# Monitoring International Trends

#### posted June 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 5 to 27. Selected highlights:

## **Products and Treatments (pp.5-12)**

#### Treating Haemophilia

- At the World Federation of Hemophilia Congress presentations included:
  - 1. New data for Bioverativ's BIVV001, an investigational recombinant factor VIII therapy
  - 2. New Phase III results for Genentech's Hemlibra
  - 3. A study that showed NovoEight remains effective after three months of storage at a temperature of 40°C
  - 4. Results from BioMarin's ongoing Phase I/II study of its investigational gene therapy, valoctocogene roxaparvovec, for severe haemophilia A
  - 5. New data on Octapharma's Nuwiq in haemophilia A
  - 6. Pre-clinical data for Octapharma's SubQ-8
  - 7. Data on surgery and bleed management from Uniqure's AMT-060 study in haemophilia B.
- At the American Society of Gene & Cell Therapy LogicBio Therapeutics presented on its gene editing treatment for haemophilia B.
- Octapharma announced patient enrolment is open for its ten-year PREVAIL clinical study of Wilate in Canadian haemophilia A patients with inhibitors.
- Catalyst Biosciences provided an update on the ongoing Phase I/II trial investigating its next generation Factor IX candidate CB 2679d/ISU304 for the treatment of severe haemophilia B.
- Catalyst said its Phase II study of daily subcutaneous injections of its next generation Factor VIIa, marzeptacog alfa (activated), for the treatment of haemophilia A or B with inhibitors, is progressing as planned.
- The coreHEM initiative published a core outcome set for clinical trials of gene therapy in haemophilia.

#### Treating beta thalassemia and sickle cell disease

- At the European Hematology Association (EHA) Congress presentations included:
  - 1. Updated results from Acceleron Pharma's ongoing Phase II trials of luspatercept in beta thalassemia
  - 2. New data from Bluebird bio's completed Phase I/II Northstar (HGB-204) study of its gene therapy in adolescents and adults with transfusion-dependent  $\beta$ -thalassemia and data from Bluebird bio's Phase III Northstar-2 (HGB-207) multicentre clinical study
  - 3. New 24-week data from patients treated with the 900 mg dose of Global Blood Therapeutics' voxelotor in the ongoing HOPE-KIDS I Study, a Phase IIa open-label study in adolescents with sickle cell disease.

# Safety and Patient Blood Management (pp12-15)

#### Appropriate Transfusion

- At the EHA Congress, Cerus Corporation reported results from SPARC, its European Phase III study evaluating the efficacy and safety of INTERCEPT-treated red blood cells in thalassemia major patients.
- Perioperative red blood cell transfusions have been associated with the development of new or progressive postoperative venous thromboembolism.
- Whole genome sequencing enables the differentiation of hundreds of blood type differences, improving the precision in matching for future blood transfusions.
- Research shows that it is now possible to tailor the antigenic profile of blood cell lines to the needs of patients for whom it is difficult or impossible to find a donor.

#### <u>Other</u>

- Researchers recommend that unfractionated heparin should not be used as an additional mode of venous thromboembolism prophylaxis when aspirin is prescribed in patients who underwent total hip arthroplasty or total knee arthroplasty.
- Research presented at the European Society of Anaesthesiology Congress examined perioperative use of aspirin in patients undergoing coronary artery bypass graft surgery.
- A study has found that extended international normalized ratio (INR) testing can be successfully and safely implemented for stable warfarin-treated patients.
- Researchers reported at the Fourth European Stroke Conference that patients with stroke caused by intracerebral haemorrhage may benefit from being given tranexamic acid.
- Research has highlighted the number of Victorian women suffering potentially dangerous levels of blood loss after childbirth.
- Case Western Reserve University scientists have developed SynthoPlate, very tiny nanoparticles that, when injected into the bloodstream, mimic how platelets cluster to stop bleeding from major trauma.
- Researchers at the University of California, San Diego have developed cell-like nanorobots powered by ultrasound that can clear bacteria and bacterial toxins from blood.
- Pharmazz reported on its interim analysis of a Phase II study of PMZ-2010 as a resuscitative agent for hypovolemic shock due to excessive blood loss.

## **Regulatory matters (pp 15-17)**

- The US Food and Drug Administration (FDA) approved a label expansion for Shire's hereditary angioedema (HAE) drug Cinryze which makes it available for preventing HAE attacks in children as young as six.
- Shire received approval from the FDA for the company's first submission for its new US plasma manufacturing facility for the production of Gammagard Liquid in Georgia.
- The FDA is expected to decide by 4th October whether to approve Roche's Hemlibra for use in adults and children with haemophilia A but without factor VIII inhibitors.
- The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of Sanofi"s Cablivi (caplacizumab) for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP).
- Alexion submitted a Biologics License Application to the FDA for approval of ALXN1210 for the treatment of patients with paroxysmal nocturnal haemoglobinuria.
- Bio Products Laboratory Limited announced that the FDA had accepted for Priority Review a supplemental Biologics License Application for its plasma-derived blood coagulation factor X concentrate.
- Japan's health ministry gave approval for cardiac surgeons to take wafer-thin sheets of tissue derived from induced pluripotent stem cells (iPS cells) and graft them onto diseased human hearts.

- CRISPR Therapeutics and Vertex Pharmaceuticals announced that the FDA had placed a clinical hold on their Investigational New Drug Application (IND) for CTX001 for the treatment of sickle cell disease.
- Bioverativ and Sangamo Therapeutics announced the FDA had accepted the Investigational New Drug (IND) application for BIVV003, a gene-edited cell therapy candidate for the treatment of people with sickle cell disease.

## Company news (p 18)

- A group of Takeda shareholders, attempting to build support to block the \$US 62 billion acquisition of London-listed Shire Plc, failed to have their proposal passed at the company's annual general meeting
- MaxCyte entered into an agreement with the US National Institutes of Health (NIH) to develop treatments for sickle cell disease.
- Internal bleeding detection device developer Saranas of Houston, Texas, raised \$US 2.8 million to support its Early Bird bleeding monitor system.
- Cerus was awarded a further \$US 15 million under its contract with the US Dept. of Health & Human Services' Biomedical Advanced Research and Development Authority.

## Country news (p19)

- Screening each US blood donation individually for Zika "had a low yield and a high cost".
- The American Society of Hematology (ASH) will collaborate with the International Society on Thrombosis and Haemostasis (ISTH), National Hemophilia Foundation (NHF), World Federation of Hemophilia (WFH), and the University of Kansas Medical Center to develop clinical practice guidelines on the diagnosis and management of von Willebrand Disease.
- The US Department of Defense (DoD) will study the PLX-R18 cell therapy product as a treatment for long-term lung injuries caused by mustard gas exposure.
- The Canadian Association for the study of the liver recommended that everyone born between 1945 and 1975 should be screened to see if they carry chronic hepatitis C.

## Research not included elsewhere (pp 19-21)

- An international research team found that healthy red blood cells assemble into a twodimensional crystal pattern whereas pathological red blood cells succumb to disorder.
- The Korea Polar Research Institute of Marine Research Placement developed the technology to freeze blood using microorganisms in the Antarctic Sea without damage such as red blood cell destruction.
- Analysis of health data found that within normal ranges, higher levels of bilirubin in the blood were associated with lower rates of heart failure, heart attack and stroke.
- Scientists have developed a synthetic tissue in which human blood stem cells remain functional for an extended period.
- A team led by scientists at the University of Cambridge has created a "genetic atlas" of such genetic links that could help reveal biomarkers for potential drugs to develop.
- Australian researchers have developed a blood test that predicts the long-term risk of a heart attack and death among those with severe coronary artery disease.
- A known risk of gene editing is that some editing may be unintentional. Two new studies show that CRISPR editing could raise the risk of targeted cells developing tumours.

## Infectious diseases (pp 21-27)

## Mosquito-borne diseases

- An article in *The New England Journal of Medicine* confirmed that people who have no prior exposure to dengue and receive Dengvaxia then have an increased risk of severe disease.
- Scientists are working to create a plant-based dengue vaccine which can be taken orally.

- Scientists have identified a molecule found on human cells and some animal cells that could be a target for drugs against chikungunya (an alphavirus) and related diseases.
- A Ugandan inventor has won the Royal Academy of Engineering's Africa Prize for developing a method of testing for malaria without drawing blood.
- In addition to circulating in blood, *Plasmodium vivax*, a parasite that causes malaria, also accumulates in bone marrow.
- Advances have been made in testing for the Zika virus.
- <u>Influenza</u>
- Research warns that the flu can jump from pigs to dogs and the diversity of flu strains found in canines is continuing to grow. The types of combinations of viruses possible in dogs represent potential risk for humans.
- University of Hong Kong scientists reported that they have found a new method that can effectively suppress the influenza virus by using virus genes and proteins.
- In February 2018, Shionogi received Japanese approval for its novel flu drug Xofluza (baloxavir marboxil). In the US an FDA priority review has made it possible for its partner Roche to receive a regulatory decision by 24 December this year.

#### Middle East respiratory syndrome coronavirus (MERS-CoV)

- From 2012 to the second week of June the World Health Organization had recorded 2,220 cases of MERS-CoV, including 790 associated deaths. Most cases had been reported from Saudi Arabia (1,844 cases, including 716 deaths).
- Inovio Pharmaceuticals announced positive Phase I results from its collaborative MERS-CoV vaccine study with INO-4700 (GLS-5300).
- Hong Kong researchers have identified two drugs that, when combined, prevented the replication of MERS-CoV in human lung tissue.
- An early-stage clinical trial to test the safety of two human monoclonal antibodies to treat people infected with MERS-CoV is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health.

<u>Ebola</u>

- At 12 June the number of confirmed and probable Ebola cases in the Democratic Republic of Congo (DRC) outbreak had reached 66 of whom 28 had died.
- Merck's vaccine was used in a "ring vaccination" strategy in which all contacts of known patients were vaccinated.
- In the 2014-16 Ebola outbreak in West Africa laboratory tests could take up to a week. In the recent DRC outbreak, there has been a new test that takes hours, not days.

#### Other diseases

- Researchers report that new discoveries about syphilis may make a vaccine possible.
- At the US Centers for Disease Control and Prevention (CDC) a new rapid test has been developed for rabies infection in animals.
- India's outbreak of Nipah virus should be monitored closely, especially if there is evidence that this is a respiratory-spread strain.
- Researchers at Ohio State University, and Utrecht University in the Netherlands are collaborating to develop understanding of the porcine delta coronavirus (PDCoV) and its possible public health implications.
- Valneva reported positive Phase I interim data for its candidate vaccine for Lyme disease, VLA15. Valneva plans to launch a Phase study II in the second half of 2018.

