Monitoring International Trends

posted September-October 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 17. Highlights are listed below:

Products and Treatments

Treating Haemophilia

- The results of the multi centre, open-label, randomized phase III HAVEN 3 study published in *The New England Journal of Medicine* showed that emicizumab prophylaxis significantly reduced the bleeding rate among people 12 and older with haemophilia A without factor VIII inhibitors.
- Sangamo Therapeutics and Pfizer are developing a potential gene therapy, SB-525, for haemophilia A. Preliminary results of a Phase I/ II clinical trial suggest it is tolerated well by patients, and dose-dependent responses are positive.
- Aptevo Therapeutics says it "is intensifying its focus on additional market expansion opportunities for Ixinity both within and outside the US market." Ixinity is its recombinant factor IX.
- CSL Behring's haemophilia B treatment Idelvion (albutrepenonacog alfa) is now available in a 3500 IU vial size.
- A review found one-third of European and North American haemophilia patients are overweight or obese, meaning increased joint dysfunction and chronic pain.

Other products

- Sancilio Pharmaceuticals' said a Phase II trial of its drug Altemia (SC411) showed promising results in treating children with sickle cell disease.
- Imara presented an update on its Phase II clinical trial of IMR-687 for sickle cell disease at the Annual Sickle Cell and Thalassaemia Conference.
- A report suggests that a subset of children with autism spectrum disorder, who have an immune abnormality, may benefit from intravenous immunoglobulin treatment.
- A study found that a patient's baseline level of thrombopoietin may help to predict response to treatment with eltrombopag or romiplostim for immune thrombocytopenia (ITP).
- A study has found that Rigel Pharmaceuticals' fostamatinib produces clinically meaningful responses in adults with immune thrombocytopenia.
- Positive topline results were announced by argenx from its Phase II proof-of-concept clinical trial of efgartigimod (ARGX-113) in adult primary immune thrombocytopenia (ITP) patients.
- New data suggests that in patients with chronic liver disease and thrombocytopenia, avatrombopag (Doptelet, Dova Pharmaceuticals) is superior to placebo in increasing platelet count and reducing the proportion of patients requiring a platelet transfusion or rescue procedure for bleeding.
- BioCryst Pharmaceuticals, Inc. announced initial results from the ZENITH-1 trial of its drug BCX7353 in hereditary angioedema (HAE).

Safety and Patient Blood Management

Appropriate Transfusion

- Cerus Corporation gave a number of presentations at the 2018 AABB Annual Meeting. Topics included the economic impact of implementing pathogen-reduced platelets at blood centres and hospitals, additional data reinforcing the clinical utility of pathogen-reduced platelets, and results from SPARC, Cerus' European Phase III study of pathogen-reduced red blood cells.
- A study found that intravenous oxytocin for the third stage of labour results in less frequent severe postpartum haemorrhage, reduced need for blood transfusion, and reduced admission to a high dependency unit compared with intramuscular oxytocin, and without excess side effects.
- A study has found that hidden blood loss in the perioperative period should not be ignored in patients undergoing hip hemiarthroplasty for displaced femoral neck fractures, because it is a significant portion of total blood loss.

Other

- A study has found that survivors of sepsis are at increased risk for stroke and heart attack for four weeks after leaving the hospital.
- Whether low molecular weight heparin is started pre-operatively or post-operatively does not change mortality or risk of reoperation in patients with hip fractures treated with osteosynthesis, according to a recent study.

Regulatory matters

- The US Food and Drug Administration (FDA) approved Jivi (damoctocog alfa pegol/ formerly BAY94-9027) for the routine prophylactic treatment of haemophilia A in previously-treated adults and adolescents 12 years of age or older. The FDA also approved Jivi for on-demand treatment and perioperative management of bleeding in the same group of patients.
- Japan's Ministry of Health, Labour and Welfare approved Jivi (BAY94-9027) to prevent bleeds in adults and adolescents 12 years of age or older. As in the US, the drug had been approved in Japan for on-demand treatment and bleeding management during surgeries.
- Shire announced that Japan's Ministry of Health, Labour and Welfare had granted manufacturing and marketing authorisation for Firazyr (icatibant injection), for the acute treatment of hereditary angioedema attacks in adults.
- Shire has filed its second submission to the FDA for its new plasma manufacturing facility in Georgia. This submission is for the manufacturing of Flexbumin 25% [Albumin (Human)], USP, 25% Solution.
- The FDA has granted orphan drug designation to Adverum Biotechnologies' gene therapy candidate, ADVM-053, for the treatment of hereditary angioedema.
- The FDA has granted fast track designation to Protagonist Therapeutics' candidate PTG-300 for the treatment of chronic anaemia due to ineffective erythropoiesis in patients with beta-thalassemia.
- The European Commission has authorised Sanofi's Cablivi (caplacizumab) as the first therapeutic specifically indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura.
- Dova Pharmaceuticals filed a marketing application with the FDA seeking approval to use Doptelet (avatrombopag) to treat adults with immune thrombocytopenia who have not responded adequately to prior therapy.
- The European Medicines Agency (EMA) has accepted for consideration Rigel's Marketing Authorization Application, seeking approval for Tavalisse (fostamatinib disodium hexahydrate) for the treatment of chronic immune thrombocytopenia in adult patients.

- Progenika Biopharma S.A., a Grifols company, received FDA approval for its ID CORE XT, a molecular-based assay to help determine blood donor and patient non-ABO red blood cell types.
- The FDA has approved Grifols' new formulation of immune globulin (GamaSTAN) for hepatitis A virus and measles post-exposure prophylaxis. The new formulation uses a caprylate chromatography process which removes prions.
- The FDA has approved updated labelling for Coagadex (coagulation factor X [human] from Bio Products Laboratory. The drug is now indicated, in the US, for adults and children with hereditary Factor X deficiency, for:
    1. routine prophylaxis to reduce the frequency of bleeding episodes
    2. on-demand treatment and control of bleeding episodes
    3. perioperative management of bleeding in patients with mild and moderate hereditary Factor X deficiency
- The Japanese government approved a plan for blood transfusions to include platelets created from artificially derived stem cells for patients with intractable diseases.
- The FDA has approved revised labelling for Johnson & Johnson's blood thinner Xarelto (rivaroxaban tablets) to include a claim of reduced risk of major cardiovascular events, in combination with aspirin, in patients with chronic coronary artery disease or peripheral artery disease.
- The FDA lifted its clinical hold on Vertex and CRISPR Therapeutics' gene-edited stem cell therapy for sickle cell disease.
- The FDA granted Orphan Drug status for Omeros' OMS721 for the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy.

