cold-storage platelets. It said clinical trials are underway to re-examine the safety and efficacy of different storage conditions for platelets.

- Although a meta-analysis of randomized controlled trials had shown no difference for in-hospital mortality between patients receiving fresh versus stored red blood cells, it remained unclear whether red blood cells stored for the maximum time— 36 to 42 days — increased the risk for morbidity or mortality compared with storage of no longer than 7 days<sup>30</sup>. A secondary analysis<sup>31</sup> of the randomized controlled INFORM trial has investigated the effects on in-hospital morbidity or mortality from short- and long-term storage of red blood cells for transfusions. It found that transfusing red blood cells stored longer than 35 days did not increase risk for in-hospital death compared with fresh blood<sup>32</sup>.

### Recognising and treating anaemia

- A new study<sup>33</sup> has suggested that oral iron monotherapy has limited efficacy in the treatment of anaemia in patients with non-dialysis-dependent chronic kidney disease (ND-CKD).

### Other

- The American College of Cardiology (ACC) released a new expert consensus decision pathway intended to guide clinicians in the management of acute bleeding in patients treated with oral anticoagulants (OACs) and to supplement the 2017 ACC Expert Consensus Decision Procedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation (AF)<sup>34</sup>.
- PhaseBio Pharmaceuticals of Malvern, Pennsylvania, announced that it has entered an exclusive, worldwide licence agreement with MedImmune, the global biologics research and development arm of AstraZeneca, for PB2452 (formerly MEDI2452), a Phase I-ready reversal agent for ticagrelor. Ticagrelor differs from other antagonist antiplatelet agents because of its ability to bind reversibly rather than permanently to the receptor. In preclinical studies, PB2452 demonstrated high affinity and specific

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<sup>30</sup> Cooper DJ, et al. “Age of transfused cells does not affect mortality rate”, *N Engl J Med.* 2017; doi:10.1056/NEJMoa1707572.

<sup>31</sup> Conducted by Nancy Heddle, director of the transfusion research program at McMaster University, and colleagues. Heddle said: “This study ... alleviates any concern for harm that could occur when blood stored for 36 to 42 days is transfused and suggests that inventory management practices do not need to be changed.” She also drew attention to a trend which occurred among patients who received fresh blood: “Intriguing to me is the fact that so many of the randomized controlled trials have shown a trend of higher mortality when fresh blood is transfused. Perhaps our future focus should be on understanding whether fresh blood is harmful and, if so, what the mechanism could be.”

<sup>32</sup> Cook RJ, et al. “Red blood cell storage and in-hospital mortality: a secondary analysis of the INFORM randomised controlled trial”, *Lancet Haematol.* 2017;doi:10.1016/S2352-3026(17)30169-2. In an editorial by two members of the department of pathology at Johns Hopkins University School of Medicine (Gehrie EA and Tobian AAR. *Lancet Haematol.* 2017; doi:10.1016/S2352-3026(17)30179-5.), they wrote: “After so many studies, it seems that the transfusion medicine community can finally be reassured that patient outcomes are not meaningfully altered by transfusing red blood cells that are approaching their 42-day outdate.”

<sup>33</sup> Macdougall IC, Bock AH, Carrera F, et al. “[Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial](#)”. *Clin Nephrol.* 2017 Dec;88(12):301-310. doi: 10.5414/CN109198.

<sup>34</sup> Tomaselli GF, Mahaffey KW, Cuker A, et al; on behalf of the Task Force on Expert Consensus Decision Pathways. 2017 “ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulation. A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways” [published online December 1, 2017]. *J Am Coll Cardiol.* doi: 10.1016/j.jacc.2017.09.1085

binding to ticagrelor, and was shown to reverse ticagrelor-mediated inhibition of platelet aggregation and normalize bleeding.<sup>35</sup> Jonathan P. Mow, CEO of PhaseBio, said: “There is a clear need for treatments that reverse the effects of antiplatelet therapies in acute care situations, like urgent surgery or severe bleeding. PB2452’s compelling preclinical data support its potential to be a first-in-class reversal agent for ticagrelor. The profile of PB2452 and the planned development pathway fits nicely with PhaseBio’s niche focus on orphan cardiovascular disorders.” He said the company plans to initiate a Phase I study in the first half of 2018.” Cardiologist Cam Patterson<sup>36</sup> said PB2452 importantly had the potential to reduce “the current waiting period required ahead of emergency surgeries for patients on antiplatelet therapy.”