# **Table of Contents**

1.	<b>PRODUCTS AND TREATMENTS</b>	5
	Treating haemophilia	5
	Treating beta thalassemia and sickle cell disease	9

	Other products	11
2.	SAFETY AND PATIENT BLOOD MANAGEMENT	12
	Appropriate Transfusion	12
	Other	13
3.	<b>R</b> EGULATORY	15
4.	MARKET STRUCTURE AND COMPANY NEWS	18
5.	SPECIFIC COUNTRY EVENTS	19
6.	<b>Research not included elsewhere</b>	19
7.	INFECTIOUS DISEASES	21
	Mosquito-borne diseases	21
	Dengue and chikungunya	21
	Malaria	
	Z1Ка	22
	Influenza	23
	Seasonal influenza	
	MERS-CoV	24
	Ebola	25
	HIV26	
	Ather diseases: accurrance diagnosis prevention and treatment	77
	other diseases, occurrence, diagnosis, prevention and treatment	41

# 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**

• At the World Federation of Hemophilia (WFH) 2018 World Congress in Glasgow<sup>1</sup>, Bioverativ (now a Sanofi company) announced preliminary Phase I/IIa safety and

- Impact of pain on health-related quality of life in persons with hemophilia from the Hemophilia Utilization Group Studies Part VI (HUGS VI): USA Experience
- Distribution of rFIXFc and FIX using in vivo PET imaging analysis in non-human primatesn
- Allosteric activation of Factor IXa by an antibody binding to the protease domain: Poster #36
- (jointly with Sobi) Economic impact of recombinant factor VIII Fc fusion protein (rFVIIIFc) compared to conventional factor VIII for immune tolerance induction (ITI) of Hemophilia A patients with inhibitors: Poster #77

<sup>&</sup>lt;sup>1</sup> 20<sup>th</sup> to 24<sup>th</sup> May. Bioverativ gave six presentations (oral or poster) at the Congress, including a joint presentation with Sobi:

<sup>•</sup> BIVV001 – a novel, weekly dosing, VWF-independent, extended half-life FVIII therapy: first-inhuman safety, tolerability, and pharmacokinetics

<sup>•</sup> Comparisons in physical activity and bleed rate among severe hemophilia A and B patients on prophylactic treatment with rFVIIIFc/rFIXFc vs conventional rFVIII/rFIX: Poster #50

pharmacokinetic clinical data for BIVV001<sup>2</sup>, an investigational recombinant factor VIII therapy for people with haemophilia A. It incorporates Amunix's XTEN technology to improve circulatory half-life. Data from the ongoing EXTEN-A clinical study showed that a single low dose of BIVV001 extended the half-life of factor VIII to 37 hours, with high factor activity levels, and was generally well-tolerated. Bioverativ indicated that it is now planning to explore twice-a-month dosing with BIVV001. Bioverativ also presented real-world data demonstrating improvements in quality-of-life measures, like physical activity and joint pain, in patients treated prophylactically with Eloctate [Antihemophilic Factor (Recombinant), Fc Fusion Protein] for haemophilia A and Alprolix [Coagulation Factor IX (Recombinant), Fc Fusion Protein], for haemophilia B, when compared with short-acting factor treatments.

- At the WFH Congress, Genentech (a member of the Roche Group) presented some Phase III results for Hemlibra<sup>3</sup> (emicizumab) for the first time. Data included positive results from the pivotal HAVEN 3 study<sup>4</sup> of Hemlibra every week or every two weeks in people with haemophilia A without factor VIII inhibitors, and the pivotal HAVEN 4 study<sup>5</sup> of Hemlibra dosed every four weeks in people with haemophilia A with or without factor VIII inhibitors. The company said the data supported the promising potential of Hemlibra for all people with haemophilia A. The US Food and Drug Administration (FDA) recently granted Breakthrough Therapy Designation for Hemlibra in people with haemophilia A without factor VIII inhibitors, based on data from this study. Gallia Levy, a haematologist and associate group medical director for Genentech, said in an interview with <u>Hemophilia News Today</u>: "The ultimate goal for the development program, when we started, was to have Hemlibra approved for haemophilia A patients with and without inhibitors, with three dosing schedules: every week, every two weeks, and every four weeks. The Haven 3 and 4 trials will hopefully support that ultimate vision"<sup>6</sup>.
- All oral and poster presentations can be accessed at the WFH 2018 World Congress website here.

Bioverativ and Sobi co-hosted two scientific symposia at the Congress:

- <u>Advances in Haemophilia: Factor-Based Therapies and Long-Term Evidence versus New</u> <u>Treatment Modalities</u>. The session was chaired by Professor K. John Pasi, Barts and the London School of Medicine and Dentistry, London and was open only o healthcare practitioners.
- <u>Inhibitor Eradication: Clinician and Patient Perspectives on Safety Considerations and Long-Term Outcomes.</u> The session was chaired by Victor Blanchette, Pediatric Thrombosis and Hemostasis Program, The Hospital for Sick Children, Toronto and was open to all congress attendees.

<sup>2</sup> Bioverativ says BIVV001 (rFVIIIFc-VWF-XTEN) is the first factor VIII therapy in clinical development that is designed to overcome the half-life ceiling imposed by von Willebrand factor.

<sup>3</sup> Hemlibra was created by Chugai Pharmaceutical Co., and is being co-developed by Chugai, Roche and Genentech. It is a bispecific factor IXa- and factor X-directed antibody. It is designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood clotting process for haemophilia A patients. Hemlibra is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly.

<sup>5</sup> NCT03020160

<sup>&</sup>lt;sup>4</sup> NCT02847637

<sup>&</sup>lt;sup>6</sup> Hemlibra was developed as a once weekly self-administered injection to avoid the immunogenicity arising from standard recombinant FVIII therapy (Immunogenicity is the ability of a substance, such as an antigen, to cause an immune response in the body). Speaking about Roche's Hemlibra, Johnny Mahlangu from the University of the Witwatersrand, Johannesburg, commented: "Hemlibra is the first medicine to show superior efficacy to prior factor VIII prophylaxis, the current standard of care therapy, as demonstrated by a statistically significant reduction in treated bleeds in the HAVEN 3 study intra-patient comparison. Even with current prophylactic treatments, many people with haemophilia A continue to have bleeds that can lead to long-term joint damage, and there is a need for more treatment options."

- The WFH Congress included the report from a long-term study that showed NovoEight (turoctocog alfa) remains effective after three months of storage at a temperature of 40°C (104°F).
- The Congress also received the report<sup>7</sup> of a head-to-head pharmacokinetic study showing that adults with haemophilia B who received a single dose (50 IU/kg) of Rebinyn [Coagulation Factor IX (Recombinant), GlycoPEGylated] achieved high factor IX activity for longer than those treated with rFIXFc [Coagulation Factor IX (Recombinant), Fc Fusion Protein]. Rebinyn is the brand name in the US; in Europe nonacog beta pegol, N9-GP, is known as Refixia.
- At the WFH Congress Unique presented data on surgery and bleed management from the AMT-060 study in haemophilia B patients<sup>8</sup>.
- At the WFH Congress BioMarin Pharmaceutical in an oral presentation highlighted results from the ongoing Phase I/II study of its investigational gene therapy, valoctocogene roxaparvovec<sup>9</sup>, for people with severe haemophilia A<sup>10</sup>. The company also contributed three poster presentations<sup>11</sup>.
- At the WFH Congress Octapharma presented during a symposium new data on the benefits of Nuwiq <sup>12</sup> in patients with haemophilia A<sup>13</sup>. Octapharma presented preclinical data for SubQ-8 at another Congress symposium.<sup>14</sup>

<sup>10</sup>Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvovec (BMN 270): long-term efficacy and safety results in patients with severe haemophilia A, presented by primary investigator John Pasi, Barts and the London School of Medicine and Dentistry. The data set evaluated the long-term efficacy and safety of both the 6e13 vg/kg and 4e13 vg/kg doses of valoctocogene roxaparvovec. This presentation of data followed the publication of 1.5 years of clinical data in the New England Journal of Medicine (December 2017) and the dosing of the first participants in the Phase I/II study evaluating people with severe haemophilia A with pre-existing AAV5 antibodies and the initiation of the global GENEr8-1 and GENEr8-2 Phase III registrational program.

<sup>&</sup>lt;sup>7</sup> Escuriola-Ettingshausen C, et al, *A head-to-head pharmacokinetic comparison of N9-GP and rFIXFc in patients with haemophilia B.* This was the paradigm 7 trial.

<sup>&</sup>lt;sup>8</sup> Surgery and Bleed Management in Patients Receiving AMT-060 in a Phase I/II trial: Evaluation of the Safety of Exogenous FIX Treatment after Gene Transfer, presented by by Prof. W. Miesbach, investigator in the trial.

<sup>&</sup>lt;sup>9</sup> The US Food and Drug Administration (FDA) granted valoctocogene roxaparvovec Breakthrough Therapy Designation. To qualify for this designation, preliminary clinical evidence must show that that the drug may demonstrate substantial improvement over existing therapies. The European Medicines Agency (EMA) also granted the treatment access to its Priority Medicines (PRIME) regulatory initiative. Valoctocogene roxaparvovec has also received orphan drug designation from the FDA and EMA for the treatment of severe haemophilia A. The Orphan Drug Designation program is intended to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. BioMarin has constructed a gene therapy manufacturing facility in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced to support clinical development activities and future commercial demand. <sup>10</sup>Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvovec

<sup>&</sup>lt;sup>11</sup> Poster #180: *Feasibility study on the psychometric analysis and qualitative assessment of EQ-5D and Haemo-QoL-A*; Poster #51: *Prednisolone treatment does not regulate* 

*FVIII expression in mice treated with valactocogene roxaparvovec*; and Poster #135: *Relationship between treatment strategy and impairment in severe hemophilia* 

 <sup>&</sup>lt;sup>12</sup> Nuwiq is a 4<sup>th</sup> generation human cell line-derived recombinant FVIII (rFVIII) approved for the prevention and treatment of bleeding episodes in patients of all ages with haemophilia A.
 <sup>13</sup> The symposium, entitled *Going further to meet clinical needs: New data with Nuwiq (simoctocog*)

<sup>&</sup>lt;sup>13</sup> The symposium, entitled *Going further to meet clinical needs:* New data with Nuwiq (simoctocog alfa; human-cl rFVIII) from clinical trials and real-world experience, dealt with the challenges within the current haemophilia treatment landscape and opportunities to improve patient care. It addressed the fact that no two haemophilia A patients are the same so that an optimal treatment approach should reflect each patient's profile. Two approaches to using pharmacokinetic (PK) data to personalise prophylaxis with Nuwiq were presented in the symposium. John Pasi (The Royal London Hospital) shared a summary of the NuPreviq study, which uses an individual's PK profile to optimise the

- At the annual meeting of the American Society of Gene & Cell Therapy<sup>15</sup> LogicBio Therapeutics presented on its gene editing treatment strategy for haemophilia B<sup>16</sup>.
- Octapharma announced patient enrolment was open for the ten-year PREVAIL clinical study (NCT03344003), which will investigate the use of Wilate in Canadian haemophilia A patients with inhibitors<sup>17</sup>. A standard approach for eliminating inhibitors, immune tolerance induction (ITI), aims to make patients more tolerant to FVIII through prolonged, daily exposures to high-doses of FVIII<sup>18</sup>. Earlier studies have shown that Wilate<sup>19</sup>, which contains both FVIII and the FVIII stabilizing protein, von Willebrand Factor (VWF), has been successful in achieving ITI.
- An Italian study has examined treatment costs and quality of life for haemophilia patients who develop inhibitors<sup>20</sup>. Patients with inhibitors are more likely to have deteriorated joint structures requiring surgery, with pre-surgical treatment with NovoSeven or Feiba (in haemophilia A) necessary to control bleeds. The authors draw attention to the newly available prophylactic treatment for haemophilia A, <u>Hemlibra</u> (emicizumab, <u>Genentech</u>). They emphasised that clinical trials showed the drug improved quality of life as well as reducing bleeding rates and that its less-invasive method of delivery was a "significant improvement in care".
- A French study found that oxidation of clotting protein factor VIII (<u>FVIII</u>) increased the immune response to the replacement therapy in a mouse model of severe haemophilia A<sup>21</sup>.
- Catalyst Biosciences on 18 June provided an update on the ongoing Phase I/II trial investigating its next generation Factor IX (FIX) candidate CB 2679d/ISU304 for the treatment of severe haemophilia B. Nassim Usman, CEO of Catalyst, said: "The most recent data from the ongoing Phase I/II trial have demonstrated clinical proof of concept for subcutaneous dosing of a potent FIX as a treatment for hemophilia B. Patients in Cohort 6 of the trial were able to maintain Factor IX levels over 30 per cent which is at the upper end of mild hemophilia and higher than currently approved

treatment plan. A second approach, using WAPPS (Web Accessible Population Pharmacokinetics Program), was presented by Stacy Croteau (Boston Children's Hospital).