Company news

- The US Federal Trade Commission approved a final order that settles charges that Grifols' acquisition of Biotest US Corporation would be anticompetitive and violate federal antitrust law.
- Japan's FairTrade Commission approved Takeda's $US 62 billion acquisition of Shire.
- Shire announced the acquisition of sanaplasma AG, a source plasma collection company headquartered in Switzerland.
- Bayer is laying off 227 workers at a California manufacturing plant as it restructures to improve the efficiency of its haemophilia business.
- Five years after retiring as CEO of CSL, Brian McNamee has taken over as Chairman.

Country news

- In the US, the Office of Naval Research has developed the Far-Forward Blood Storage Container, a rugged, climate-controlled box that keeps blood fresh for up to three days.
- London's Air Ambulance is trialling red blood cells and plasma given in a single transfusion for critical patients suffering major injury.
- In Ghana, Mirasol Pathogen Reduction Technology has been made available with the support of the Japanese international Cooperation Agency.
- The Australian Commission on Safety and Quality in Health Care has launched its clinical care standard for the prevention of venous thromboembolism.
- The UK inquiry into what has been called the "contaminated blood scandal" has begun.

Research not included elsewhere

- Researchers say they have found evidence that blood deposits in the brain may not require a blood vessel tear.
- New research suggests that older adults with atrial fibrillation experience faster global cognitive decline and have an increased risk for dementia compared with people of similar age who do not have atrial fibrillation.

- Researchers at the Massachusetts Institute of Technology have found how to help blood cells regenerate faster.
- Researchers from the University of Alabama believe “Trojan Horse" enzyme delivery could potentially treat thrombotic thrombocytopenic purpura.
- Scientists have developed a new therapeutic to deliver oxygen to tissues which are hypoxic.

Infectious diseases

- Containing the ebola outbreak in a war zone in the Democratic Republic of Congo has proved difficult.
- A farm in Scotland has had one of its cows die from mad cow disease.
- The FDA approved Genentech’s Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.
- An investigational vaccine designed to protect people from both Lassa fever and rabies showed promise in preclinical testing.

Table of Contents

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

- The results of the multi centre, open-label, randomized phase III HAVEN 3 study published in *The New England Journal of Medicine*[1] showed that emicizumab prophylaxis significantly reduced the bleeding rate among people 12 and older with haemophilia A without factor VIII inhibitors. Emicizumab (the Roche drug Hemlibra) is a bispecific humanized monoclonal antibody delivered by subcutaneous injection. It was approved by the US Food and Drug Administration (FDA) for routine prophylaxis to prevent or reduce frequency of bleeding episodes among adults and children with hemophilia A with factor VIII inhibitors. In June the FDA granted priority review to emicizumab for treatment of adults and children with haemophilia A without factor VIII inhibitors based on these study results.
- The study found patients receiving either 1.5mg/kg weekly or 30mg/kg fortnightly emicizumab had annualised bleeding rates of 1.5 or 1.3 events respectively compared with 38.2 events with no prophylaxis. Associate Professor Huyen Tran, director of the Ronald Sawers Haemophilia Centre at the Alfred Hospital, Melbourne, said that in the Australian context of care, relevant comparisons for emicizumab were not with patients on placebo, but with patients who had been receiving factor VIII concentrate prophylaxis. He cautioned: "The only unknown is the potential synergistic effects or interactions if we had to give Factor VIII concentrate for breakthrough bleeds"[2]. He said oversight of the use of emicizumab through haemophilia centres would be important. "This is a rare disease with significant complications and when it comes to rare disease, you need collective knowledge. We don't want this drug to be placed on the PBS [so that] any doctors can prescribe it."
- Catalyst Biosciences announced the peer-reviewed publication[3] of previously reported data from the Phase 1 trial of marzeptacog alfa (activated) (MarzAA) in individuals with haemophilia A or B with or without inhibitors.
- Sangamo Therapeutics and Pfizer are developing a potential gene therapy, SB-525, for haemophilia A. Preliminary results of a Phase I/II clinical trial suggest it is tolerated well by patients, and dose-dependent responses are positive. The therapy consists of fragments of genetic material containing the information to produce factor VIII.
- In late October Aptevo Therapeutics provided an update on its growth strategy for Ixinity [Coagulation Factor IX (Recombinant)]. Mike Adelman, Senior Vice President, Commercial Operations, said: "We reached an important milestone in our Ixinity program this year as Ixinity became cash flow positive for our organization. With our manufacturing process stabilized and our commercial efforts in the US now solidly on track, Aptevo is intensifying its focus on additional market expansion opportunities for Ixinity both within and outside the US market." For a start, Aptevo hopes to attract new users by beginning process development and manufacturing enabling activities

[1] Johnny Mahlangu, "Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors", August 30, 2018 *N Engl J Med* 2018; 379:811-822 https://www.nejm.org/doi/full/10.1056/NEJMoa1803550

[2] In event of, say, a car accident.

[3] R A Gruppo et al., "Phase 1, single-dose escalating study of marzeptacog alfa (activated), a recombinant factor VIIa variant, in patients with severe hemophilia," *Journal of Thrombosis and Haemostasis*, 27 August 2018 https://doi.org/10.1111/jth.14247 The paper details the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending intravenous bolus doses of MarzAA.

to support the launch of a new 3000 IU vial assay for Ixinity, to be available in mid-2019. The company has also initiated plans to commence a Phase IV study of Ixinity in about 20 patients under 12 years of age for potential label expansion to a paediatric setting. Previously reported data showed that the product appeared to be safe and well tolerated in this subject population and were comparable to the results from the overall patient population studied in the pivotal clinical trial.