- In a challenge to current medical practice, new research<sup>37</sup> suggests the use of powerful clot-busting drugs in people with dangerous leg clots may not be routinely warranted. One approach after a deep vein thrombosis (DVT) is to use a catheter to deliver a powerful clot-busting drug, such as tissue plasminogen activator (tPA), at the site of the clot. This was thought to help prevent post-thrombotic syndrome which can, amongst other effects, make walking difficult. Researchers led by Dr. Suresh Vedantham of Washington University in St Louis concluded that this approach did not really help all patients<sup>38</sup>. Further, use of the drugs raised the risk of dangerous bleeding for patients. The researchers concluded that standard therapy (the use of blood-thinning drugs) may still be the most prudent course to take after a DVT. Vedantham said the other procedure might still be used as a "second-line" treatment when post-thrombotic syndrome is severe and doesn't respond to blood thinners. The study was funded by the US National Heart, Lung, and Blood Institute (NHLBI).

### 3. Regulatory

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

- Software to help personalize treatment of haemophilia A has received clearance from the US Food and Drug Administration (FDA).
- Shire announced it is seeking FDA approval for a new plasma manufacturing facility within its Covington, Georgia, site which is expected to increase the site’s production capacity by 30 per cent, supporting amongst other things the growth of the company’s interest in immunology<sup>39</sup>. It has filed the first of two planned submissions to the FDA, which would allow the transfer of Gammagard Liquid [Immune Globulin Infusion (Human)] 10% Solution, a replacement therapy for primary humoral

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<sup>35</sup> Buchanan A, Newton P, Pehrsson S, et al. “Structural and functional characterization of a specific antidote for ticagrelor.” *Blood*. 2015;125(22):[3484-3490](#). doi:10.1182/blood-2015-01-622928.

<sup>36</sup> Senior Vice President and Chief Operating Officer of New York-Presbyterian/Weill Cornell Medical Center

<sup>37</sup> Suresh Vedantham, “Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis”, *New England Journal of Medicine*, December 7, 2017 *N Engl J Med* 2017; 377:2240-2252, DOI: 10.1056/NEJMoa1615066

<sup>38</sup> The study of nearly 700 US patients with DVTs found that using catheters to clear the blockage with clot-busting drugs did *not* reduce the risk of post-thrombotic syndrome. The condition occurred in 47 per cent of those who had the procedure, and 48 per cent of those who did not. In people given the clot-busters, there was a benefit in terms of reductions in the severity of post-thrombotic syndrome.

<sup>39</sup> Immunology generated \$US 1.516 billion of Shire’s \$US 11.4 billion in 2016 revenues. During the third quarter of 2017, Shire reported 32 per cent growth in its Immunology franchise—the company’s fastest-growing franchise—to \$US 802 million, second in sales to haematology at \$US 916 million, helping account for a 7 per cent increase in product sales overall to \$US 3.534 billion. Shire expanded into immunology in 2016 when it [completed its \\$US 32 billion acquisition of Baxalta](#).

immunodeficiency (PI) in adults and children 2 years old and older<sup>40</sup>. The second submission will be filed during 2018 and will seek approval for albumin. Shire also expects to continue expanding its plasma collection network through its subsidiary, BioLife Plasma Services.

