Monitoring International Trends

Posted February 2020

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.

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1. Safety and patient blood management

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

Appropriate Transfusion; Bleeding Risk

- **A study[1] in hip and knee replacement surgery has questioned "the effectiveness of postoperative autotransfusion as a component of a patient blood management programme".** The authors also said that "safety concerns were raised by clear signs of inflammatory reactions and coagulation activation".
- Cerus Corporation announced[2] that 16th Annual Hemovigilance report by the French National Agency for Medicines and Health Products (ANSM) **highlighted the safety and effectiveness of INTERCEPT platelets** during the first full year of routine use.
- A Victorian study[3] found that **patients who have a stroke or transient ischaemic attack while on a direct oral anticoagulant are missing out on timely thrombolysis compared with patients on warfarin**. Researchers reported that of 154 patients with a new diagnosis of stroke while prescribed an oral anticoagulant, 45 per cent of those on warfarin received tissue plasminogen activator within 4.5 hours, but only 16 per cent of patients receiving one of the direct oral anticoagulants received reperfusion.
- Alydia Health, a clinical-stage medical device company, announced that **enrolment had been completed in the PEARLE IDE Study. This is investigating the safety and effectiveness of the Jada System, designed to control and treat abnormal postpartum haemorrhage quickly.** It encourages the uterus to contract, naturally compressing the open blood vessels. In a pilot study[4], the device rapidly and effectively controlled postpartum bleeding, with haemorrhage controlled within two minutes for each mother. Alydia initiated the PEARLE Study to support its submission to the US Food and Drug Administration (FDA) for marketing clearance. Over 100 women enrolled and were treated with Jada after experiencing abnormal bleeding. The primary endpoint of the study is lack of further intervention to control bleeding. The safety analysis includes a six-week follow-up visit. See clinicaltrials.gov (NCT02883673).
- **Scientists have developed a device to identify "super donors" whose blood can remain viable for longer** in transit and in the recipient's body[5]. Led by Professor Hongshen Ma[6], a team of researchers at the University of British Columbia used a custom-made microfluidic device to monitor the way the red blood cells of eight recipients changed during storage, which revealed two samples that were significantly better able to maintain their structure. Team member Dr Mark Scott[7] explained[8] that "people who need frequent blood transfusions benefit tremendously

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[1] Sebastian Mayer-Rollnik et al., "Evaluation of autologous retransfusion from a closed suction drainage system for patient blood management in elective total hip and knee replacement: A two cohort study", December 2019, European Journal of Anaesthesiology 37(3), December 2019 DOI: 10.1097/EJA.0000000000001125

[2] https://finance.yahoo.com/news/french-hemovigilance-report-highlights-safety-133000990.html

[3] Michael Valente et al., "Ischaemic stroke and transient ischaemic attack on anticoagulants: outcomes in the era of direct oral anticoagulants", *Internal Medicine Journal*, Volume50, Issue1 January 2020. Pages 110-113 https://doi.org/10.1111/imj.14652

[4] Purwosunu Y, et al. "Control of Postpartum Hemorrhage Using Vacuum-Induced Uterine Tamponade." *Obstetrics & Gynecology.* Vol. 128, No. 1, July 2016.

[5] Emel Islamzada, Mark D. Scott, Hongshen Ma et al., "Deformability based sorting of stored red blood cells reveals donor-dependent aging curves", Lab on a Chip, Issue 2, 2020. https://doi.org/10.1039/C9LC01058K

[6] a professor of mechanical engineering and biomedical engineering

[7] a clinical professor in pathology and laboratory medicine

[8] See statement

from red blood cells that are able to appropriately circulate in the blood vessels to deliver oxygen. A method that can swiftly and accurately test the 'squeezability' of these cells can make transfusions safer for these patients and ultimately for anyone who needs a critical transfusion." Professor Ma and his team plan to work with Canadian Blood Services to test further samples and validate the device's efficiency.

- A systematic literature review[9] found that **primary postpartum haemorrhage (PPH) remains a significant complication for pregnant women with type 3 von Willebrand disease** (VWD), the most severe form of the disease.
- A study in liver transplantation[10] has concluded that: **"The intraoperative use of fibrinogen concentrate did not seem to have any statistically significant difference in the amount of blood loss during surgery. However, the amount of cryoprecipitate used was significantly reduced with the introduction of fibrinogen concentrate**."
- Researchers have concluded[11] that while "**the perioperative management of antithrombotic therapy in urological patients is potentially challenging" the inconsistency of clinical practice guidelines "of varying quality may create uncertainty as to best practices to minimize thromboembolic and bleeding risk**".

Other

- **Researchers from Mount Sinai Hospital and Rutgers University[12] have developed a robot to sample blood.** It has built-in ultrasound technology to guide the placement of the needle, while the entire system also includes a module to handle samples and a centrifuge-based blood analyser.
- **Researchers found[13] that haemoglobin levels above the recommendations of 10.0 to 11.5 g/dL are associated with improved health-related quality of life** among anaemic patients with chronic kidney disease who are not dialysis-dependent.
- **The Vinyl Institute says eliminating plastic polyvinyl chloride (PVC) and the additive diethylhexyl phthalate (DEHP) from medical settings would leave patients at "significant risk".** President Ned Monroe said: "PVC is used in dozens of applications and thousands of individual medical products because it is durable, easy to clean, and can withstand strong disinfectants better than other materials." The Institute's comments were in response to a 29 January position statement from Health Care Without Harm (HCWH), which encouraged health care facilities to avoid the plastic PVC and the additive DEHP. A study[14] has also reported that exposure to phthalates may affect fine motor skills in girls.