- CSL Behring announced that its haemophilia B treatment Idelvion (albutrepenonacog alfa), approved for up to 14-day dosing, is now available in a 3500 IU vial size[4].
- A recent review[5] found around one-third of European and North American haemophilia patients are overweight or obese, meaning increased joint dysfunction and chronic pain.
- A case series has suggested that single or combination therapy with bypassing agents used for haemophilia A patients with inhibitors can also be suitable treatment options for children with haemophilia B with factor IX inhibitors.[6]

Treating beta thalassemia and sickle cell disease

- Glycoprotein acetylation (GlycA), a biomarker for conditions linked to vascular inflammation, has been found[7] to be an unreliable indicator of inflammation in patients with sickle cell disease (SCD).
- Sancilio Pharmaceuticals' said a Phase II clinical trial of its oral drug Altemia (SC411)[8] showed promising results in treating children with sickle cell disease (SCD)[9]. The randomized, double-blind, placebo-controlled, parallel-group SCOT trial (NCT02973360) evaluated the clinical safety and tolerability of three doses of Altemia in children with SCD compared with a placebo group.
- On 24 October Imara presented an update on its sickle cell disease program at the Annual Sickle Cell and Thalassaemia Conference (ASCAT) held in London. Dr Biree Andemariam, founding director of the New England Sickle Cell Institute (NESCI) at the University of Connecticut Health Center, and a principal investigator of Imara's Phase II clinical trial of IMR-687, provided a summary of the ongoing clinical trial in a presentation titled, *IMR-687: A Potent PDE9i in Phase 2 for Sickle Cell Disease*. IMR-687 is a highly selective, potent small molecule inhibitor of PDE9, to treat patients with sickle cell disease by reducing both red blood cell sickling and blockage of blood vessels.

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[4] It was already available in four sizes of single-use vials: 250 IU, 500 IU, 1000 IU, 2000 IU. Idelvion is a freeze-dried powder which needs to be reconstituted with sterile water before injection into a vein. The larger size is more convenient for patients requiring high doses.

[5] J Wilding et al., "Obesity in the global haemophilia population: prevalence, implications and expert opinions for weight management," *Obesity Reviews*, 6 September 2018 https://doi.org/10.1111/obr.12746

[6] Asaf Arie Barg et al., "Alternative treatment options for pediatric hemophilia B patients with high-responding inhibitors: A thrombin generation-guided study," in the journal *Pediatric Blood & Cancer*. 19 September 2018 https://doi.org/10.1002/pbc.27381

[7] Julie K Weisman et al., "GlycA is not a useful biomarker of inflammation in sickle cell disease," First published in the *International Journal of Laboratory Hematology*, 27 August 2018. https://doi.org/10.1111/ijlh.12907

[8] In sickle cell disease, the membranes from red blood cells lack a fat molecule called docosahexaenoic acid (DHA), that has antioxidant, anti-inflammatory, anti-adhesion[8] and anti-aggregation[8] functions. Altemia contains a DHA formulation developed by Sancilio's delivery platform, Advanced Lipid Technology, which enhances DHA bioavailability.

[9] Ahmed A Daak et al., "Double-blind, randomized, multicenter phase 2 study of SC411 in children with sickle cell disease (SCOT trial)," in *Blood Advances* 2018 2:1969-1979; doi: https://doi.org/10.1182/bloodadvances.2018021444

Other products

- Richard E. Frye[10] and colleagues reported[11] that a subset of children with autism spectrum disorder (ASD), who have an immune abnormality, may benefit from intravenous immunoglobulin (IVIg) treatment.
- A retrospective study[12] found that a patient's baseline level of thrombopoietin may help to predict whether he or she will respond to treatment with eltrombopag or romiplostim for immune thrombocytopenia (ITP).
- A study[13] has found that Rigel Pharmaceuticals' fostamatinib produces clinically meaningful responses in adults with immune thrombocytopenia (ITP).
- Positive topline results were announced by argenx from its Phase II proof-of-concept clinical trial of efgartigimod (ARGX-113) in adult primary immune thrombocytopenia (ITP) patients. The company said the Phase II data showed a favourable safety and tolerability profile consistent with the Phase I healthy volunteer trial and the Phase II proof-of-concept trial in generalized myasthenia gravis. Patients treated with efgartigimod exhibited clinically meaningful platelet count improvements across doses and ITP patient classifications, including newly diagnosed, persistent and chronic.
- New data suggests that in patients with chronic liver disease and thrombocytopenia, avatrombopag (Doptelet, Dova Pharmaceuticals) is superior to placebo in increasing platelet count and reducing the proportion of patients requiring a platelet transfusion or rescue procedure for bleeding. In a poster presented at the American College of Gastroenterology (ACG) meeting in Philadelphia, efficacy associated with the primary endpoint was generally similar regardless of BMI category in both patient cohorts who took avatrombopag, and similarly superior to placebo in meeting the secondary endpoint. In May, avatrombopag received first-of-its-kind approval from the FDA for its indication to treat thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a medical or dental procedure. The most common adverse events associated with avatrombopag were fever, abdominal pain, nausea, headache, fatigue, and oedema in the hands or feet.
- BioCryst Pharmaceuticals, Inc. announced initial results from the ZENITH-1 trial of its drug BCX7353 in hereditary angioedema (HAE). The results showed that a single 750 mg oral dose of was well tolerated and superior to placebo ($p<0.05$) against the majority of efficacy endpoints evaluated in HAE patients suffering an acute attack. BCX7353 is a novel oral plasma kallikrein inhibitor being developed for both prophylactic and acute treatment of HAE attacks.