- The European Commission approved Shire's haemophilia A therapy Adynovi, the new longer-acting version of its long-established Advate product. It reduces the frequency of use from daily to twice per week. Adynovi (rurioctocog alfa pegol) was approved for on-demand and prophylactic use in haemophilia A patients. The drug was approved for marketing in the US in 2015 under the Adynovate brand name.
- Pharming Group submitted a supplemental Biologics License Application (BLA) to the FDA for Ruconest [Recombinant Human C1 Esterase Inhibitor/ conestat alfa] for routine prophylaxis to prevent attacks in adult and adolescent patients with hereditary angioedema (HAE)<sup>41</sup>.
- Grifols received FDA approval for its blood-based alpha-1 antitrypsin (AAT) deficiency test. Developed by Grifols subsidiary Progenika Biopharma, the test is now approved in the US for use with DNA extracted from either a blood sample or a dry blood spot. The test is already approved for use in Europe. Grifols says the test is part of its growth strategy for its Prolastin-C line of AAT augmentation and maintenance therapy products.
- The [FDA will extend its review](#) of Portola Pharmaceuticals' AndexXa biologic drug by 90 days to May 4, 2018. Initially, approval is sought for AndexXa for reversal of the anticoagulant effects of anti-coagulants apixaban and rivaroxaban in patients experiencing uncontrolled or life-threatening bleeding. The company says it has submitted additional data requested by the FDA for the ongoing ANNEXA-4 study as part of the continuing review process.
- Organovo Holdings received from the FDA orphan drug designation<sup>42</sup> for its treatment of [alpha-1 antitrypsin deficiency](#) with its 3D bioprinted liver therapeutic tissue. The deficiency is a rare inherited disorder that severely damages the lungs and liver.
- ADMA Biologics announced the filing of a Biologics License Application for its third plasma collection centre, located in Kennesaw, Georgia. Adam Grossman, ADMA's President and Chief Executive Officer, said: "This new facility is expected to increase our ability to obtain raw material source plasma internally as we plan for the growth of our commercial immunoglobulin business which includes Nabi-HB and Bivigam".
- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended<sup>43</sup> the suspension of the marketing authorizations for hydroxyethyl-starch (HES) solutions for infusion across the European Union. These products have been used for plasma volume replacement following acute blood loss. The most recent review was triggered by results from two studies indicating that HES-containing products were still being used in critically ill patients and patients with sepsis and kidney injury despite 2013 restrictions introduced to lower the risks of kidney problems and deaths.

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<sup>40</sup> HyQvia [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase], which is indicated for PI in adults, was also mentioned, along with Adynovate [Antihemophilic Factor (Recombinant), PEGylated], a human antihemophilic factor indicated in children and adults with haemophilia A (congenital factor VIII deficiency).

<sup>41</sup> The submission included data from two completed trials of Ruconest for the prophylaxis of HAE attacks: a randomized, double-blind, placebo-controlled trial and an open-label study. The two studies enrolled a total of 56 patients and showed consistent efficacy and safety results. HAE is a genetic disorder featuring spontaneous and recurrent episodes of swelling (oedema) of the skin in different parts of the body, as well as in the airways and internal organs.

<sup>42</sup> Orphan drug status conveys a seven-year period of market exclusivity for the indication, if the drug is approved.

<sup>43</sup> At its January 8-11, 2018 meeting.

#### 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.*

- Shire Plc has partnered with California-based Rani Therapeutics to develop a new way to administer a drug to treat hemophilia A. Rani has developed a technology to enable oral delivery rather than injections of peptides, proteins and therapeutic antibodies. The drug stays in the body until it enters the small intestine and transfers the medicine into the intestinal wall. The method is claimed not to expose the medication to digestive enzymes and to be pain free. Shire has made an equity investment in Rani and has the option to negotiate a licensing deal to develop and market the drug delivery approach after further studies.
- Novo Nordisk proposed acquiring Ablynx. Ablynx's lead asset is caplacizumab for the treatment of the rare bleeding disorder acquired Thrombotic Thrombocytopenic Purpura ("aTTP"). The acquisition did not proceed and by the end of January Sanofi and Ablynx had entered into a definitive agreement under which Sanofi would offer to acquire all of the outstanding ordinary shares in Ablynx.
- [Vertex Pharmaceuticals Incorporated](#) and CRISPR Therapeutics AG will co-develop and co-commercialize CTX001, a gene editing treatment, under the companies' previously announced arrangements aimed at the discovery and development of new gene editing treatments that use the CRISPR/Cas9 technology. CTX001 is the first gene-based treatment that Vertex exclusively licensed from CRISPR Therapeutics as part of that arrangement. The companies will share equally all research and development costs and profits globally for this candidate. A Clinical Trial Application has been submitted for CTX001 in a Phase I/II trial in  $\beta$ -thalassemia in Europe, and an Investigational New Drug Application will be submitted for a Phase I/II trial in sickle cell disease in the US. Preclinical data presented for CTX001 at the American Society for Hematology on December 10, 2017 showed clinically relevant increases in foetal haemoglobin and a high editing rate that support the advancement of CTX001 into these trials in 2018.
- Japanese drugmaker [Otsuka Holdings](#) has invested in startup Megakaryon, a venture that creates platelets out of induced pluripotent stem cells, and hopes to commercialize the technology by 2020. The Otsuka group is now Megakaryon's second-largest shareholder, after the public-private Innovation Network Corp. of Japan, which holds a 50 per cent-plus interest. Megakaryon intends to begin clinical trials in Japan in 2019 and build production lines capable of producing about 5,000 packs a year of iPS-derived platelets. It is also looking to expand abroad. Conventional platelets keep around four days, but those derived from iPS cells are thought to be good for two weeks.
- South Korea's Green Cross has been working with the FDA to prepare additional production-related data on its drug IVIG-SN, human normal immunoglobulin G for intravenous administration. The development comes around a year since the US drug regulator rejected Green Cross' biologics license application for IVIG-SN, asking the company to provide supplementary information on the drug's manufacturing procedures. The drug is already sold in more than 30 countries in Asia, South America and the Middle East. The US is currently the largest and the most lucrative market for IVIG-SN. It generates around \$US 6.1 billion in annual sales, accounting for around 40 percent of the global market. As part of ongoing efforts to expand its presence in North America, Green Cross has built a new plant for producing plasma-derived protein therapies in Montreal. Commercial production of intravenous