<sup>14</sup> The symposium was entitled *Taking FVIII into the future: The development of subcutaneous recombinant human FVIII for the treatment of haemophilia A* and reviewed the daily challenges that intravenous administration poses to people with haemophilia A. Data was presented on the uptake of SubQ-8 into the vasculature following subcutaneous administration in animal models. Christoph Kannicht (Octapharma Research & Development, Berlin) addressed the challenge of achieving sufficient FVIII bioavailability after subcutaneous infusion. Andreas Tiede (Hannover Medical School, Germany) addressed the immunogenicity risk of protein therapeutics administered subcutaneously or intravenously, concluding that there is no evidence for a difference in risk. The immunogenicity of SubQ-8 has been studied in mice and subcutaneous administration of SubQ-8 resulted in a slower development of anti-FVIII antibodies than intravenous administration of FVIII.

<sup>15</sup> Chicago, 6<sup>th</sup> to 19<sup>th</sup> May

 <sup>16</sup> <u>Promoterless Targeting without Nucleases of Hyperactive Factor IX Corrects the Bleeding Diathesis</u> <u>in Hemophilia B Mice</u>
 <sup>17</sup> Who have either recently recently developed inhibitors to a factor VIII (FVIII) concentrate, or who

<sup>17</sup> Who have either recently recently developed inhibitors to a factor VIII (FVIII) concentrate, or who have had long-term inhibitors against FVIII, or who have experienced re-occurrence of inhibitors to FVIII.

<sup>18</sup> <u>Paul Moorehead</u>, from the <u>Janeway Children's Health and Rehabilitation Centre</u> in St. John's, Newfoundland and Labrador, said in a <u>press release</u>: "The presence of a FVIII inhibitor in the body will rapidly inactivate the infused factor VIII concentrate, thus making bleed control and prevention of joint damage a clinical challenge in these patients. ITI can result in inhibitor resolution, but it can take several years to succeed."

<sup>19</sup> Wilate is a lyophilized (freeze-dried) powder to be reconstituted and injected.

<sup>20</sup> Angiolella, LS et al., "<u>The socio-economic burden of patients affected by Hemophilia with inhibitors</u>," in the <u>European Journal of Haematology</u>

<sup>&</sup>lt;sup>21</sup> Ivan Peyron et al., "Oxidation of factor VIII increases its immunogenicity in mice with severe hemophilia A", *Cellular Immunology*, Volume 325, March 2018, pp64-68 <u>https://doi.org/10.1016/j.cellimm.2018.01.008</u>

extended half-life (EHL) intravenous Factor IXs." Catalyst also said its Phase II study of daily subcutaneous injections of its next generation Factor VIIa marzeptacog alfa (activated) for the treatment of haemophilia A or B with inhibitors and Catalyst's preclinical dry age-related macular degeneration (dry AMD) programs are continuing to progress as planned.

- A study<sup>22</sup> has described in detail a 16-year follow up of young patients with haemophilia A who were treated with frequency-escalated prophylaxis. It found, amongst a number of matters of interest, that weekly Factor VIII prophylaxis reduced bleeding.
- The coreHEM<sup>23</sup> initiative published a core outcome set for clinical trials of gene therapy in haemophilia. These outcomes were developed through consensus of experts, patients, clinicians, funding bodies, health technology assessment groups, regulators, life sciences companies and others. The guidelines recommend a specific, minimum set of outcomes to include in haemophilia gene therapy clinical trials, to allow comparisons between alternative treatments. The final report, coreHEM: Developing Comparative Effectiveness Outcomes for Gene Therapy in Hemophilia, details the final core outcome set, and preliminary work on measurements and instruments identified for those outcomes. The recommended core set includes: frequency of bleeds, clotting factor activity level, duration of expression of clotting factor gene, chronic pain, utilization of healthcare system (direct costs), and mental health status $^{24}$ .

# Treating beta thalassemia<sup>25</sup> and sickle cell disease

Acceleron Pharma announced updated positive results from its ongoing Phase II trials of luspatercept<sup>26</sup>, in patients with beta thalassemia, both transfusion-dependent and non-transfusion-dependent, in an oral presentation at the 23<sup>rd</sup> Annual Congress of the European Hematology Association (EHA) in Stockholm<sup>27</sup>. Luspatercept is being developed as part of a global collaboration between Acceleron and Celgene. Habib Dable, President and CEO of Acceleron, said: "These results reinforce our

<sup>&</sup>lt;sup>22</sup> Brian M Feldman et al., "Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort", The Lancet Haematology, Volume 5, No. 6, e252-e260, June 2018, DOI: https://doi.org/10.1016/S2352-3026(18)30048-6. See "Tailored frequency-escalated primary prophylaxis for severe haemophilia A:

results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort". <sup>23</sup> coreHEM is run by the Green Park Collaborative, in partnership the National Hemophilia Foundation and McMaster University. It was funded by a grant from the National Hemophilia Foundation and with support from life science companies and academic gene therapy groups. The Green Park Collaborative is an initiative of the Center for Medical Technology Policy, a non-profit organization dedicated to improving the quality, relevance, and efficiency of clinical research. <sup>24</sup> Research from the coreHEM initiative was published in <u>Haemophilia</u>. Iorio A, Skinner MW, Clearfield E, et al.; for the coreHEM panel. "Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project". Haemophilia. 2018; 00:1-6. https://doi.org/10.1111/hae.13504

Beta thalassemia is a hereditary blood disorder that is especially prevalent in the Mediterranean, Middle East, Africa, central Asia, the Indian subcontinent and eastern Asia. It is characterized by reduced levels of haemoglobin, decreased red blood cell production and anaemia. Patients with the "major" form of the disease—also known as Cooley's anaemia—usually require regular blood transfusions and lifelong, ongoing medical care for the consequent iron overload.

<sup>&</sup>lt;sup>26</sup> Luspatercept is an erythroid (red blood cell) maturation agent for patients with a late-stage defect in the maturation of red blood cells. It is designed to repair this defect to restore-and increase-red blood cell production. As a ligand trap, luspatercept works by targeting specific transforming growth factor beta (TGF-beta) proteins involved in late-stage red blood cell maturation.

<sup>&</sup>lt;sup>27</sup> 14-17 June 2018

enthusiasm for luspatercept's potential as a safe, efficacious therapy for betathalassemia patients over the long term. We now have patients with both nontransfusion- and transfusion-dependent beta-thalassemia continuing on treatment for three years. We look forward to sharing top-line results from the BELIEVE Phase III trial over the next few months."

- At the EHA Congress, Bluebird bio presented new data from the completed Phase I/II Northstar (HGB-204) study<sup>28</sup> in adolescents and adults with transfusion-dependent  $\beta$ -thalassemia (TDT) and any genotype<sup>29</sup>. Data from the ongoing Phase III Northstar-2 (HGB-207) multicentre clinical study<sup>30</sup> of LentiGlobin investigational gene therapy in patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes were also presented<sup>31</sup>. David Davidson, chief medical officer, Bluebird bio said: "The maturing data from HGB-204 and HGB-207 suggest that one-time treatment with LentiGlobin may address the underlying genetic cause of TDT. With our refined manufacturing process, the majority of patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes are transfusion-free and producing total hemoglobin at normal or near-normal levels. We are on track to submit a marketing authorization application in the European Union later this year, and we continue to work closely with clinical investigators and regulatory authorities to complete our ongoing clinical trials and bring this important treatment option to patients as soon as possible."
- Bluebird bio also has new interim data from the HGB-206 Phase I study of LentiGlobin in severe sickle cell disease (SCD) which show the therapy can reduce the characteristic sickling of red blood cells in for patients with severe disease by 30 per cent to 60 per cent, above the threshold bluebird bio has set for a clinically relevant response. Bluebird's Chief Medical Officer, David Davidson, has said that the data suggest that LentiGlobin could convert patients with severe disease to experiencing only the less debilitating symptoms known as "sickle cell trait", with their expected lifespan extended beyond the current 44 years on average for patients with SCD.
- At the EHA Congress on 15 June Global Blood Therapeutics announced new 24week data from patients treated with the 900 mg dose of voxelotor in the ongoing HOPE-KIDS I Study, a Phase IIa open-label study in adolescents aged 6 to 17 years with sickle cell disease (SCD). These showed sustained and lasting improvements in haemoglobin levels and a reduction in clinical measures of haemolysis with voxelotor in adolescents with SCD. GBT presented five posters at the Congress<sup>32</sup>.

<sup>&</sup>lt;sup>28</sup> For more information on the Northstar study, please visit <u>www.northstarclinicalstudies.com</u> or <u>clinicaltrials.gov</u> using identifier NCT01745120.
<sup>29</sup> By France Leastelling M.D., Dr. D., Dr. Karner (Contraction)

<sup>&</sup>lt;sup>29</sup> By Franco Locatelli, M.D., Ph.D., Professor of Pediatrics, University of Pavia, Italy and Director, Department of Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome

<sup>&</sup>lt;sup>30</sup> For more information on the Northstar-2 study, please visit <u>www.northstarclinicalstudies.com</u> or <u>clinicaltrials.gov</u> using identifier NCT02906202. <sup>31</sup> LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia (TDT) in Patients with Non-

<sup>&</sup>lt;sup>31</sup> LentiGlobin Gene Therapy for Transfusion-Dependent  $\beta$ -Thalassemia (TDT) in Patients with Non- $\beta 0/\beta 0$  Genotypes: Updated Results from Northstar-2. Oral presentation by Franco Locatelli, Ospedale Pediatrico Bambino Gesù, Rome. Recent Progress in Gene Therapy for Severe Sickle Cell Disease: Updated Interim Results from a Phase 1 Clinical Study of LentiGlobin Gene Therapy was an oral presentation by Julie Kanter, Medical University of South Carolina, Charleston

<sup>&</sup>lt;sup>32</sup> Results from a Phase 2a Study (GBT440-007) Evaluating Adolescents with Sickle Cell Disease Treated with Multiple Doses of Voxelotor (GBT440), a HbS Polymerization Inhibitor (Sickle Cell Disease Abstract #PF709) ; Compassionate-Use Voxelotor (GBT440) for Patients with Severe Sickle Cell Disease (SCD) and Life-Threatening Comorbidities (Sickle Cell Disease Abstract #PF711) ; Pharmacokinetics (PK) of Voxelotor (GBT440) Using Population Pharmacokinetic (PPK) and Physiologically Based Pharmacokinetic (PBPK) Modeling in Pediatric Subjects with Sickle Cell Disease (SCD) (Sickle Cell Disease Abstract #PF713) ; Sickle Cell Disease Severity Measure: Development, Translation, and Patient Cultural Sensitivity Validation (Sickle Cell Disease Abstract #PS1455) ; and Novel Trial Design to Evaluate Oral Voxelotor for the Treatment of Sickle Cell

 Global Blood Therapeutics on 29 June announced the completion of its review of Part A of the Phase III HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization) Study. This is trialling voxelotor for the treatment of sickle cell disease (SCD). Ted W. Love, president and chief executive officer of GBT, said: "Given the well-established association between chronic hemolytic anemia and SCDrelated morbidity and mortality, we believe the clinically meaningful increase in hemoglobin and improvement in hemolysis together with the safety profile demonstrated in Part A<sup>33</sup> are highly encouraging. Based upon voxelotor's robust impact on hemolytic anemia, we believe it meets the standard for accelerated approval, and we look forward to providing further updates on our regulatory discussions as soon as possible, but no later than year-end."

# **Other products**

- A poster presentation at the EHA Congress suggested that subcutaneous romiplostim leads to favourable long-term platelet response rates among children with <u>immune thrombocytopenic purpura (ITP)<sup>34</sup></u>.
- According to interim results of a Novartis survey, called I-WISh<sup>35</sup>, presented at the EHA Congress<sup>36</sup> many patients with immune thrombocytopenia (ITP) find the disease has a negative impact on their everyday quality of life<sup>37</sup>.
- At the EHA Congress, Protalex presented data highlighting results from its European Phase Ib open-label, dose-escalation study<sup>38</sup> of PRTX-100 in adult patients with persistent/ chronic immune thrombocytopenia (ITP). Protalex's lead drug candidate PRTX-100 is a highly purified form of staphylococcal protein A. The poster<sup>39</sup> was made available on the Company's website at <u>www.protalex.com</u>. Richard J. Francovitch, Protalex's Vice President, ITP Programs, said: "We are pleased to present data demonstrating the safety and tolerability of PRTX-100 in the target ITP patient population. The increase in platelets observed in many patients is similarly positive and this data will contribute to developing an advanced clinical trial strategy".
- At the EHA Congress Protagonist Therapeutics presented clinical and preclinical Information concerning PTG-300, the Company's injectable hepcidin mimetic in development for treatment of anaemia and iron overload in rare blood disorders<sup>40</sup>.