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[10] Chief of Neurodevelopmental Disorders at the Barrow Neurological Institute at Phoenix Children's Hospital

[11] Kathleen Connery et al., "Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism" , Transl Psychiatry. 2018; 8: 148. Published online 2018 Aug 10. doi: 10.1038/s41398-018-0214-7

[12] Al-Samkari H, Kuter DJ. Thrombopoietin level predicts response to treatment with eltrombopag and romiplostim in immune thrombocytopenia [published online September 6, 2018]. *Am J Hematol.* doi:10.1002/ajh.25275. Of the 67 patients studied, there were 11 who did not achieve overall response when treated with the maximum doses of eltrombopag or romiplostim. With the addition of prednisone to their regimens, 9 of these patients achieved an overall response. The researchers noted that one of the limitations to the study was its retrospective nature, and that a prospective study "would be helpful."

[13] James Bussel et al, "Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials", *American Journal of Hematology,* Volume93, Issue7 July 2018 Pages 921-930 https://doi.org/10.1002/ajh.25125

2. Safety and patient blood management

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

Appropriate Transfusion

- Cerus Corporation gave a number of presentations at the 2018 AABB Annual Meeting in Boston on 13th to 16th October. Topics included the economic impact of implementing pathogen-reduced platelets at blood centres and hospitals, additional data reinforcing the clinical utility of pathogen-reduced platelets, and results from SPARC, Cerus' European Phase III study of pathogen-reduced red blood cells. Dr. Richard Benjamin, Cerus chief medical officer, said the company's presentations underscored the growing interest in pathogen-reduction and increasing awareness of the risks associated with transfusion transmitted infections[14].
- A study[15] funded by Trinity College, University of Dublin and Coombe Women and Infants University Hospital found that intravenous oxytocin for the third stage of labour results in less frequent severe postpartum haemorrhage, reduced need for blood transfusion, and reduced admission to a high dependency unit compared with intramuscular oxytocin, and without excess side effects.
- A study[16] has found that hidden blood loss in the perioperative period should not be ignored in patients undergoing hip hemiarthroplasty for displaced femoral neck fractures, because it is a significant portion of total blood loss. Some categories of patients have a greater amount of hidden blood loss than others-women, patients with higher ASA[17] classification and perioperative gastrointestinal bleeding/ulcer, patients who were administered general anaesthesia, or patients who underwent transfusion. The authors suggested that having a correct understanding of hidden blood loss may help surgeons improve clinical assessment capabilities and ensure patients' safety.

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[14] There was a Cerus Industry Workshop, *The Role of Pathogen Reduction in Reversing Blood Component Commoditization*. A full list of Cerus related abstracts can be found at https://intercept-usa.com/aabb2018. Presentations included:

- *Neonatal and Pediatric Platelet Transfusion: Unresolved Clinical Issues*. The session included a presentation on the incidences of transfusion reactions following transfusion of conventional and pathogen-reduced platelets.
- *Platelet Availability and Economic Impact of Bacterial Risk Reduction Strategies at US Blood Centers*
- *Complete Inactivation of Mers-Coronavirus in Human Apheresis Platelets with Amotosalen and Ultraviolet a Light Treatment;*
- *Bacterial Mitigation Strategies for Platelet Concentrates: The Transfusion Service Perspective*. The session included a presentation discussing the impact of implementing pathogen reduction on utilization, transfusion reactions, and hospital finances.
- *Transfusion of Pathogen Reduced Vs. Conventional Platelets in Pediatric Patients: An Assessment of Platelet Usage and Incidence of Transfusion Reactions*
- *Simultaneous Inactivation of Co-Circulating Arboviruses through Nucleic Acid Crosslinking*
- *Optimization of Pathogen Reduction Compatibility at 13 Blood Centers*
- *Platelet Availability and Economic Impact of Bacterial Risk Reduction Strategies at US Hospitals*

[15] D J Murphy et al., "Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: randomised controlled trial", *BMJ* 2018; 362 doi: https://doi.org/10.1136/bmj.k3546

[16] Wei-jun Guo et al, "Hidden blood loss and its risk factors after hip hemiarthroplasty for displaced femoral neck fractures: a cross-sectional study", Clinical Interventions in Aging » Volume 13 Pages 1639—1645 https://doi.org/10.2147/CIA.S174196

[17] American Society of Anesthesiologists

Other

- A study[18] has found that the Theraflex UV-Platelets and Theraflex MB-Plasma pathogen inactivation systems effectively reduce Ebola and MERS-CoV infectivity in platelet concentrates and plasma, respectively.
- Verseon announced on 13 September that it had received ethics committee approval and acknowledgement from Australia'sTherapeutic Goods Administration for the phase I clinical trial of VE-1902, the first clinical candidate from its precision oral anticoagulants (PROACs). In preclinical testing, these demonstrated efficacy with low bleeding, potentially making them suitable for stroke prevention in atrial fibrillation or prolonged co-administration with antiplatelet drugs for patients with coronary artery disease.
- A study[19] has found that survivors of sepsis are at increased risk for stroke and heart attack for four weeks after leaving the hospital.
- Whether low molecular weight heparin is started pre-operatively or post-operatively does not change mortality or risk of reoperation in patients with hip fractures treated with osteosynthesis, according to a recent study[20].

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 Jivi (damoctocog alfa pegol/ formerly BAY94-9027) for the routine prophylactic treatment of haemophilia A in previously-treated adults and adolescents 12 years of age or older[21]. The FDA also approved Jivi for on-demand treatment and perioperative management of bleeding in the same group of patients. Jivi is a long acting PEGylated recombinant human Factor VIII (rFVIII) replacement therapy. The recommended initial prophylactic regimen for Jivi is twice weekly, with the possible options subsequently to dose every five days and further adjust to less or more frequent dosing based on individual bleeding episodes.
- Japan's Ministry of Health, Labour and Welfare approved Jivi (BAY94-9027) to prevent bleeds in adults and adolescents 12 years of age or older. As in the US, the drug had been approved in Japan for on-demand treatment and bleeding management during surgeries.
- Shire plc announced that the Ministry of Health, Labour and Welfare in Japan had granted manufacturing and marketing authorisation for Firazyr (icatibant injection), for the acute treatment of hereditary angioedema attacks in adults.
- Shire has filed its second submission to the FDA for its new plasma manufacturing facility near Covington, Georgia. This second submission is for the manufacturing of Flexbumin 25% [Albumin (Human)], USP, 25% Solution, a treatment primarily used