immunoglobulin and albumin is expected to start in 2020, after the facilities obtain regulatory clearance. Until then, Green Cross will produce IVIG-SN to be sold in the US at its existing FDA-compliant facilities in Ochang of North Chungcheong Province in Korea. Green Cross has recently won a contract to supply immunoglobulin worth \$US 42.9 million to Brazil. Its previous contract with Brazil was worth \$US 25.7 million.

- Chinese investor Creat Group Corp has withdrawn its application for US approval of a planned 1.3-billion-euro (\$US 1.51-billion) takeover of Biotest, the German blood plasma products maker, sending the Biotest share price falling sharply. The Committee on Foreign Investment in the United States had national security concerns about the transaction that Biotest said could not be mitigated under the planned deal structure. Creat and Biotest will file a new application. Biotest agreed in April to be taken over by Creat in a cash deal.

## 5. Specific country events

- The US National Institutes of Health (NIH) has lifted a three-year freeze in federal funding for research projects pertaining to [germs that can cause pandemics](#). The Department of Health and Human Services (HHS) released a new framework setting out how research that could develop novel and more lethal germs with pandemic potential will be funded<sup>44</sup>. NIH director Francis S. Collins in a [statement published on the Institutes' website](#) wrote: "We have a responsibility to ensure that research with infectious agents is conducted responsibly, and that we consider the potential biosafety and biosecurity risks associated with such research. I am confident that the thoughtful review process laid out by the HHS P3CO Framework will help to facilitate the safe, secure, and responsible conduct of this type of research in a manner that maximizes the benefits to public health".
- In Canada, the first author of a study on congenitally-transmitted Chagas disease<sup>45</sup> has commented that: "The key message is that persons who have immigrated to Canada from endemic Central and South American countries should be screened for Chagas disease to make sure that they are not infected, especially women of childbearing age before they get pregnant, to prevent congenital transmission in Canada". One current estimate based on immigration patterns, and seroprevalence of Chagas disease by country, suggests there are between 6000-10 000 persons in Canada with undiagnosed Chagas. Since Canadian Blood Services and Héma-Québec began screening for Chagas disease less than a decade ago, an increasing number of people with the disease have been identified<sup>46</sup>.
- Seven years of work by researchers at the Australian Red Cross Blood Service and the Department of Defence has led to the ability to freeze and thaw blood without compromising its use. The technology will mean medics can have stores of blood on

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<sup>44</sup> Researchers want to manipulate existing pathogens, ostensibly to understand their capability and contemplate countermeasures, but a series of incidents involving [avian flu](#) and anthrax raised concerns about the consequences of laboratory accidents. Any research involving influenza, severe acute respiratory syndrome (SARS), or Middle East Respiratory Syndrome (MERS) viruses was blocked.

<sup>45</sup> Plourde PJ, Kadkhoda K Ndao M. "Congenitally transmitted Chagas disease in Canada: a family cluster". *CMAJ* 2017 December 4;189: E1489-92. doi:10.1503/cmaj.170648

<sup>46</sup> Fearon MA, Scalia V, Huang M, et al. "A case of vertical transmission of Chagas disease contracted via blood transfusion in Canada". *Can J Infect Dis Med Microbiol* 2013; 24:32-4 and Mongeau-Martin G, Ndao M, Libman M, et al. "A family cluster of Chagas disease detected through selective screening of blood: a case report and brief review". *Can J Infect Dis Med Microbiol* 2015; 26:157-61.

hand to help Australian military personnel in conflict zones. Surgeon General Air Vice-Marshal Tracy Smart says the technology has added benefits on top of saving lives: "It will reduce waste as well, otherwise we have to bring the blood there and if we don't use it ... after six weeks we will just have to get rid of it. It just makes it that much easier, we don't have to rely on that logistics chain nearly as much if we've got this stuff on the shelf and we can keep it from anywhere from two to 10 years."