*Disease: The Phase 3 Hemoglobin Oxygen Affinity Modulation to Inhibit Sickle Hemoglobin Polymerization (HOPE) Trial* (Sickle Cell Disease Abstract #PS1461). The EHA abstracts were made available at <u>www.ehaweb.org</u>. <sup>33</sup> The independent Data and Safety Monitoring Board (DSMB) completed its most recent clinical

<sup>&</sup>lt;sup>33</sup> The independent Data and Safety Monitoring Board (DSMB) completed its most recent clinical safety review in May 2018 and did not identify safety concerns with voxelotor at either dose level across all patients dosed in the ongoing SCD clinical program, including adult patients in the Phase III HOPE Study and adolescent patients in the HOPE-KIDS I (GBT440-007) Study. The DSMB supported the initiation of dosing in children as young as age 4.

supported the initiation of dosing in children as young as age 4. <sup>34</sup> Grainger J, et al. <u>A single-arm, open-label, long-term efficacy and safety study of subcutaneous</u> (<u>SC</u>) romiplostim in children with immune thrombocytopenia (ITP). <sup>35</sup> I-WISh is the result of a collaboration among global ITP experts, patient groups and Novartis. The

<sup>&</sup>lt;sup>35</sup> I-WISh is the result of a collaboration among global ITP experts, patient groups and Novartis. The survey involved 130 patients across 13 countries

<sup>&</sup>lt;sup>36</sup> Abstract #PF654

<sup>&</sup>lt;sup>37</sup> Fatigue was reported by two-thirds of respondents. Emotional well-being and ability to work also figured as challenging areas

<sup>&</sup>lt;sup>38</sup> the PRTX-100-203 Study

<sup>&</sup>lt;sup>39</sup> entitled A Phase 1B Open-Label Dose-Escalation Study of PRTX-100, a Highly Purified Form of Staphylococcal Protein A (SpA), in Adult Patients with Persistent/Chronic Immune Thrombocytopenia

<sup>&</sup>lt;sup>40</sup> The oral presentations were Hepcidin mimetic PTG-300 for treatment of ineffective erythropoiesis and chronic anemia in hemoglobinopathy diseases, and Hepcidin Mimetic PTG-300 induces dose-related and sustained reductions in serum iron and transferrin saturation in healthy subjects

- At the EHA Congress Rigel Pharmaceuticals gave an oral presentation<sup>41</sup> on the Phase II Stage I interim results for fostamatinib in patients with warm antibody haemolytic anaemia (AIHA)<sup>42</sup>.
- At the 78<sup>th</sup> Scientific Sessions of the American Diabetes Association<sup>43</sup> Kamada presented results from the company's Phase II trial of Alpha-1 Antitrypsin (AAT) in newly diagnosed type-1 diabetes (T1D)<sup>44</sup>. Kamada's CEO, Amir London, said: "Based on the results generated to date, and feedback received from the medical community, we believe that further studies in a larger population are warranted. We are actively seeking the appropriate partner for the continued development of our T1D program."
- A team<sup>45</sup> from Massachusetts Institute of Technology (MIT) has developed a portable, non-invasive monitor to identify a decrease in white blood cells in chemotherapy patients in one minute without drawing blood<sup>46</sup>.

# 2. Safety and patient blood management

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

# **Appropriate Transfusion**

- Results from SPARC, Cerus Corporation's European Phase III study evaluating the efficacy and safety of INTERCEPT-treated red blood cells (RBCs) in thalassemia major patients<sup>47</sup>, were presented at the 23<sup>rd</sup> Congress of European Hematology Association (EHA) in Stockholm<sup>48</sup>. Dr. Richard Benjamin, Cerus' chief medical officer, said: "Patients in need of chronic transfusions of red blood cells are at elevated risk of transfusion transmitted infections (TTI) from existing and emerging pathogens. We believe the INTERCEPT-treated RBCs have the potential to reduce the risk of TTI and improve patient care."
- Being female and receiving a blood transfusion are risk factors for *Clostridium difficile* infection (CDI) following <u>radical cystectomy</u> for bladder cancer, according to data presented at the American Urological Association 2018 annual meeting<sup>49</sup>. CDI was associated with a significantly longer hospital stay.

<sup>&</sup>lt;sup>41</sup> Fostamatinib, a spleen tyrosine kinase inhibitor, for the treatment of warm antibody hemolytic anemia: preliminary results of the SOAR Phase II, multicenter, open-label study, Abstract Code: S145 <sup>42</sup> Autoimmune haemolytic anaemia (AIHA) is a serious blood disorder in which the immune system produces antibodies that result in the destruction of the body's own red blood cells. AIHA can be a severe, debilitating disease.

severe, debilitating disease. <sup>43</sup> Orlando. Florida 22<sup>nd</sup> to 26<sup>th</sup> June

<sup>&</sup>lt;sup>44</sup> Alpha-1 Antitrypsin Therapy in Recent-Onset Type 1 Diabetes, presented by Dr. Yael Lebenthal, Director, Paediatric Endocrinology and Metabolic Disease Unit, Dana-Dwek Children's Hospital, Tel Aviv, Israel.

Aviv, Israel. <sup>45</sup> Led by Carlos Castro-González and funded by the US National Institute of Biomedical Imaging and Bioengineering (NIBIB).

<sup>&</sup>lt;sup>46</sup> Aurélien Bourquard, et al., "Non-invasive detection of severe neutropenia in chemotherapy patients by optical imaging of nailfold microcirculation". *Scientific Reports*, 2018; 8 (1) DOI: <u>10.1038/s41598-</u><u>018-23591-0</u>

<sup>&</sup>lt;sup>47</sup> Thalassemia major patients require life-long RBC transfusions.

<sup>&</sup>lt;sup>48</sup> The poster presentation was entitled, "A Randomized, Controlled, Phase III Study to Evaluate S-303/Glutathione Pathogen-Inactivated Red Blood Cells in Thalassemia Major Patients (SPARC)."

<sup>&</sup>lt;sup>49</sup> Nguyen KA, Hsiang W, Syed JS, et al. <u>Incidence, risk factors, and outcomes of C. difficile infection</u> <u>following radical cystectomy: A National Surgical Quality Improvement Program (NSQIP) study</u>. Data presented in poster format at the American Urological Association 2018 annual meeting, San Francisco, May 18–21. Abstract MP10-14.

- Whole genome sequencing enables the differentiation of hundreds of blood type differences, improving the precision in matching for future blood transfusions<sup>50</sup>.
- Perioperative red blood cell transfusions have been associated with the development • of new or progressive postoperative venous thromboembolism (VTE)<sup>51</sup>. Researchers used prospectively collected registry data from the American College of Surgery National Surgical Quality Improvement Program database to examine the correlation between perioperative red blood cell transfusions and postoperative VTE within 30 days of surgery. They included 750,937 patients, 6.3 per cent of whom received at least 1 perioperative red blood cell transfusion and 0.8 per cent of whom had postoperative VTE. Perioperative red blood cell transfusion was correlated with increased odds of VTE, deep vein thrombosis, and pulmonary embolism, independent of various possible risk factors. As the number of intraoperative and/or postoperative red blood cell transfusion events increased, there was a significant dose-response effect. The correlation between any perioperative RBC transfusion and postoperative VTE remained statistically significant across all surgical subspecialties considered. The authors commented: "These findings, if validated, should reinforce the importance of rigorous perioperative management of blood transfusion practices".
- Research from Ashley Toye and colleagues at the University of Bristol, UK, and NHS Blood and Transplant shows that it is now possible to tailor the antigenic profile of blood cell lines to the needs of patients for whom it is difficult or impossible to find a donor<sup>52</sup>.

# Other

- Researchers recommend that unfractionated heparin should not be used as an additional mode of venous thromboembolism prophylaxis when aspirin is prescribed in patients who underwent total hip arthroplasty or total knee arthroplasty<sup>53</sup>.
- A study has found that extended international normalized ratio (INR) testing can be successfully and safely implemented for stable warfarin-treated patients<sup>54</sup>.
- International research<sup>55</sup> presented at the Fourth European Stroke Conference<sup>56</sup> has found that patients with stroke caused by intracerebral haemorrhage may benefit from being given tranexamic acid, already in use to treat both blood loss from major trauma and postpartum haemorrhage. The drug was found to decrease the number of deaths in the early days following the stroke. The study also found that both the amount of bleeding in the brain and number of associated serious complications were lower in the patients who had received tranexamic acid. However, the trial did

<sup>&</sup>lt;sup>50</sup> William J Lane, et al., "Automated typing of red blood cell and platelet antigens: a whole-genome sequencing study". *The Lancet Haematology*, 2018; DOI: <u>10.1016/S2352-3026(18)30053-X</u>

 <sup>&</sup>lt;sup>51</sup> Ruchika Goel et al., "Association of Perioperative Red Blood Cell Transfusions With Venous Thromboembolism in a North American Registry", *JAMA Surg.* Published online June 13, 2018. doi:10.1001/jamasurg.2018.1565
 <sup>52</sup> Joseph Hawksworth, Ashley M Toye et al., "Enhancement of red blood cell transfusion compatibility

<sup>&</sup>lt;sup>52</sup> Joseph Hawksworth, Ashley M Toye et al., "Enhancement of red blood cell transfusion compatibility using CRISPR-mediated erythroblast gene editing", *EMBO Molecular Medicine* (2018) e8454, Published online 26.04.2018 <u>doi:10.15252/emmm.201708454</u>

<sup>&</sup>lt;sup>53</sup> Ali H Sobh et al., "The Role of Aspirin and Unfractionated Heparin Combination Therapy Immediately After Total Hip and Knee Arthroplasty", *Orthopedics*. 2018;41(3):171-176 <u>https://doi.org/10.3928/01477447-20180320-08</u>

<sup>&</sup>lt;sup>54</sup> G.D.Barnes et al., "Extended International Normalized Ratio testing intervals for warfarin-treated patients", *Journal of Thrombosis and Haemostasis,* First published: 15 May 2018 <a href="https://doi.org/10.1111/jth.14150">https://doi.org/10.1111/jth.14150</a>

<sup>&</sup>lt;sup>55</sup> Led by experts at The University of Nottingham and funded by the National Institute for Health Research (NIHR) Health Technology Assessment Program

<sup>&</sup>lt;sup>56</sup> in Gothenburg, Sweden, on May 16.

not discover a difference in the number of people who were left disabled or had died at three months after their stroke (the study's primary outcome). The researchers recommended further study on larger groups of patients to develop better understanding of potential benefits<sup>57</sup>.