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[18] Markus Eickman et al., Inactivation of Ebola virus and Middle East respiratory syndrome coronavirus in platelet concentrates and plasma by ultraviolet C light and methylene blue plus visible light, respectively. *Transfusion,*2018 Sep 6;58(9):2202-2207. Epub May 6. http://dx.doi.org/10.1111/trf.14652

[19] Chih-Cheng Lai et al., "Susceptible period for cardiovascular complications in patients recovering from sepsis", CMAJ September 10, 2018 190 (36) E1062-E1069; DOI: https://doi.org/10.1503/cmaj.171284

[20] Leer-Salvesen S, et al., "Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register". Published October 17, 2018. *Acta Orthop*. 2018:17;1-7. DOI:10.1080/17453674.2018.1519101

[21] FDA approval has been based on results from the phase II/III PROTECT VIII study. Bayer also submitted a marketing authorization application for Jivi in the European Union.

as plasma-volume replacement therapy in immune disorders, trauma and other critical conditions. The Georgia facility has already received its first FDA approval, to manufacture Gammagard Liquid [Immune Globulin Infusion (Human)] 10% Solution.

- The FDA has granted orphan drug designation to Adverum Biotechnologies' gene therapy candidate, ADVM-053, for the treatment of hereditary angioedema[22] (HAE). The gene therapy is intended to be a single-administration treatment to prevent breakthrough attacks by sustaining the release of C1 esterase inhibitor protein. The company was encouraged by preclinical studies in mice.
- The FDA has granted fast track designation to Protagonist Therapeutics' candidate PTG-300 for the treatment of chronic anaemia due to ineffective erythropoiesis in patients with beta-thalassemia. The drug is an injectable hepcidin mimetic that has also been granted Orphan Drug Designation by the FDA for beta-thalassemia.
- The European Commission has authorised Sanofi's Cablivi (caplacizumab) as the first therapeutic specifically indicated for the treatment of adults experiencing an episode of the rare clotting disorder acquired thrombotic thrombocytopenic purpura (aTTP).
- Dova Pharmaceuticals filed a marketing application with the FDA seeking approval to use Doptelet (avatrombopag) to treat adults with immune thrombocytopenia who have not responded adequately to prior therapy. The FDA in May approved the drug for adults with thrombocytopenia with chronic liver disease who are scheduled to undergo a procedure.
- The European Medicines Agency (EMA) has accepted for consideration Rigel's Marketing Authorization Application (MAA), seeking approval for Tavalisse (fostamatinib disodium hexahydrate) for the treatment of chronic immune thrombocytopenia (ITP) in adult patients. Rigel expects a decision from the Committee on Human Medicinal Products in the fourth quarter of 2019. The company plans to partner with third parties to commercialize Tavalisse in Europe and Asia. In April 2018, Tavalisse was approved by the FDA and was commercially launched in the US in May.
- Progenika Biopharma S.A., a Grifols company, received FDA approval for its ID CORE XT, a molecular-based assay to help determine blood donor and patient non-ABO red blood cell types. It is the second molecular assay approved by the FDA for use in transfusion medicine[23], and the first to report genotypes as final results. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, said: "The approval of the ID CORE XT Test can streamline blood compatibility testing and provides an additional alternative to testing blood with antisera. "We know that DNA testing holds great promise – to provide more informative, accurate and cost-effective methods that can enhance patient care."
- The FDA has approved Grifols' new formulation of immune globulin (GamaSTAN) for hepatitis A virus and measles post-exposure prophylaxis[24]. The new formulation

[22] HAE is associated with recurrent episodes of severe swelling of the skin and mucous membranes, often on the face and around the lips but it can occur much more widely. It can be very serious, for example if the swelling occurs in the throat or tongue and blocks the airway. Hereditary angioedema type I and type II are caused by mutations in the *SERPING1* gene, which plays a critical role in creating the C1 inhibitor protein that is essential for controlling inflammation. In hereditary angioedema type I the mutations reduce levels of C1 inhibitor in the blood. In type II mutations cause the production of abnormal C1 inhibitors. When C1 inhibitors are not functioning properly, large amounts of bradykinin are created, which encourages inflammation by increasing the leakage of fluid through blood vessel walls into body tissues.

[23] A study compared the typing results of the ID CORE XT Test with licensed serological reagents, the first FDA-approved molecular assay, and DNA sequencing tests. The methods performed comparably.

[24] Stephen Scholand, infectious disease specialist at MidState Medical Center, said: "Vaccination, while a valuable option for hepatitis A and measles post-exposure prophylaxis, may take several

uses a caprylate chromatography process which removes prions. The drug is contraindicated in patients who have anaphylaxis or severe sensitivity reactions to immune globulin and in IgA-deficient patients with antibodies against IgA. GamaSTAN is injected intramuscularly. The drug should not be administered intravenously due to the potential for renal failure and lung injuries.

- In the UK, the National Institute for Health and Care Excellence (NICE) has published draft guidelines rejecting NHS use of CSL Behring's Respreeza for treating emphysema in adults with severe alpha-1-proteinase inhibitor deficiency[25].
- The FDA has approved updated labelling for Coagadex (coagulation factor X [human] from Bio Products Laboratory. The drug is now indicated, in the US, for adults and children with hereditary Factor X deficiency, for:
  i) routine prophylaxis to reduce the frequency of bleeding episodes
  ii) on-demand treatment and control of bleeding episodes
  iii) perioperative management of bleeding in patients with mild and moderate hereditary Factor X deficiency
- The Japanese government approved a plan for blood transfusions to include platelets created from artificially derived stem cells for patients with intractable diseases. Researchers from Kyoto University will begin a transfusion trial using induced pluripotent stem cells (iPS cells). It will be the fourth clinical test plan using iPS cells approved by the health ministry and the first using blood components[26]. Researchers will generate platelets from the iPS cells of an individual with aplastic anemia, a disease that diminishes red blood cells and platelets, and transfuse them to the individual three times, gradually increasing the number of platelets transfused up to 100 billion in the final round. As well as the approved plan, the researchers are trying to create platelets from the iPS cells of healthy people stored at the university to transfuse to several individuals.
- The FDA has approved revised labelling for Johnson & Johnson's blood thinner Xarelto (rivaroxaban tablets) to include a claim of reduced risk of major cardiovascular events, in combination with aspirin, in patients with chronic coronary artery disease or peripheral artery disease.
- The FDA lifted its clinical hold on Vertex and CRISPR Therapeutics' gene-edited stem cell therapy for sickle cell disease[27]. The companies are on track to start a