- In an Australian pilot, a dedicated plasma donor centre will open in Canberra in April.

## 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.*

- CSL Behring announced on 4 December during its annual R&D Investor Briefing that it will proceed with a global Phase III cardiovascular morbidity and mortality trial for plasma-derived CSL112, the company's novel apolipoprotein A-I (apoA-I) infusion therapy. The study, ApoA-I Event reducInG in Ischemic Syndromes II (AEGIS-II), will enrol over 17,000 patients from around 1,000 sites to evaluate whether CSL112 reduces cardiovascular events in high-risk patients during the critical 90 days after a heart attack<sup>47</sup>. C. Michael Gibson, Professor of Medicine at Harvard Medical School and co-lead investigator of the AEGIS-II study, said: "We are optimistic that CSL112 will offer a novel, rapid approach to reduce these events during the 90-day period when heart attack survivors are most vulnerable." Positive results from AEGIS-I were presented at the American Heart Association Scientific Sessions in New Orleans, in November 2016 and published online in *Circulation*<sup>48</sup>. AEGIS-II is expected to be completed over four years, with patient enrolment beginning in early 2018.
- Researchers from the University of Sheffield and COMSATS Institute of Information Technology, Pakistan have discovered that sugar can encourage new [blood vessel formation](#), which is crucial for wound healing<sup>49</sup>. A combination of simple and inexpensive sugar is added to a hydrogel bandage. Professor Sheila MacNeil from the Department of Materials Science and Engineering at the University of Sheffield said: "Throughout the world, people are living longer and unfortunately experiencing more non-healing skin [wounds](#) associated with age, poor blood supply and diabetes.

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<sup>47</sup> In the US each year about 800,000 people suffer an acute myocardial infarction (MI), or heart attack, and nearly one in five survivors will experience a recurrent cardiovascular event (non-fatal MI, stroke, cardiovascular death) within the following year. The majority of these recurrent events happen within the first 90 days and carry a high risk of morbidity and mortality. Early recurrent cardiovascular events are commonly caused by the rupture or erosion of cholesterol-rich plaque in the arteries. CSL112 is designed to facilitate the rapid enhancement of cholesterol efflux capacity, where cholesterol is removed from plaque and transported to the liver for elimination from the body.

<sup>48</sup> The multicentre, randomized, double-blind, placebo-controlled, dose-ranging, Phase IIb safety and proof of mechanism trial enrolled 1,258 acute MI patients. That study met its co-primary safety endpoints, showing that CSL112 does not cause significant changes in liver or kidney function and demonstrating that it is well tolerated when administered in the acute MI setting. The study also provided confirmation of CSL112's unique mechanism of action, cholesterol efflux enhancement, as demonstrated by an immediate, up to four-fold increase compared to baseline in cholesterol efflux capacity.

<sup>49</sup> Muhammad Yar et al. "Deoxy-sugar releasing biodegradable hydrogels promote angiogenesis and stimulate wound healing", *Materials Today Communications* (2017). [DOI: 10.1016/j.mtcomm.2017.10.015](https://doi.org/10.1016/j.mtcomm.2017.10.015)



These are often difficult to treat and are very expensive for healthcare systems to manage. The new skin healing technique using simple sugars, promises to aid wound healing more simply, meaning patients would need less treatment, clinicians could treat more patients and significant savings could be made by national healthcare systems."

- A retrospective chart review<sup>50</sup> comparing treatment for Kawasaki disease in two Canadian hospitals has found that the use of low-dose aspirin in conjunction with a single dose of intravenous immunoglobulin (IVIg) in children was associated with three times the risk of requiring a second IVIg dose compared with high-dose aspirin.
- Scientists at The Ottawa Hospital and the University of Ottawa found in the laboratory that the Maraba virus, or MG1, can target and destroy the type of HIV-infected cells that standard antiretroviral therapies can't reach<sup>51</sup>. The next step is to try the virus in animal models, and then humans.
- Researchers found an increased risk of developing cardiovascular disease among patients with idiopathic thrombocytopenic purpura (ITP), especially those who undergo splenectomy<sup>52</sup>.