- Research<sup>58</sup> from La Trobe University has highlighted the number of Victorian women • suffering potentially dangerous levels of blood loss after childbirth. The rate of postpartum haemorrhage<sup>59</sup> rose 50 per cent relative to birth rate in Victoria between 2003 and 2013. Blood transfusions, admissions to intensive care or high dependency units and hysterectomies also increased. One in five women who gave birth in Victoria between 2009 and 2013 had primary postpartum haemorrhage, while one in 71 women experienced severe primary postpartum haemorrhage<sup>60</sup>. Lead researcher Margaret Flood said:" While death is relatively rare in Australia, the impact on women and their families can be substantial." The researchers recommended maternity health providers conduct drills, establish response teams and review management protocols and documentation to address the concerning trend. Ms Flood said: "Our findings support the need for vigilance in the early postpartum period to enable clinicians to promptly detect and initiate treatment for excessive blood loss".
- Case Western Reserve University scientists have developed SynthoPlate<sup>61</sup>, very tiny nanoparticles that, when injected into the bloodstream, mimic how platelets cluster to stop bleeding from major trauma. The artificial platelets have a lipid (fatty) core with a peptide coating. The latter allows the nanoparticles to stick to a wound and recruit nearby platelets (natural and artificial) to participate in clot formation. A layer of polymers between the lipid core and the peptide coating prevents white blood cells from detecting the artificial platelets which are then able to remain in the bloodstream for two to three days.
- Researchers at the University of California, San Diego have developed cell-like • nanorobots powered by ultrasound that can clear bacteria and bacterial toxins from blood<sup>62</sup>.
- Pharmazz reported on its interim analysis of a prospective, multi-centric, randomized, • double-blind, parallel, saline controlled phase II study of PMZ-2010 (centhaquin) as a resuscitative agent for hypovolemic shock due to excessive blood loss<sup>63</sup>. It said PMZ-2010 has a unique property of increasing blood pressure and cardiac output, and decreasing vascular resistance, following haemorrhagic shock and that if approved it is likely to be a novel first-in-class resuscitative agent for the treatment of patients with hypovolemic shock.

<sup>&</sup>lt;sup>57</sup> Nikola Sprigg et al., "Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial", The Lancet, published 16 May 2018, DOI: <u>https://doi.org/10.1016/S0140-6736(18)31033-X</u> <sup>58</sup> Margaret Flood et al., "Incidence, trends and severity of primary postpartum haemorrhage in

Australia: A population-based study using Victorian Perinatal Data Collection data for 764 244 births", Australian and New Zealand Journal of Obstetrics and Gynaecology, 22 May 2018 https://doi.org/10.1111/ajo.12826

Defined as excessive blood loss in the first 24 hours after giving birth.

<sup>&</sup>lt;sup>60</sup> Women who had a caesarean delivery had the highest incidence of primary postpartum haemorrhage, while those who had a forceps delivery had the highest incidence of severe postpartum haemorrhage.

<sup>&</sup>lt;sup>61</sup> Case Western Reserve University and its spin-off, <u>Haima Therapeutics</u>, have agreed that Haima can license this artificial platelet product. Anirban Sen Gupta, a CWRU professor of biomedical engineering, is co-founder and chief scientific advisor at Haima Therapeutics. The company is currently overseeing large animal tests. The US military has provided some development funding.

<sup>&</sup>lt;sup>62</sup> Berta Esteban-Fernández de Ávila et al., <u>Hybrid biomembrane-functionalized nanorobots for</u> concurrent removal of pathogenic bacteria and toxins, Science Robotics 30 May 2018: Vol. 3, Issue 18, eaat0485 DOI: 10.1126/scirobotics.aat0485

Research<sup>64</sup> presented at the European Society of Anaesthesiology Congress<sup>65</sup> examined perioperative use of aspirin in patients undergoing coronary artery bypass graft (CABG) surgery. The study leader (Professor Sun) said: "Our study showed that aspirin was associated with similar effectiveness to other proven medical treatments in patients with cardiovascular disease, such as statins and ACE inhibitors", and concluded: "Among patients undergoing CABG, perioperative uses of aspirin were associated with significant reduction in 30-day mortality and improvement in long-term survival, without significant increased postoperative bleeding complications. We believe that all patients undergoing CABG should take aspirin before and after the procedure, except those for whom aspirin is contraindicated."

# 3. Regulatory

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

- The US Food and Drug Administration (FDA) approved a label expansion for Shire's hereditary angioedema (HAE) drug Cinryze which makes it available for preventing HAE attacks in children as young as six. This is the first treatment option approved by the FDA for such young patients. Cinryze is in the market with CSL's Haegarda. Haegarda can be injected subcutaneously, while Cinryze is given intravenously twice a week. Both drugs fend off HAE attacks, which can cause swelling of hands, feet and other areas of the body and can lead to life-threatening airway blockages.
- Shire received approval from the FDA for the company's first submission for its new US plasma manufacturing facility for the production of Gammagard Liquid [Immune Globulin Infusion (Human)]. The plant is located in Georgia. The FDA announcement permits Shire to add 30 per cent capacity to its internal plasma manufacturing network. Shire expects to make a second submission to the FDA in 2018 for development of its albumin therapy. Shire will continue expanding its plasma collection network in Georgia and elsewhere in the US through BioLife Plasma Services.
- Under priority review arrangements, the FDA is expected to decide by 4<sup>th</sup> October whether to approve Roche's Hemlibra for use in adults and children with haemophilia A but without factor VIII inhibitors. Hemlibra was approved by the FDA last November for routine bleeding prophylaxis in patients with factor VIII inhibitors. The approval followed two studies, Haven I and Haven 2. The current priority review is based on data from Haven 3, a Phase III study showing a reduction in bleeding in at least 96 per cent of patients receiving the drug.
- Having completed its \$US 4.5 billion Ablynx acquisition, Sanofi now has a European recommendation for the first product from that deal. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of Cablivi (caplacizumab) for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), a rare autoimmune blood-clotting disorder. Cablivi is a bivalent anti-vWF<sup>66</sup> nanobody. If approved, it will also be the first drug specifically indicated for aTTP. In its opinion, CHMP wrote: "The benefits with Cablivi are its ability to reduce time to platelet count response, the recurrence rate of the disease, the number of days of plasma exchange, the volume of plasma used, and the length of hospitalization and intensive care unit stay." That efficacy profile was proved in the Phase III HERCULES studies. A three-year follow-up is further

<sup>&</sup>lt;sup>64</sup> By Professor Jianzhong Sun, Director of Clinical Outcomes Research at the Department of Anesthesiology, Thomas Jefferson University and Hospitals, Philadelphia, USA, and colleagues <sup>65</sup> Euroanaesthesia, 2<sup>nd</sup> to 4<sup>th</sup> June 2018, Copenhagen

<sup>&</sup>lt;sup>66</sup> vWF=von Willebrand factor

evaluating the drug's long-term safety and efficacy. In the US the drug is under an FDA Fast Track designation for the same indication, and Sanofi plans to file for approval by the end of 2018. Cablivi will be positioned in Genzyme's new blood disorder franchise, which includes the haemophilia assets gained from Sanofi's \$US 11.6 billion buyout of Bioverativ and also its renewed agreement with <u>Alnylam</u> which gives it worldwide rights to haemophilia candidate fitusiran.

- Alexion Pharmaceuticals (ALXN) submitted a Biologics License Application to the FDA for approval of ALXN1210 for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH)<sup>67</sup>. Alexion is preparing submissions for the approval of ALXN1210 as a treatment for patients with PNH in the European Union by mid-year and in Japan before year's end. ALXN1210 has received Orphan Drug Designation for the treatment of patients with PNH in both the US and EU and for the subcutaneous treatment of patients with atypical haemolytic uremic syndrome (aHUS) in the US.
- Bio Products Laboratory Limited (BPL) announced that the FDA had accepted for filing and Priority Review a supplemental Biologics License Application for Coagadex. Coagadex, a plasma-derived blood coagulation factor X concentrate, is the only FDA-approved treatment for hereditary factor X deficiency. It was approved in 2015 for adults and children ages 12 and older with hereditary factor X deficiency for ondemand treatment and control of bleeding episodes, as well as perioperative management of bleeding in patients with mild hereditary factor X deficiency. Now the company's hope is that it can be approved for prophylactic treatment of hereditary factor X deficiency, as well as treatment in children under 12 years of age. The supplemental submission was based on results from the Phase III TEN02 prospective study of Coagadex for prophylaxis of bleeding episodes in children under 12 years old with moderate to severe hereditary factor X deficiency.
- The FDA approved Dova Pharma's New Drug Application for Doptelet (Avatrombopag) tablets to treat low blood platelet count (thrombocytopenia) in adults with chronic liver disease who are scheduled to undergo a procedure<sup>68</sup>.
- Pfizer has announced the approval of Retacrit by the FDA. The drug is a biosimilar version of Johnson & Johnson's Procrit and Amgen's Epogen. Retacrit, which is already established in Europe, is registered for the treatment of anaemia.
- The FDA has approved Mircera<sup>69</sup> (methoxy polyethylene glycol-epoetin beta; Vifor) for the treatment of anaemia associated with chronic kidney disease (CKD) in paediatric patients 5–17 years of age on haemodialysis who are converting from another erythropoiesis-stimulating agent after their haemoglobin level was stabilized. Mircera is also indicated to treat CKD-associated anaemia in adult patients.

<sup>&</sup>lt;sup>67</sup> PNH is a chronic, progressive, and potentially life-threatening ultra-rare blood disorder with an average age of onset in the thirties. It is not gender-specific and affects all races. The application was supported by data from two Phase III clinical trials in the largest population of patients with PNH ever studied: more than 440 of them, including some who were stable on Soliris (eculizumab) and switched to ALXN1210. Weight-optimized treatment with ALXN1210 every eight weeks demonstrated non-inferiority to treatment every two weeks with Soliris.

<sup>&</sup>lt;sup>68</sup> This is the first drug approved by the FDA for this use. Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA'sCenter for Drug Evaluation and Research, said: "Patients with chronic liver disease who have low platelet counts and require a procedure are at increased risk of bleeding. Doptelet was demonstrated to safely increase the platelet count. This drug may decrease or eliminate the need for platelet transfusions, which are associated with risk of infection and other adverse reactions."

<sup>&</sup>lt;sup>69</sup> Mircera is an erythropoietin receptor activator with greater activity *in vivo* and increased half-life, when compared with erythropoietin. It is formulated as a sterile, preservative-free protein solution for intravenous (adult and paediatric) or subcutaneous (adult only) administration and is supplied in single-dose prefilled syringes.

- Japan's health ministry gave approval for cardiac surgeons to take wafer-thin sheets of tissue derived from induced pluripotent stem cells (iPS cells) and graft them onto diseased human hearts. The team's leader, Yoshiki Sawa, says that the tissue sheets can help to regenerate the heart's muscle when it becomes damaged by a build-up of plaque or by a heart attack. Three people will be treated in the next year, with approval then being sought for a clinical trial with ten patients<sup>70</sup>.
- Novartis, the manufacturer of the oral thrombopoietin-receptor agonist eltrombopag (Promacta), has been granted a priority review by the FDA for a supplemental New Drug Application: for the drug to be approved for use in combination with standard immunosuppressive therapy as a frontline treatment for patients with severe aplastic anaemia<sup>71</sup>.
- On 30 May CRISPR Therapeutics and Vertex Pharmaceuticals announced that the FDA had placed a clinical hold on their Investigational New Drug Application (IND) for CTX001 for the treatment of sickle cell disease<sup>72</sup>. The companies said<sup>73</sup> they had been ordered not to proceed with the trial until they answered certain questions about the treatment. Meanwhile, the first CRISPR trial in the US, conducted by the University of Pennsylvania, continued to enrol patients. CRISPR Therapeutics said a European trial, for the inherited blood disorder beta thalassemia, involves a similar procedure, but would not be affected by the FDA order. That study is expected to begin in the second half of the year.
- Bioverativ and Sangamo Therapeutics announced the FDA had accepted the Investigational New Drug (IND) application for BIVV003, a gene-edited cell therapy candidate for the treatment of people with sickle cell disease. BIVV003 is a non-viral approach using zinc finger nuclease (ZFN) gene-editing technology. By modifying a short sequence of the BCL11A gene in a patient's red blood cell precursors, sickle haemoglobin production is suppressed, and the production of foetal haemoglobin is reactivated to levels which limit the progression of the patient's sickle cell disease. This IND enables Bioverativ to initiate a Phase I/II clinical trial to assess the safety, tolerability, and efficacy of BIVV003 in adults with sickle cell disease. Bioverativ expects to initiate several clinical sites across the US during 2018. Meanwhile, Sangamo is enrolling patients with transfusion-dependent beta thalassemia in a Phase I/II trial evaluating the safety, tolerability, and efficacy of ST-400, which uses the same gene-editing approach as BIVV003.
- The FDA approved a larger vial size (3,500 IU) of <u>CSL Behring's</u> <u>Idelvion</u> (albutrepenonacog alfa) for the treatment of <u>haemophilia B</u> patients<sup>74</sup>.