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weeks to take effect as your immune system works to build the antibodies it needs to fight these viruses. Immune globulins such as GamaSTAN® have been a valuable treatment option for many decades because they offer immediate and rapid protection with antibodies that fight infection." The US Centers for Disease Control (CDC) recommends immune globulin as hepatitis A post-exposure prophylaxis treatment for patients who have weakened immune systems, infants less than one year old, adults over 40, and people with cancer or chronic liver or kidney disease. When administered within 2 weeks after exposure to hepatitis A, immune globulin is 80 per cent to 90 per cent effective in preventing hepatitis A infection.

[25] This condition is an incurable, rare and life-limiting genetic disorder in where a lack of a specific protein makes the body – particularly the lungs - vulnerable to attack from its own infection-fighting enzymes. Sufferers are at high risk of emphysema, which is managed but not cured with bronchodilators and inhaled corticosteroids. Respreeza (human alpha-1-proteinase inhibitor) aims to supplement the missing protein. Nice said it is a lifelong therapy costing £57,200 per patient per year on average. NICE acknowledged that the drug may slow progression of lung tissue damage and improve survival, but the appraisal committee concluded that cost-effectiveness estimates for Repreeza are "much higher than the range NICE normally considers acceptable for highly specialised technologies."

[26] The government-backed Riken institute conducted the world's first transplant of retina cells grown from iPS cells to an individual with a serious disease in 2014. Osaka University, which is planning a clinical test for treating heart failure by using a heart muscle cell sheet created from iPS cells, and Kyoto University, which is planning to treat Parkinson's disease with iPS cells, have also received government approval.

[27] The FDA placed the hold in May 2018.

human study in sickle cell by the end of the year. CRISPR Therapeutics and Vertex are currently enrolling patients in a phase I/ II beta thalassemia trial in Europe—the first company-backed CRISPR trial.

- The FDA granted Orphan Drug status[28] for Omeros' OMS721 for the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA), a very serious complication of HSCT as it involves blood clotting in the smallest blood vessels in the body. The FDA designated OMS721 a Breakthrough Therapy for the indication in April 2018, which allows accelerated review. A US marketing application is in process.

4. Market structure and company news

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

- The US Federal Trade Commission approved a final order that settles charges that Grifols' acquisition of Biotest US Corporation would be anticompetitive and violate federal antitrust law.
  i) According to the complaint, the acquisition, as originally proposed, would have given Grifols a monopoly in the markets for collection of human blood plasma in Lincoln, Nebraska, in Augusta, Georgia, and in Youngstown, Ohio. The settlement requires Grifols to divest its plasma collection centres in these three cities to KedPlasma, a subsidiary of Kedrion Biopharma. Kedrion Biopharma is the fifth-largest producer of plasma proteins worldwide.
  ii) The complaint also alleged the acquisition would harm the US market for hepatitis B immune globulin. Grifols supplies the product in the US and in December 2017, when Grifols announced its proposed acquisition of Biotest US, Biotest US owned 41 percent of ADMA Biologics, which had the largest share of hepatitis B immune globulin in the US. Biotest US has transferred its ownership share in ADMA to The Biotest Divestiture Trust, the parent company of Biotest US. Grifols is acquiring only Biotest US. It will not acquire any shares of ADMA. The consent agreement prohibits Grifols, without prior notification, from acquiring any ownership interest in ADMA or obtaining any rights to nominate or obtain representation on the ADMA Board of Directors.
  iii) The consent agreement also requires Grifols to provide prior notice to the Commission if it seeks to purchase any ADMA stock or re-purchase any of the divested plasma collection centres.
- Takeda Pharmaceutical, which is in the process of buying Shire PLC, has its global headquarters in Tokyo. It announced it will move its US headquarters from Chicago to the Boston area.
- Japan's FairTrade Commission approved Takeda's $US 62 billion acquisition of Shire. Regulators in the US, Brazil and China had already cleared the deal. Approval from EU antitrust regulators was still awaited.
- Takeda set October 19, 2018 as the record date for determining voting rights at the Extraordinary General Meeting of Shareholders to vote on the Shire takeover. Takeda has completed loan arrangements for the takeover; confirmed the key

[28] The most significant benefit of Orphan Drug status is a seven-year period of market exclusivity, if the drug is approved.

therapeutic areas it will focus on post-closing[29], planned a lean post-closing organizational structure with clearly-defined accountabilities and ownership, and received clearance from regulatory agencies in several jurisdictions. Takeda may consider divestitures of non-core businesses.