## 7. Legal Matters

*These may include patent disputes and product liability matters.*

- Roche's haemophilia drug Hemlibra, approved in November by the FDA, has the company in a patent dispute with Shire in the US district court of Delaware. Shire's motion for a preliminary injunction is part of an ongoing case in which it contends Roche infringed a key patent to develop Hemlibra. Roche denies the allegation. The dispute emphasises Hemlibra's potential to encroach on Shire's market for older drugs<sup>53</sup>. Roche hopes to expand Hemlibra's regulatory approvals beyond inhibitor patients to include those who have not yet developed resistance.
- A Philadelphia court found Johnson & Johnson and Bayer AG liable for a patient's gastrointestinal haemorrhaging, which she attributed to the anticoagulant [Xarelto](#). The companies were ordered to pay \$US1.8 million in compensatory damages and \$US 26 million in punitive damages. This was the first loss for the companies in ongoing Xarelto litigation. In the US, Bayer and Johnson and Johnson have been named defendants in more than 2,100 lawsuits filed on behalf of patients who suffered gastrointestinal bleeds, brain haemorrhages, haemorrhagic stroke, or other serious episodes of internal bleeding while taking blood thinner Xarelto.

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<sup>50</sup> [Dhanrajani A, et al "Aspirin dose in Kawasaki disease -- the ongoing battle" \*Arthritis Care Res\* 2017; DOI:10.1002/acr.23504.](#)

<sup>51</sup> Nischal Ranganath, Teslin S Sandstrom, Stephanie C Burke Schinkel, Sandra C Côté, Jonathan B Angel, "The oncolytic virus, MG1, targets and eliminates latently HIV-1-infected cells: implications for an HIV cure." *The Journal of Infectious Diseases*, 2017; DOI: [10.1093/infdis/jix639](#)

<sup>52</sup> Chandan, J. S., Thomas, T., Lee, S., Marshall, T., Willis, B. and Nirantharakumar, K., "The Association between Idiopathic Thrombocytopenic Purpura and Cardiovascular Disease: a retrospective cohort study". *Journal of Thrombosis and Haemostasis*. Published online 3 January 2018 doi:10.1111/jth.13940

<sup>53</sup> Roche's ACE910, brand name emicizumab, market name after approval Hemlibra, presents a direct [challenge](#) to Shire's dominance in the \$US 11 billion haemophilia market. It offers subcutaneous prophylaxis for adults, children, and adolescents with haemophilia A with factor VIII inhibitors. In the HAVEN trial, the drug showed an 87 per cent reduction in bleed rate in patients who had developed resistance to standard treatment, compared with those who instead received so-called bypassing agents that are currently used as standard therapy. Market leader in the bypassing agent segment is Shire's FEIBA.

## 8. 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

- The Brazilian government suggested restrictions on the use of Sanofi's dengue vaccine which has been suspended elsewhere after the company said it could worsen the disease in some cases. Brazil's healthcare regulator Anvisa approved the vaccine for use in Brazil at the end of 2015.
- A team of Indian and South Korean researchers has devised a biofilm that could destroy larvae of *Aedes aegypti*, a mosquito that spreads dengue and chikungunya. The biofilm needs to be immersed in water collected in tanks, drums and other sources for 12 hours. During this process, the biofilm acts as a destroying agent against the vector that breeds in water.
- After reporting positive Phase II results on its chikungunya vaccine, which has been studied in 600 patients across the US, EU and South and Central America, Themis has raised new funds to continue with its development.
- Laboratory tests in cell cultures showed a new drug known as NGI-1 can shut down flaviviruses (mosquito-borne viruses like Zika, dengue and West Nile). The drug cuts off access to key proteins in mammalian cells that invading viruses rely on. By robbing them of their energy sources, the drug thwarts invasion.<sup>54</sup>
- Results from two Phase I clinical trials show an experimental Zika vaccine developed at the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health, is safe and induces an immune response in healthy adults<sup>55</sup>. NIAID is now leading an international effort to evaluate the investigational vaccine in a Phase II/IIb safety and efficacy trial.
- Takeda Pharmaceutical is testing its Zika vaccine candidate in a Phase I clinical trial.
- Researchers sought evidence in Venezuela of mother-to-child transmission of Zika through breast-feeding. They said the results of genetic testing of Zika virus isolates from a mother's breast milk and her child's urine "strongly suggest" transmission through breast-feeding<sup>56</sup>. The virus has been identified in breast milk before<sup>57</sup>.