<sup>&</sup>lt;sup>70</sup> Nature 557, 619-620 (2018) doi: 10.1038/d41586-018-05278-8

<sup>&</sup>lt;sup>71</sup> Eltrombopag is currently approved for the treatment of patients with severe aplastic anaemia who have an insufficient response to immunosuppressive therapy. It is also approved for the treatment of thrombocytopenia in adult and paediatric patients aged  $\geq 1$  year with chronic immune (idiopathic) thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

<sup>&</sup>lt;sup>72</sup> The IND was submitted to the FDA in April to support the initiation of a Phase I/II US trial in adult patients with sickle cell disease. The treatment involves extracting stem cells from a patient's own bone marrow, editing them with CRISPR in the laboratory and infusing them back into the patient. The expectation is that the edited cells would then give rise to healthy red blood cells.

<sup>&</sup>lt;sup>73</sup> statement

<sup>&</sup>lt;sup>74</sup> Idelvion is supplied as a powder for intravenous use and must be reconstituted with a liquid diluent before it is injected. The larger vial size is a more convenient alternative for patients who require higher doses. The 3500 IU size had already been approved in Canada, had been recommended for marketing authorization by the <u>European Medicines Agency's</u> Committee for Medicinal Products for Human Use, and was the subject of marketing applications in Australia, Switzerland, and Japan.

# 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.

- A group of Takeda shareholders, attempting to build support to block the US\$62 billion acquisition of London-listed Shire Plc, failed to have their proposal passed at the company's annual general meeting. The proposal received about 10 per cent of votes.
- Humacyte has achieved a \$US 150 million equity investment from Fresenius Medical Care. This will see Fresenius take a 19 per cent fully diluted ownership stake in Humacyte and obtain the exclusive global rights to commercialize Humacyte's human acellular vessel Humacyl once approved by certain health authorities. A Phase III trial of Humacyl in patients with end-stage renal disease has completed enrolment with data expected later this year. The product has the potential to become part of a person's living tissue as well as last longer and produce fewer complications than synthetic vessels.
- <u>MaxCyte</u> entered into an agreement with the US National Institutes of Health (NIH)<sup>75</sup> to develop treatments for sickle cell disease. They will do so using next-generation CRISPR/Cas9-based single-nucleotide correction technologies enabled by the company's cell engineering platform<sup>76</sup>.
- Internal bleeding detection device developer Saranas of Houston, Texas, raised \$US 2.8 million to support its Early Bird bleeding monitor system<sup>77</sup>. Funds will be used to support a multi -centre clinical pilot trial of the system in the US, as well as the company's continued commercialization plan. In April Saranas said that it had <u>submitted an FDA application seeking *de novo* classification for its Early Bird bleed monitoring system.
  </u>
- Freeline Therapeutics (London), which has just raised \$US 116.9 million, has a gene therapy platform to develop adeno-associated virus (AAV) vectors that transduce liver cells and deliver a functional gene copy. Its FLT180a, a replication-incompetent AAV vector containing DNA encoding Factor IX, is in a Phase I/II trial to treat haemophilia B. Data is expected in the next year.
- <u>Cerus</u> was awarded a further \$US 15 million amendment to its contract with the US Dept. of Health & Human Services' Biomedical Advanced Research and Development Authority (BARDA), making the total potential value of its assistance deal to \$US 201 million. The expansion will support additional clinical trials of the company's INTERCEPT blood transfusion technology.

<sup>&</sup>lt;sup>75</sup> The collaboration will be with National Heart, Lung and Blood Institute, which is part of the NIH.
<sup>76</sup> On 24 May MaxCyte had announced the successful correction of a genetic mutation associated with sickle cell disease (SCD) in a patient's hematopoietic stem cells (HSCs), the type of cells that give rise to blood cells. The mutation was corrected in the haemoglobin gene using MaxCyte's non-viral cell engineering technology based on the gene editing tool CRISPR. It led to the production of functional haemoglobin in 60 percent of the patient's red blood cells. The preclinical data was presented in a poster, "<u>GMP-compliant Non-viral CRISPR-mediated Process Correcting the Sickle Cell Disease Mutation in SCD Patient CD34+ Cells Achieves 60% Wild Type Adult Hemoglobin Expression in Differentiated Erythrocytes," by Linghong Li, director of cell engineering at MaxCyte, at the American Society of Gene and Cell Therapy meeting in Chicago.</u>

<sup>&</sup>lt;sup>77</sup> The Early bird device is designed to detect bleeding from accidentally ruptured blood vessels during cardiac procedures, including transcatheter aortic valve replacements.

# 5. Specific country events

- For the first time since 1989, Venezuela reported a case of vaccine-derived Sabintype 3 poliovirus. Measles, tuberculosis, and diphtheria have also returned to Venezuela. Brazil has had a measles outbreak thought to have been imported from Venezuela.
- The New Zealand Blood Service has celebrated its twentieth anniversary.
- In the US the Agency for Healthcare Research and Quality (AHRQ) is closing down its National Guideline Clearinghouse website, owing to a lack of federal funding. ECRI Institute, an independent non-profit organization has announced plans to continue providing what is seen as a critical service to the healthcare community.
- On 19<sup>th</sup> June, World Sickle Cell Day, The <u>Sickle Cell Disease Association of America</u> (SCDAA) launched a patient-driven registry for <u>sickle cell disease</u> (SCD), called <u>Get</u> <u>Connected</u>. The registry is intended for children and adults with sickle cell disease, their families and healthcare providers, as well as advocacy groups, researchers, and people with <u>sickle cell trait</u>.
- Researchers found that screening each US blood donation individually for Zika "had a low yield and a high cost" <sup>78</sup>.
- It was announced on 21 June that The American Society of Hematology (ASH) will collaborate with the International Society on Thrombosis and Haemostasis (ISTH), National Hemophilia Foundation (NHF), World Federation of Hemophilia (WFH), and the University of Kansas Medical Center to develop clinical practice guidelines on the diagnosis and management of von Willebrand Disease (VWD).
- The US Department of Defense (DoD) will study the PLX-R18 cell therapy product as a treatment for long-term lung injuries caused by mustard gas exposure. The DoD and the US Army Medical Research Institute of Chemical Defense (USAMRICD) have entered an additional collaboration agreement with placenta-based cell therapy products developer Pluristem Therapeutics for its PLX-R18 product. Funded by the US National Institutes of Health (NIH), the new agreement is the second project selected by the defence department for this Pluristem product. The DoD is also currently studying its effectiveness as a new medical countermeasure for Acute Radiation Syndrome (ARS) prior to exposure to high levels of radiation. PLX-R18 has so far been effective in recovering the bone marrow, leading to regeneration of progenitor cells and the three blood lineages, namely blood cells, red blood cells and platelets.
- West-Ward Pharmaceuticals (a subsidiary of Hikma Pharmaceuticals) and Lupin have launched methylergonovine maleate tablets in the US. These are a semi-synthetic ergot alkaloid used to prevent and control postpartum haemorrhage, a generic equivalent to Novartis' Methergine.
- The Canadian Association for the study of the liver has recommended that everyone born between 1945 and 1975 should be screened to determine if they are carriers of chronic hepatitis C<sup>79</sup>.

# 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

 <sup>&</sup>lt;sup>78</sup> Paula Saa et al., "Investigational Testing for Zika Virus among U.S. Blood Donors" 10 May, *N Engl J Med* 2018; 378:1778-1788 DOI: 10.1056/NEJMoa1714977 see <u>The New England Journal of Medicine</u>.
 <sup>79</sup> Hemant Shah, et al., "The management of chronic hepatitis C: 2018 guideline update from the

Canadian Association for the Study of the Liver", *CMAJ* June 04, 2018 190 (22) E677-E687; DOI: https://doi.org/10.1503/cmaj.170453

from "useful tomorrow" to "at least ten years away". Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

- An international research team found that healthy red blood cells assemble into a two-dimensional crystal pattern whereas pathological red blood cells succumb to disorder<sup>80</sup>. <u>Petia Vlahovska</u><sup>81</sup> commented: "In diseases such as sickle cell anaemia, red blood cells are hardened and do not form 'crystals,' so the ordering can distinguish between healthy and diseased red blood cells and lead to a diagnostics tool to detect cardiovascular pathologies".
- Researchers have undertaken site-specific gene editing in a mouse foetus, correcting a mutation that causes a severe form of anaemia<sup>82</sup>.
- A baby who <u>received an infusion of her mother's stem cells</u> as a foetus critically ill with alpha thalassemia major was outwardly healthy when born. The stem cells were injected into the foetus's umbilical vein, allowing them to circulate through the bloodstream and develop into healthy blood cells.
- The Korea Polar Research Institute of Marine Research Placement (KOPRI), run under the Ministry of Oceans and Fisheries, developed the technology to freeze blood using microorganisms (pseudoalteromonas) in the Antarctic Sea without damage such as red blood cell destruction. Currently, blood can be refrigerated for up to 35 days. The KOPRI has finished testing the technology on animals. The KOPRI's technology makes the freezing fast.
- Analysis of health data from almost 100,000 US veterans, both with and without HIV infection, found that within normal ranges, higher levels of bilirubin<sup>83</sup> in the blood were associated with lower rates of heart failure, heart attack and stroke<sup>84</sup>. The authors concluded that the study "provides epidemiologic rationale for future studies to investigate how the antioxidant effect of bilirubin could be harnessed to reduce chronic disease morbidity risk. Future studies should explore the use of bilirubin as a biomarker for other inflammation-mediated conditions and all-cause mortality".
- Researchers found that loss of an important part of the antioxidant cell defence system decreases production of haemoglobin in the blood and aggravates spleen damage and inflammation in a mouse model of <u>sickle cell disease<sup>85</sup></u>.
- Scientists<sup>86</sup> have developed a synthetic tissue in which human blood stem cells remain functional for an extended period<sup>87</sup>.

 <sup>&</sup>lt;sup>80</sup> Zaiyi Shen et al., "Blood Crystal: Emergent Order of Red Blood Cells Under Wall-Confined Shear Flow", *Physical Review Letters*, 120(26) November 2017, DOI:10.1103/PhysRevLett.120268102
 <sup>81</sup> an associate professor of engineering sciences and applied mathematics at Northwestern University's McCormick School of Engineering and Applied Science.
 <sup>82</sup> Adela S Discional at al., "University of the science of the sci

 <sup>&</sup>lt;sup>82</sup> Adele S Ricciardi, et al., "In utero nanoparticle delivery for site-specific genome editing", published 26 June 2018, *Nature Communications* volume 9, Article number: 2481 (2018)
 <u>Original Study</u> DOI: 10.1038/s41467-018-04894-2
 <sup>83</sup> Bilirubin, a yellow-orange pigment, results from the breakdown of red blood cells and is eliminated

<sup>&</sup>lt;sup>83</sup> Bilirubin, a yellow-orange pigment, results from the breakdown of red blood cells and is eliminated by the liver.