- Shire announced the acquisition of sanaplasma AG, a source plasma collection company headquartered in Switzerland. The acquisition will extend long-term plasma supply in support of Shire's growing Immunology business. It adds 14 new centres in the Czech Republic and Hungary to Shire's European-based plasma collection network.
- Emmaus Life Sciences, Inc., announced it had entered into a distribution agreement with McKesson Plasma and Biologics LLC. The agreement makes Endari™ (L-glutamine oral powder), indicated to reduce the acute complications of sickle cell disease in adult and paediatric patients 5 years of age and older, available throughout the US to pharmacies that utilize McKesson as their primary and exclusive distributor.
- Global Blood Therapeutics (GBT) signed an exclusive global licensing agreement with F. Hoffmann-La Roche Ltd. for the development and commercialization of inclacumab, a fully human monoclonal antibody against P-selectin. P-selectin inhibition is a clinically validated target in sickle cell disease (SCD), known to reduce the incidence of vaso-occlusive crises. Roche previously was developing inclacumab for patients with coronary artery disease. The pharmacokinetic, safety, and tolerability profile of inclacumab are therefore well characterized based upon Roche's prior clinical studies, which enrolled more than 500 patients. Roche discontinued the inclacumab program following Phase II clinical trials.
- Bayer is laying off 227 workers at a California manufacturing plant as it restructures to improve the efficiency of its haemophilia business.
- Five years after retiring as CEO of CSL, Brian McNamee has taken over as Chairman. During his last chairman's address, John Shine listed some of the CSL achievements during his seven years as Chairman: "Since 2011, the company has entered 12 new countries as well as making a number of acquisitions, including a strategically important manufacturer of plasma products in China – where we have had a presence for over 20 years to become the leading supplier of imported albumin. In five years, we have opened 127 new plasma centres to meet unprecedented demand for our products and made investments into emerging adjacent fields such as gene therapy with strategic acquisitions in companies such as Calimmune." He also referred to the acquisition of the influenza vaccine assets of Novartis to create the second-biggest influenza vaccines business in the world.

5. Specific country events

- In the US, the Office of Naval Research has developed the Far-Forward Blood Storage Container, a rugged, climate-controlled box that keeps blood fresh for up to three days. The box can hold up to fourteen 450ml units of blood (which will probably be from universal donors) and can be moved by a single person. The container can fit into the back of a Humvee and can be strapped to a drone. It can run on batteries, solar power or traditional power sources. It has an alarm which sounds if the temperature falls outside the desired range, though the alarm can be turned off in a tactical setting. ONR plans to deliver the first Far-Forward Blood Storage Containers

[29] including gastroenterology, oncology, neuroscience, rare diseases, vaccines and plasma-derived therapies.

to the Marine Corps Warfighting Laboratory in December this year, so they can be assessed in a training exercise.

- London's Air Ambulance has launched a study to reduce deaths from catastrophic bleeding. The two-year investigation is trialling a new blood product for critical patients suffering major injury who might not survive being air-lifted to the trauma centre at the Royal London Hospital. The product consists of red blood cells and plasma given in a single transfusion. The Air Ambulance base at Whitechapel used red blood cell transfusion when it introduced 'blood on board' in 2012 on helicopters and in its rapid response cars. That resulted in a 15 per cent reduction in pre-hospital mortality.
- In Ghana, Mirasol Pathogen Reduction Technology has been made available with the support of the Japanese international Cooperation Agency (JICA) in collaboration with the Ministry of Health and other development agencies. It was piloted in the Komfo Anokye Teaching Hospital and the Korle Bu Teaching Hospital as part of the Ghana Blood Safety Programme which commenced in 2016.
- The Australian Commission on Safety and Quality in Health Care (ACSQHC) has launched *Venous thromboembolism prevention clinical care standard* with the goal of preventing death through venous thromboembolism (VTE). General practitioners are seen as playing a key role in preventing deaths from VTE after hospitalisation. The risk of VTE rises during a hospital stay, but it also remains up to three months afterwards, making it a very relevant health threat once a patient has returned to the community. The new care standard contains recommendations for improved recording of patients' VTE prevention plans while they are in hospital, and then improved transfer of that information from hospital to primary healthcare after the patient is discharged. Another feature of the care standard is an update of the list of medicines used in VTE prophylaxis, which have changed significantly in recent years. The standard includes two appendixes, one on medicines that affect bleeding risk and the other on VTE prevention medicines. The appendices include not just the names of VTE prevention medicines and information about pharmacokinetics and pharmacodynamics, but also about their monitoring requirements, which can be especially helpful for GPs in assessing patients for any problems that may arise as a result of their VTE prevention plan.

6. Research not included elsewhere

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

- Researchers say they have found evidence that blood deposits in the brain may not require a blood vessel tear[30]. They found that brain endothelial cells (the cells that line blood vessels of the brain) can engulf red blood cells and deposit them outside the blood vessels and into the substance of the brain[31].

[30] Rudy Chang, et al., "Brain Endothelial Erythrophagocytosis and Hemoglobin Transmigration Across Brain Endothelium: Implications for Pathogenesis of Cerebral Microbleeds". *Frontiers in Cellular Neuroscience*, 2018; 12 DOI: 10.3389/fncel.2018.00279

[31] Cerebral microbleeds (CMB) on magnetic resonance imaging (MRI), are very small deposits associated with increasing age, cerebrovascular diseases, hypertension, and chronic kidney disease. They are regarded as a common cause of cognitive decline and contribute to risk of stroke. Using MRI, cerebral microbleeds are almost universal by age 70.

- New research suggests[32] that older adults with atrial fibrillation experience faster global cognitive decline and have an increased risk for dementia compared with people of similar age who do not have atrial fibrilation, although use of anticoagulant drugs may reduce this risk.
- Researchers at the Massachusetts Institute of Technology have found how to help blood cells regenerate faster, by stimulating a particular type of stem cell to secrete growth factors that help blood cell precursor cells differentiate into mature blood cells[33]. This could be of particular importance to cancer patients who receive bone marrow irradiation.
- Researchers from the University of Alabama believe "Trojan Horse" enzyme delivery could potentially treat thrombotic thrombocytopenic purpura[34].
- Scientists from the University of California at San Francisco have developed a new therapeutic to deliver oxygen to tissues which are hypoxic (under-oxygenated)[35]. This could restore to cardiac cells the contractile function heavily compromised under hypoxic conditions. The therapeutic restored the function of oxygen-starved heart tissue in an animal model of global hypoxia. Follow-up studies being conducted are further investigating more specific models to determine if this may be applicable to infants undergoing bypass.