### 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*

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<sup>54</sup> Andreas S. Puschnik, Caleb D. Marceau, Yaw Shin Ooi, Karim Majzoub, Natalie Rinis, Joseph N. Contessa, and Jan E. Carette, "A Small-Molecule Oligosaccharyltransferase Inhibitor with Pan-flaviviral Activity", *Cell Reports*, DOI: <http://dx.doi.org/10.1016/j.celrep.2017.11.054>

<sup>55</sup> M Gaudinski et al. "Zika Virus DNA Vaccine Candidates are Safe and Immunogenic in Healthy Adults". *The Lancet* DOI: 10.1016/S0140-6736(17)33105-7 (2017).

<sup>56</sup> Blohm GM, et al. "Evidence for Mother-to-Child Transmission of Zika Virus Through Breast Milk", *Clin Infect Dis*. 2017; doi:10.1093/cid/cix968. Published 30 December 2017.

<sup>57</sup> [Sotelo JR, et al. \*Emerg Infect Dis\*. 2017; doi:10.3201/eid2305.161538.](http://dx.doi.org/10.1093/cid/cix968)

*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.*

- Chinese scientists are now permitted to use recombinant chicken  $\alpha$ -interferon to prevent and treat avian influenza infection.
- An expert from the World Health Organization's collaborating centre in Australia has said that the detection of the highly pathogenic form of H7N9 avian influenza in China serves as a second warning<sup>58</sup> of pandemic potential. Researchers have identified a high level of genetic diversity in H7N9 viruses from China, including seven highly pathogenic viruses bearing four different hemagglutinin sequences. An isolate from a human carries a mutation that may make it more virulent. By the time of writing<sup>59</sup> 28 human infections with highly pathogenic H7N9 had been reported. Kanta Subbarao<sup>60</sup> wrote that concentrating control measures on only poultry flocks infected with highly pathogenic H7N9 won't solve the problem, that both forms of H7N9 need to be eradicated from avian species, and that human isolates need to be monitored very closely indeed.

## **MERS**

- As of 27 January 2018, there had been a total of 1780 laboratory-confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection in Saudi Arabia, including 724 deaths.
- A Malaysian man tested positive for MERS-CoV after his return from a pilgrimage.
- A small Phase I [clinical trial](#)<sup>61</sup> has demonstrated the safety and tolerability of a fully human polyclonal IgG antibody (SAB-301) produced from the hyperimmune plasma of transchromosomal cattle<sup>62</sup> immunized with a MERS coronavirus vaccine<sup>63</sup>. The next step for SAB-301 is to test the treatment in study populations facing MERS, preferably Saudi Arabia which continues to experience new cases. SAB-301 was developed by SAB Biotherapeutics of Sioux Falls, South Dakota.

## **Other diseases: occurrence, diagnosis, prevention and treatment**

- Oceania is thought to be the region of highest incidence of leptospirosis<sup>64</sup>, and climate change is expected to increase its prevalence throughout the region. A recent training course for health professionals, aiming to improve knowledge and skills in surveillance and control of leptospirosis, was held in Noumea involving the Pasteur Institute of New Caledonia (IPNC). Vincent Richard, Director of IPNC, said "cases are often under-recognized or misdiagnosed as dengue, malaria or influenza due to the non-specific manifestations of early-phase leptospirosis." The South Pacific Community's Deputy Director of the Public Health Division, Dr Salanieta Saketa

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<sup>58</sup> Kanta Subbarao, "Avian influenza H7N9 viruses: a rare second warning", *Cell Research* volume 28, pages 1–2 (2018) doi:10.1038/cr.2017.154

<sup>59</sup> The commentary was published online 1 December 2017

<sup>60</sup> WHO Collaborating Centre for Reference and Research on Influenza and the Department of Microbiology and Immunology, University of Melbourne, and The Peter Doherty Institute. The Institute is a joint venture between the University of Melbourne and the Royal Melbourne Hospital  
<sup>61</sup> conducted by the US National Institute of Health's National Institute of Allergy and Infectious Diseases (NIAID).

<sup>62</sup> cattle that have been genetically altered to contain human antibodies to MERS-CoV, the MERS virus. Using cattle allows researchers to harvest a large number of antibodies and is a relatively fast process, with the polyclonal therapy manufactured in about three months.