 <sup>&</sup>lt;sup>84</sup> Vincent C. Marconi et al., "Bilirubin Is Inversely Associated With Cardiovascular Disease Among HIV-Positive and HIV-Negative Individuals in VACS (Veterans Aging Cohort Study)". *Journal of the American Heart Association*, 2018; 7 (10): e007792 DOI: <u>10.1161/JAHA.117.007792</u>
 <sup>85</sup> Xingguo Zhu, et al., "Loss of Nrf2 function exacerbates the pathophysiology of sickle cell disease in

<sup>&</sup>lt;sup>85</sup> Xingguo Zhu, et al., "Loss of Nrf2 function exacerbates the pathophysiology of sickle cell disease in a transgenic mouse model", *Blood* 2018 131:558-562; doi: https://doi.org/10.1182/blood-2017-10-810531

<sup>&</sup>lt;sup>86</sup> from the University of Basel, University Hospital Basel, and ETH Zurich

<sup>&</sup>lt;sup>87</sup> Paul E. Bourgine et al, "In vitro biomimetic engineering of a human hematopoietic niche with functional properties", *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1805440115

- Researchers have created <u>artificial human prion</u> material in the laboratory<sup>88</sup>.
- A team led by scientists at the University of Cambridge has created a "genetic atlas" of such genetic links that could help reveal biomarkers for potential drugs to develop<sup>89</sup>.
- Australian researchers have developed a blood test that predicts the long-term risk of a heart attack and death among those with severe coronary artery disease. Researchers at Austin Health and the University of Melbourne found patients with coronary artery disease were more likely to die or have a heart attack over the next 10 years if they have a high level of an enzyme called ACE2<sup>90</sup>. Researcher Dr Louise Burrell said: "Future studies are planned to investigate if intensification of the medical treatment in those patients will reduce the risk of death. If this were the case, the ACE2 blood test could be offered to all patients with coronary artery disease as part of their risk assessment."
- An acknowledged risk of gene editing is that some editing may be unintentional. Two
  new studies show that CRISPR editing could <u>raise the risk</u> of targeted cells
  developing tumours<sup>91</sup>.

# 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**

#### Dengue and chikungunya

• An article in *The New England Journal of Medicine* confirmed that people who have no prior exposure to dengue and receive Dengvaxia then have an increased risk of

<sup>&</sup>lt;sup>88</sup> The experiment is <u>detailed</u> here: Chae Kim et al., "Artificial strain of human prions created in vitro". *Nature Communications* volume 9, Article number: 2166 (2018)

 <sup>&</sup>lt;sup>89</sup> Benjamin B Sun, Adam S Butterworth et al., "Genomic atlas of the human plasma proteome", <u>Nature</u> volume 558, pages73–79 (2018)
 <sup>90</sup> The research was <u>published</u> here: Jay Ramchand et al, "Elevated plasma angiotensin converting

<sup>&</sup>lt;sup>90</sup> The research was <u>published</u> here: Jay Ramchand et al, "Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease". Published: June 13, 2018 *PLOS One* <u>https://doi.org/10.1371/journal.pone.0198144</u>

<sup>&</sup>lt;sup>91</sup> Emma Haapaniemi, et al., "CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response", published 11 June 2018, *Nature Medicine* volume 24, pages 927–930 (2018), <u>LINK</u> and Robert J Ihry et al., "p53 inhibits CRISPR–Cas9 engineering in human pluripotent stem cells", published 11 June 2018. *Nature Medicine* volume 24, pages 939–946 (2018) <u>LINK</u>

severe disease. The vaccine is protective in people who have been previously exposed to the dengue virus<sup>92</sup>.

- A research team from the University of Nottingham Malaysia is working to create a
  plant-based dengue vaccine which can be taken orally. Professor Sandy Loh said that
  the team has so far verified that an immune response was created using the plantbased vaccine in an animal model and the antibodies produced could neutralise the
  dengue virus.
- Recent blood-feeding experiments with *Aedes aegypti* mosquitoes showed that people with asymptomatic and pre-symptomatic dengue infections are capable of infecting mosquitoes<sup>93</sup>.
- Dengue was reported in the Far North Queensland town of Mareeba for the first time in fifteen years.
- A team led by scientists at Washington University School of Medicine in St. Louis has identified a molecule found on human cells and some animal cells that could be a target for drugs against chikungunya, an alphavirus, and related diseases<sup>94</sup>. The research was funded in part by the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health.

#### Malaria

- A Ugandan inventor has won the Royal Academy of Engineering's prestigious Africa Prize for developing a method of testing for malaria without drawing blood. Brian Gitta and his team developed a low-cost, reusable invention which clips onto a patient's finger and provides a result within one minute on a mobile phone. A red beam shining through the patient's finger detects changes in shape, colour and concentration of his or her red blood cells.
- |A study has shown that, in addition to circulating in blood, *Plasmodium vivax*, a parasite that causes malaria, also accumulates in bone marrow<sup>95</sup>.
- Researchers from Louisiana State University say<sup>96</sup> they've discovered that a small number of lizard species in New Guinea have green blood—tinted by bile pigment that may wipe out <u>malaria parasites</u>.

#### Zika

• Brazilian researchers have developed a new artificial intelligence platform that can detect the Zika virus even after the 30-day acute phase of the disease. The platform uses mass spectroscopy to detect metabolic disease markers in blood<sup>97</sup>.

<sup>&</sup>lt;sup>92</sup> Saranya Sridhar et al, "Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy", New England Journal of Medicine, 13 June 2018. <u>Sridhar S, et al. N Engl J Med. 2018</u> doi:10.1056NEJMoa1800820.

Linda Rosenbaum, "Trolleyology and the Dengue Vaccine Dilemma", New England Journal of Medicine, 13 June 2018. <u>Rosenbaum L. N Engl J Med. 2018;doi:10.1056/NEJMp1804094</u>.

See also: Scott B. Halstead, "Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age", *Vaccine*, Volume 35, Issue 47, 7 November 2017, Pages 6355-6358. <u>Halstead</u> <u>SB. Vaccine</u>. 2017;doi:10.1016/j.vaccine.2017.09.089.

Scott B. Halstead and Phillip K. Russell, "Protective and immunological behavior of chimeric yellow fever dengue vaccine", *Vaccine*, Volume 34, Issue 14, 29 March 2016, Pages 1643-1647. <u>Halstead SB, Russell PK. *Vaccine*. 2016;doi:10.1016/j.vaccine.2016.02.004.</u> <sup>93</sup> Quirine A. ten Bosch et al., "Contributions from the silent majority dominate dengue virus

<sup>&</sup>lt;sup>93</sup> Quirine A. ten Bosch et al., "Contributions from the silent majority dominate dengue virus transmission", in *PLOS Pathogens*, Published: May 3, 2018 https://doi.org/10.1371/journal.ppat.1006965

<sup>&</sup>lt;sup>94</sup> R Zhang *et al.* "Mxra8 is a receptor for multiple arthritogenic alphaviruses". *Nature* DOI: 10.1038/s41586-018-0121-3 (2018).

<sup>&</sup>lt;sup>95</sup> Nicanor Obaldia et al., "Bone Marrow Is a Major Parasite Reservoir in Plasmodium vivax Infection". *mBio*, 2018; 9 (3): e00625-18 DOI: <u>10.1128/mBio.00625-18</u>

<sup>&</sup>lt;sup>96</sup> Zachary B. Rodriguez, et al., "Multiple origins of green blood in New Guinea lizards", *Science Advances*, 16 May 2018: Vol. 4, no. 5, eaao5017 DOI: 10.1126 sciadv.aao5017

- Scientists from Australia, Brazil and the US have developed a fast and effective tool to detect Zika virus<sup>98</sup>.
- 2) Children and adolescents in Puerto Rico who provided specimens in the form of serum shortly after the onset of Zika symptoms had a higher viral load than those who provided urine specimens later<sup>99</sup>.

### 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.

#### Seasonal influenza

- In the US, the Centers for Disease Control and Prevention (CDC) has tracked flurelated paediatric deaths since 2004. During the 2009 H1N1 pandemic, 358 paediatric deaths were recorded, in 2011-12, 37 paediatric deaths from flu complications were reported. By mid-June this year there had been 172 paediatric deaths for the 2017-18 flu season. Eighty per cent of the children had not received a flu vaccination this season. Sixty per cent of the children died after being admitted to hospital, the rest at home or in emergency departments. Most died within a week of symptom onset. Half the deaths were in otherwise healthy children.
- Of flu specimens tested globally between May 28 and Jun 10, 71.1 per cent were influenza A and 28.9 per cent were influenza B. Of subtyped influenza A viruses, 72.8 per cent were 2009 H1N1 and 27.2 per cent were H3N2. Of the characterized influenza B viruses, 74 per cent belonged to the Yamagata lineage<sup>100</sup>.
- In June the National Drug Administration of China approved the country's first fourstrain flu vaccine, adding protection against the Yamagata lineage of Influenza B. The other three strains are H1N1 and H3N2 of Influenza A and the Victoria lineage of Influenza B.
- Research, published in the journal <u>mBio</u>, warns that the flu can jump from pigs to dogs and the diversity of flu strains found in canines is continuing to grow<sup>101</sup>. Dr. Adolfo García-Sastre of the Icahn School of Medicine at Mount Sinai said in a <u>press</u> release: "In our study, what we have found is another set of viruses that come from swine that are originally avian in origin, and now they are jumping into dogs and have been re-assorted with other viruses in dogs. "We now have H1N1, H3N2, and H3N8 in dogs. The diversity in dogs has increased so much now that the type of combinations of viruses that can be created in dogs represent potential risk for a virus to jump to a dog into a human." He said vaccination for dogs could be considered.

<sup>&</sup>lt;sup>97</sup> see <u>Frontiers in Bioengineering and Biotechnology</u>

Carlos Fernando Odir Rodrigues Mel0, et al., "A Machine Learning Application Based in Random Forest for Integrating Mass Spectrometry-Based Metabolomic Data: A Simple Screening Method for Patients With Zika Virus", *Front. Bioeng. Biotechnol.*, 11 April 2018 | https://doi.org/10.3389/fbioe.2018.00031

<sup>&</sup>lt;sup>98</sup> Jill N Fernandes et al., "Rapid, noninvasive detection of Zika virus in *Aedes aegypti* mosquitoes by near-infrared spectroscopy", *Science Advances* 23 May 2018: Vol. 4, no. 5, eaat0496 DOI: 10.1126/sciadv.aat0496

 <sup>&</sup>lt;sup>99</sup> Jennifer S.Read et al., "Symptomatic Zika Virus Infection in Infants, Children, and Adolescents Living in Puerto Rico", *JAMA Pediatr.* 2018;172(7):686-693. doi:10.1001/jamapediatrics.2018.0870
 <sup>100</sup> Jun 25 WHO global flu update

<sup>&</sup>lt;sup>101</sup> Ying Chen at al., "Emergence and Evolution of Novel Reassortant Influenza A Viruses in Canines in Southern China", 5 June 2018 mBio vol. 9 no. 3 e00909-18 doi: 10.1128/mBio.00909-18

- University of Hong Kong scientists reported in the journal Nature Communications
  that they have found a new method that can effectively suppress the influenza virus
  by using virus genes and proteins. Researchers from the microbiology department
  designed fragments which can interfere with the correct replication of the influenza
  virus genome and hence inhibit the growth of influenza virus. They found the method
  effective for both prevention and treatment in laboratory mice.
- In February 2018, Shionogi received Japanese approval for its novel flu drug Xofluza (baloxavir marboxil)<sup>102</sup>. In the US an FDA priority review has made it possible for its partner Roche<sup>103</sup> to receive a regulatory decision by 24 December this year. Xofluza acts at a different stage in the virus replication from other anti-flu medications. It inhibits the cap-dependent endonuclease protein, which flu viruses rely upon to replicate in the human body. Xofluza is given only once, instead of five days at twice-daily dosing for Tamiflu. A Phase III study showed that the drug suppressed the flu virus level in just 24 hours, compared with Tamiflu's 72 hours<sup>104</sup>. The drug is designed to target oseltamivir-resistant strains and avian flu viruses including H5N1 and H7N9.

#### Avian influenza

- In mid-June, Bangladesh and Nepal reported new highly pathogenic H5N1 avian influenza outbreaks in poultry, as South Africa detected H5N8 again at a commercial farm.
- Jonathan Van-Tam, deputy chief medical officer for England with special responsibility for pandemic planning, told *The Daily Telegraph* that the H7N9 strain of flu had proven its ability to transmit from birds to humans. It is only three mutations away from spreading from human to human and is being monitored as a potential candidate to cause a worldwide pandemic.