7. Legal Matters

- The UK inquiry into what has been called the "contaminated blood scandal"[36] has elicited broad discussion in the media as well as in the inquiry itself. This includes
  i) an allegation that 1200 patients who had been infected with HIV were required to sign a contract undertaking to drop all legal action as a condition of receiving some compensation, and that it was only after that that they were advised they had hepatitis C as well;
  ii) a report that victims have written to the health secretary asking for an immediate increase in support payments in England, Wales and Northern Ireland to the level now received by victims in Scotland; and
  iii) a report that the inquiry chair Sir Brian Langstaff wrote to the Minister for the Cabinet Office calling for "decisive action at the earliest opportunity" over financial support to victims and families.
  iv) Sir Brian has reportedly said: "'It is a truly sobering thought that if some of the claims are well-founded – and it is for this inquiry to find out if they are – there may yet be many thousands more who do not feel well, but have not yet been told that the reason for this is that they suffer from Hepatitis C".

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[32] Mozhu Ding et al., "Atrial fibrillation, antithrombotic treatment, and cognitive aging: A population-based study", published online October 10 2018 in *Neurology.* DOI: https://doi.org/10.1212/WNL.0000000000006456

[33] Frances D. Liu et al., "Improving hematopoietic recovery through modeling and modulation of the mesenchymal stromal cell secretome", published 24 October 2018 *Stem Cell Research & Therapy* 2018 9:268 https://doi.org/10.1186/s13287-018-0982-2

[34] Mohammad S.Abdelgawwad, Transfusion of Platelets Loaded With Recombinant ADAMTS13 (A Disintegrin and Metalloprotease With Thrombospondin Type 1 Repeats-13) Is Efficacious for Inhibiting Arterial Thrombosis Associated With Thrombotic Thrombocytopenic Purpura , Originally published13 Sep 2018 *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018; 38:2731–2743

[35] J. Boehme *et al*, "Preservation of myocardial contractility during acute hypoxia with OMX-CV, a novel oxygen delivery biotherapeutic". Published 18 October 2018. *PLoS Biol* 16 (10): e2005924; https://doi.org/10.1371/journal.pbio.2005924

[36] The inquiry will examine why men, women and children were given infected blood; the impact on their families; how authorities including government responded; the nature of any support provided following infection; questions of consent and whether there was a cover-up.

8. Infectious diseases

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

Mosquito-borne diseases

- Valneva is testing a vaccine candidate against chikungunya viral disease[37]. Valneva SE's VLA1553's Phase 1 clinical trial is a randomized, observer-blinded, dose-escalation, multi-centre study, investigating three different dose levels in approximately 120 healthy adults vaccinated with a single-shot immunization. The first group of study participants is now being re-vaccinated[38]. VLA1553 aims for long-lasting protection and an anticipated safety profile similar to licensed vaccines for active immunization in adults and children. Valneva expects to announce initial data from this trial in early 2019[39].
- The Zika virus has been spreading in India. By mid-October ther had been almost 100 cases confirmed in Jaipur.

Influenza

- The FDA approved Genentech's Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. This is the first new antiviral flu treatment in nearly two decades.

Ebola virus disease

- In the US, the director of the Centers for Disease Control and Prevention(CDC) said in late October that he had argued that American experts should stay in the outbreak zone of the latest Ebola epidemic but accepted that his view had not been approved by others in the Trump administration because of security concerns. The CDC was forced to withdraw workers from the outbreak zone in the Democratic Republic of Congo several weeks ago amid security concerns[40]. Response teams hoped that an experimental vaccine could help curb the epidemic but the security situation made it difficult to track the course of the virus and to deliver the vaccine to those who need it. The CDC director, Robert Redfield, said he would like to see "a small footprint of CDC employees" back in the area and added: "I'd be happy to be one of them."

[37] Chikungunya is transmitted by the bite of infected mosquitoes such as *Aedes aegypti* and *Aedes albopictus*. It leads to high fever, joint, and muscle pain, and headache. It does not often result in death, but the joint pain may last for years and result in chronic disability.

[38] See Valneva's press release. This re-vaccination will demonstrate whether subjects are protected from vaccine-induced viremia.

[39] In pre-clinicaltesting, a single-vaccine shot was shown to be highly immunogenic in vaccinated non-human primates and showed no signs of viremia after challenge, with a good safety profile.

[40] It is understood that the State Department recommended CDC staff be withdrawn.

- A synthetic DNA vaccine is demonstrating promising results against the Ebola virus in preclinical animal research. Scientists at The Wistar Institute Vaccine and Immunotherapy Centers targeted a virus surface protein called glycoprotein[41].
- Scientists have developed a double-pronged approach for targeting Ebola virus infection using linked nucleic acid (LNA) antisense oligonucleotides (ASOs) designed to interfere with both genes essential for translation of Ebola virus genes and to block production of an intracellular human protein needed for the virus to enter cells.[42]

Other diseases

- A farm in Scotland has had one of its cows die from mad cow disease, but health officials have assured the public that there is no threat to public health.
- An investigational vaccine designed to protect people from both Lassa fever and rabies showed promise in preclinical testing[43]. Called Lassarab, it was developed and tested by scientists at Thomas Jefferson University in Philadelphia; the University of Minho in Braga, Portugal; the University of California, San Diego; and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health in the US.

[41] Ami Patel et al., "Protective Efficacy and Long-Term Immunogenicity in Cynomolgus Macaques by Ebola Virus Glycoprotein Synthetic DNA Vaccines", published 10 October 2018, *The Journal of Infectious Diseases*, jiy537, https://doi.org/10.1093/infdis/jiy537

[42] Jessica Chery et al., "Development of Locked Nucleic Acid Antisense Oligonucleotides Targeting Ebola Viral Proteins and Host Factor Niemann-Pick C1", **Nucleic Acid TherapeuticsVol. 28, No. 5** , Published Online: 24 Sep 2018 https://doi.org/10.1089/nat.2018.0722

[43] T Abreu-Mota *et al.* "Non-neutralizing antibodies elicited by recombinant Lassa-Rabies vaccine are critical for protection against Lassa fever". *Nature Communications* DOI: 10.1038/s41467-018-06741-w (2018)