<sup>63</sup> Beigel J, et al. "Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody: a phase 1 randomised, double-blind, single-dose-escalation study." *The Lancet Infectious Diseases*. DOI: 10.1016/S1473-3099(18)30002-1 (2018).

<sup>64</sup> Leptospirosis is a bacterial infection in humans and livestock. More than 1 million human cases of leptospirosis are reported every year resulting in the loss of 60,000 lives worldwide.

explained to the trainees that, “leptospirosis is likely to be present in many Pacific Island countries and territories, but limited data is available, partly due to a lack of understanding of the disease and the complexity of the diagnostic.” The Australian Department of Foreign Affairs and Trade was a sponsor for the training course.

- A study<sup>65</sup> based on 12 years of data tracked diagnoses of [HIV infection](#) among older patients in 31 European countries. Conducted by researchers from the European Centre for Disease Prevention and Control (ECDC), it showed that the number of infections is increasing, and more targeted interventions are needed. Lara Tavischi, science officer for HIV/AIDs and bloodborne infections at ECDC, said: “Our study shows the need to ensure all ages are appropriately targeted by sexual health services. According to the literature review we have performed alongside the surveillance data analysis, sexuality is generally stigmatized in this age group, and also healthcare providers may not perceive older adults as a population in need of HIV testing services.” The study found that older Europeans were more likely than young people to contract the disease via heterosexual sex. They were more likely to be diagnosed in their home country, and they were more likely to be diagnosed late.
- Essential in averting future pandemics is the fast and accurate identification of viruses and pathogens so that health authorities know what they’re dealing with. Fusion Genomics in Vancouver focuses on gene sequencing and has selected IBM’s cloud platform to help analyze the extensive genomic data involved in its DNA/RNA capture technology. Mohammad Qadir, CEO of Fusion Genomics, said [in a press release](#): “We chose IBM over other cloud providers because of its ability to quickly scale up or down while ensuring that sensitive data is protected with one of the most secure clouds available.” The process currently takes 24 hours, but Fusion hopes to reduce that to eight in the near future — it involves extracting a pathogen from sample cells provided by a patient, using high-throughput sequencing to lay out the organism’s genetic code and then comparing that genetic footprint to all known pathogens using cloud computing and Fusion’s own machine learning software. The aim, says Qadir, is to identify correctly the signs of an outbreak before it reaches the pandemic stage. “The power of the platform is in pre-emergence,” [he said to the Financial Post](#).
- Researchers at the University of Copenhagen and Phillips Universität Marburg in Germany found that the ability of the Ebola virus to copy itself and spread through hosts can be “switched off” by manipulating a host factor enzyme. To date research has been in cell cultures, but there are plans for the technique to be tested on animals with the long-term goal of developing a drug to inhibit the host enzyme in humans.
- Researchers have found that survivors of the world’s first known Ebola outbreak still have immunity to the virus 40 years after they were infected<sup>66</sup>. Virologist Stephan Becker of the Philipps University of Marburg in Germany says that the discovery was “not completely unexpected”, because previous studies had found that survivors had immune responses to Ebola virus as long as 11 years after they were infected. But no one had previously studied immunity in the survivors of the first recorded Ebola outbreak, which occurred in 1976 near the town of Yambuku, in what is now the Democratic Republic of the Congo (DRC). Anne Rimoin, an epidemiologist at the University of California, Los Angeles (UCLA), and the lead author of the latest study, said: “Nobody even knew if these people were still alive.” Researchers found that cells from all 14 survivors they located could make antibodies in response to portions of the Ebola virus. Immune cells from four of the survivors could prevent Ebola viruses from infecting other cells in the lab, indicating that these people are still protected from new Ebola infections 40 years after they became ill with the virus.

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<sup>65</sup> Lara Tavischi et al., “New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2004–15: an analysis of surveillance data”, *The Lancet HIV*, [Volume 4, No. 11](#), e514–e521, November 2017 DOI: [http://dx.doi.org/10.1016/S2352-3018\(17\)30155-8](http://dx.doi.org/10.1016/S2352-3018(17)30155-8)

<sup>66</sup> Rimoin, AW et al., “Ebola Neutralizing Antibodies Detectable in Survivors 40 Years Post Infection.” *Journal of Infectious Diseases*, online 14 December 2017, jix584, <https://doi.org/10.1093/infdis/jix584>