### **MERS-CoV**

- The World Health Organization's (WHO's) Eastern Mediterranean office reported twelve new MERS-CoV cases globally in May, eleven of them in Saudi Arabia and one in the United Arab Emirates. This included seven new MERS cases in a household cluster in Najran, Saudi Arabia, bringing the total in the household to eight. The initial patient drank raw camel milk before becoming symptomatic, but the other seven patients reported no contact with camels. This was one of two household clusters in the first half of this year, during which there were also two small hospital clusters totalling ten patients.
- From 2012 to the second week of June WHO had recorded 2,220 cases of MERS, including 790 associated deaths. Most cases had been reported from Saudi Arabia (1,844 cases, including 716 deaths).
- Tests on camels, llamas and alpacas in Israel, which has not reported any human MERS-CoV cases, found that although the animals may have been exposed to the virus in the past, there wasn't any sign of active circulation during the study period<sup>105</sup>. The scientists examined blood and nasal swabs collected from 2012 to 2017.

<sup>&</sup>lt;sup>102</sup> for the treatment of influenza A and B in adult and paediatric patients

 <sup>&</sup>lt;sup>103</sup> Roche's interest is through Genentech, which obtained commercial rights to Xofluza outside Japan and Taiwan through a <u>licensing deal</u> with developer Shionogi in 2016. See Jun 25 Genentech <u>press</u>
 <sup>104</sup> Clinical studies have found that baloxavir marboxil and oseltamivir similarly reduce symptom

<sup>&</sup>lt;sup>104</sup> Clinical studies have found that baloxavir marboxil and oseltamivir similarly reduce symptom duration and fever, but that the new drug more quickly stopped viral shedding. A Phase III trial of the drug is in progress in people ages 12 and older who are at high risk of flu complications.

<sup>&</sup>lt;sup>105</sup> Dan David et al, "Middle East respiratory syndrome coronavirus specific antibodies in naturally exposed Israeli llamas, alpacas and camels", *One Health*, <u>Volume 5</u>, June 2018, Pages 65-68 <u>https://doi.org/10.1016/j.onehlt.2018.05.002</u>

- Researchers at the Li Ka Shing Faculty of Medicine of the University of Hong Kong have identified two drugs that, when combined, prevented the replication of Middle East respiratory syndrome coronavirus in human lung tissue<sup>106</sup>.
- Inovio Pharmaceuticals on 27 June announced positive Phase I results from its collaborative MERS vaccine study with INO-4700 (GLS-5300). Results for INO-4700, which is being co-developed by Inovio and GeneOne Life Science, showed that the drug was well-tolerated and demonstrated overall high levels of antibody responses in 95 per cent of trial participants, while also generating broad-based T cell responses in nearly 90 per cent of participants. The Phase I, open-label, dose-escalation trial was conducted in partnership with the Walter Reed Army Institute of Research in Maryland<sup>107</sup>.
- An early-stage clinical trial to test the safety of two human monoclonal antibodies (mAbs) to treat people infected with Middle East respiratory syndrome coronavirus (MERS-CoV) is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health, and is funded in part by the Biomedical Advanced Research and Development Authority, part of the Office of the Assistant Secretary for Preparedness and Response, Department Health and Human Services. The mAbs, REGN3048 and REGN3051, were discovered and developed by scientists at the biotechnology company Regeneron, headquartered in Tarrytown, New York. Subsequently, researchers at Regeneron and the University of Maryland School of Medicine demonstrated the ability of the antibodies to neutralize MERS-CoV in a mouse model of MERS. The new NIAID trial is the first to test these mAbs in people<sup>108</sup>.

### **Ebola**

- At 12 June the number of confirmed and probable Ebola cases in the Democratic Republic of Congo (DRC) outbreak had reached 66 of whom 28 had died.
- On 29 June the Republic's Health Ministry said that as of June 28, all people who were potentially exposed to the Ebola virus had finished a 21-day incubation period. More than 3,200 people had been vaccinated.
- Merck's vaccine was used in a "ring vaccination" strategy in which all contacts of known patients were vaccinated.
- Johnson and Johnson are still working on their Ebola vaccine. This uses a two-part vaccine which is less convenient but could maybe last longer. This vaccine has been tested on 5,000 volunteers in 11 trials and has confirmed both its safety and its ability to generate an immune response.
- In the 2014-16 Ebola outbreak in West Africa laboratory tests could take up to a week. In the recent DRC outbreak, there has been a new test that takes hours, not days.
- A research team based at the University of Pennsylvania School of Medicine exposed benign viruses containing the Ebola virus glycoprotein to physiologic concentrations of semen amyloids before infecting different human cell types, including macrophages, which are the prime target of the Ebola virus. Infection levels with the amyloid-

<sup>&</sup>lt;sup>106</sup> See : Li et al. (2018) Effect of Interferon Alpha and Cyclosporine Treatment Separately and in Combination on Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Replication in a Human *in-vitro* and *ex-vivo* Culture Model. Published in *Antiviral Research*, Volume 155, July 2018, Pages 89-96. <u>https://doi.org/10.1016/j.antiviral.2018.05.007</u>

<sup>&</sup>lt;sup>107</sup> In April of this year, The Coalition for Epidemic Preparedness Innovations (CEPI) awarded Inovio \$US 56 million to develop a MERS vaccine through Phase II trials. The MERS vaccine is expected to be available for stockpile as soon as possible for emergency use. The CEPI funding also included support for Inovio's vaccine against the Lassa virus.

<sup>&</sup>lt;sup>108</sup> Information about the trial is available at <u>clinicaltrials.gov</u>, using the identifier <u>NCT03301090</u>. The trial is funded through contract HHSN272201500005I.

exposed viruses were found to be 20 times higher than with the virus alone<sup>109</sup>. Coauthors from the US Army Medical Research Institute of Infectious Diseases (USAMRIID) found similar results in experiments involving live Ebola in a biosafety level 4 lab in Frederick, Maryland. Stephen Bart, postdoctoral fellow at the University of Pennsylvania, said in a press release from the School of Medicine: "Given the potential for sexual transmission to spark new Ebola infection chains, we feel we have found relevant factors that may be important targets for inhibiting the spread of Ebola."

#### HIV

- A team led by Professor Chen Zhiwei at Hong Kong University's AIDS Institute says its new research<sup>110</sup>, tested on mice, indicates a functional cure<sup>111</sup> for HIV. They said their discovery shows the new antibody can help control the virus and eliminate infected cells. It could be used for both prevention and treatment<sup>112</sup>. They said the antibody would be able to treat all varieties of HIV. The team hopes to have the antibody in clinical trials within three to five years.
- Researchers found<sup>113</sup> that increasing use in Australia of the HIV prevention drug Truvada was linked to declining rates of HIV infection, but also to decreased use of condoms among gay and bisexual men.
- An experimental vaccine based on the structure of a vulnerable site on HIV elicited antibodies in mice, guinea pigs and monkeys neutralized dozens of HIV strains<sup>114</sup>. The findings were reported by researchers at the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health, and their colleagues. NIAID Director Anthony S. Fauci said: "NIH scientists have used their detailed knowledge of the structure of HIV to find an unusual site of vulnerability on the virus and design a novel and potentially powerful vaccine. This elegant study is a potentially important step forward in the ongoing quest to develop a safe and effective HIV vaccine." A preliminary human trial is expected to begin in the second half of 2019.

 <sup>&</sup>lt;sup>109</sup> Stephen M Bart, et al., "Enhancement of Ebola virus infection by seminal amyloid fibrils",
 *Proceedings of the National Academies of Sciences (PNAS), published ahead of print, 25 June 2018.* <u>https://doi.org/10.1073/pnas.1721646115</u> Jun 25 *PNAS* <u>abstract</u>
 <sup>110</sup> Xilin Wu, "Tandem bispecific neutralizing antibody eliminates HIV-1 infection in humanized mice", *J*

 <sup>&</sup>lt;sup>110</sup> Xilin Wu, "Tandem bispecific neutralizing antibody eliminates HIV-1 infection in humanized mice", *J Clin Invest.* 2018;<u>128(6)</u>:2239-2251. <u>https://doi.org/10.1172/JCI96764</u>.
 <sup>111</sup> The team leader said a "functional cure" meant the virus level would be so low as to be

<sup>&</sup>lt;sup>111</sup> The team leader said a "functional cure" meant the virus level would be so low as to be undetectable in the body, as long as patients kept taking injections of the antibody, perhaps on a quarterly basis, or less frequently. The new antibody would have a significantly longer half-life than current treatments, making it easier than the daily treatment most HIV-infected patients face.
<sup>112</sup> The U.N.-supported AIDS Data Hub says about 850,000 people in China are infected with HIV.

<sup>&</sup>lt;sup>113</sup> Martin Holt et al., "Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013–17", published: 06 June 2018, *The Lancet HIV*, DOI: https://doi.org/10.1016/S2352-3018(18)30072-9

<sup>&</sup>lt;sup>114</sup> K Xu *et al.* "Epitope-based vaccine design yields fusion peptide-directed antibodies that neutralize diverse strains of HIV-1". *Nature Medicine* DOI: 10.1038/s41591-018-0042-6 (2018)

# Other diseases: occurrence, diagnosis, prevention and treatment

- Researchers from the University of Connecticut report<sup>115</sup> that new discoveries in relation to syphilis may make a vaccine possible.
- Research shows that foreign-born women of reproductive age living in the US reported significantly lower rates of hepatitis B virus screening and vaccination compared with women of the same age born in the US<sup>116</sup>. The researchers see the critical issue as the prevention of perinatal transmission. The US Advisory Committee on Immunization Practices recently updated its recommendations on this issue.
- At the US Centers for Disease Control and Prevention (CDC) a new rapid test has been developed for rabies infection in animals. This could mean fewer postexposure prophylaxis injections for people exposed to animals that may be rabid<sup>117</sup>.
- India's outbreak of Nipah virus should be monitored closely, especially if there is evidence that this is a respiratory-spread strain. Nipah virus is currently on WHO list of <u>Blueprint priority diseases</u> due to their public health risk and lack of countermeasures were they to cause an epidemic. There is no vaccine against Nipah virus, although the <u>Coalition for Epidemic Preparedness Innovations</u> has awarded <u>a</u> <u>grant of up to \$US 25 million</u> to Profectus BioSciences and Emergent BioSolutions for the development of such a vaccine.
- Researchers at Ohio State University, and Utrecht University in the Netherlands are collaborating to develop understanding of the porcine delta coronavirus (PDCoV) and its possible public health implications. Laboratory studies found that the virus readily infects human, chicken and cat cells. Beyond the laboratory, there are no known cases of humans contracting the virus; but its ability to bind to receptors in human cells is concerning as this raises the threat of an outbreak in human populations.
- Valneva reported positive Phase I interim data for its candidate vaccine for Lyme disease, VLA15. Valneva plans to launch a Phase study II in the second half of 2018. It will be carried out in Lyme-endemic regions in the US and Europe. It will include subjects previously infected with the bacterium. A few subjects in Phase I will be reenrolled to receive a booster dose.

<sup>&</sup>lt;sup>115</sup> Sanjiv Kumar et al., "Sequence Variation of Rare Outer Membrane Protein β-Barrel Domains in Clinical Strains Provides Insights into the Evolution of *Treponema pallidum* subsp. *pallidum*, the Syphilis Spirochete", *mBio*, vol. 9 no.3 e01006-18 doi: 10.1128/mBio.01006-18 <u>mBio</u>. <sup>116</sup> Schillie S, et al. *MMWR*. 2018:doi:10.15585/mmwr.rr6701a1.

<sup>&</sup>lt;sup>117</sup> Crystal M. Gigante, et al., "Multi-site evaluation of the LN34 pan-lyssavirus real-time RT-PCR assay for post-mortem rabies diagnostics", *PLOS One* May 16, 2018 https://doi.org/10.1371/journal.pone.0197074 Abstract