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[9] Makhamreh MM, Kass SL, Russo ML, Ahmadzia H, Al-Kouatly HB. Type 3 von Willebrand disease in pregnancy: a systematic literature review [published online November 22, 2019]. *American Journal of Perinatology*. doi:10.1055/s-0039-1700541

[10] Ying Ci Ho, Kai Inn Lim, Fook Onn Lai, "Impact of Incorporation of Fibrinogen Concentrate in Blood Transfusion Management During Liver Transplantation: An Early Local (Single Centre) Experience",5 February 2020, International Journal of Clinical Transfusion Medicine

[11] K Dimitropoulos, "Perioperative antithrombotic (antiplatelet and anticoagulant) therapy in urological practice: a critical assessment and summary of the clinical practice guidelines", World J Urol. 2020 Jan 14. doi: 10.1007/s00345-020-03078-2. [Epub ahead of print] DOI: 10.1007/s00345-020-03078-2

[12] Including Josh Leipheimer, a biomedical engineering doctoral student in the Rutgers University.

[13] Junichi Hoshino et al. "Associations of hemoglobin levels with health-related quality of life, physical activity, and clinical outcomes in persons with stage 3-5 non-dialysis CKD "[published online January 21, 2020]. *J Renal Nutr*. https://doi.org/10.1053/j.jrn.2019.11.003

[14] Sharon Daniel et al, "Perinatal phthalates exposure decreases fine-motor functions in 11-year-old girls: Results from weighted Quantile sum regression". *Environment International*, volume 136, March 2020. https://doi.org/10.1016/j.envint.2019.105424
and https://www.sciencedirect.com/science/article/pii/S0160412019325115?via%3Dihub

- A Korean study[15] found that **patients with chronic kidney disease are at higher risk for hyperuricemia[16] if they have anaemia**. Researchers said that declining renal function did not fully explain this association.
- **A monoclonal antibody against coagulation factor XI is being trialled** to prevent venous thromboembolism (VTE) after knee arthroplasty[17].
- **Autoimmune haemolytic anaemias** are rare and heterogeneous disorders which are characterized by the destruction of red blood cells**. International consensus recommendations on diagnosis and therapeutic management** were published in January[18].

2. Products and treatments

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

Treating haemophilia

- At the **13th Annual Congress of the European Association for Haemophilia and Allied Disorders** (EAHAD)[19]:
  i. **Catalyst Biosciences, Inc.**, **had a direct interest in one oral and three poster presentations[20]** on its developing haemophilia treatments,
  ii. **uniQure had a direct interest in seven presentations** (one oral)[21] about treating haemophilia,

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[15] Eun Y, Han K-D, Kim DH, et al. "Association between anemia and hyperuricemia: results from the Korean National Health and Nutrition Examination Survey" [published online December 13, 2019]. *Scientific Reports.* 2019;9:19067. *Sci Rep*. doi: 10.1038/s41598-019-55514-y https://www.nature.com/articles/s41598-019-55514-y

[16] Hyperuricemia" refers to an abnormally high level of uric acid in the blood. In body fluid, uric acid exists mostly as the ion form, urate. The volume of urate depends on the balance between the volume of purines ingested, the volume of urate synthesised within the body, and the volume of urate excreted in urine or faeces.

[17] Jeffrey I Weitz et al., Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial' *JAMA*. 2020;323(2):130-139. doi:10.1001/jama.2019.20687 https://jamanetwork.com/journals/jama/article-abstract/2758600

[18] Ulrich Jager et al., "Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting", *Blood Reviews*, https://doi.org/10.1016/j.blre.2019.100648

[19] The Hague, Netherlands, 5-7 February, 2020

[20] The oral presentation, *Phase 2b Trial to Evaluate the Safety and Factor IX Levels Resulting from a Daily Subcutaneous Prophylaxis Treatment Regimen of Dalcinonacog Alfa (DalcA) in Hemophilia B,* was delivered by Johnny Mahlangu, Professor of haematology and head of the School of Pathology at the University of Witwatersrand in Johannesburg, and a principal investigator in the Dalcinonacog Alfa (DalcA) Phase 2b clinical trial. The posters were: *Phase 1 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Ascending Doses of Subcutaneous Marzeptacog Alfa (Activated) (MarzAA) in Adult Subjects with Hemophilia* (Linda Neuman, vice president, clinical development); *Subcutaneous Marzeptacog Alfa (Activated) Supports on-Demand Treatment in Hemophilia A Mice Submitted to a Tail Clip Injury* (Grant Blouse, vice president, translational research); and *Hemophilia B Gene Therapy in Mice Using a Novel Chimeric AAV Capsid Combined with the Potency Enhanced CB 2679d-GT FIX Variant* (Grant Blouse, vice president, translational research). A copy of the presentation materials can be accessed on the Events and Presentations section of the Catalyst website (www.catalystbiosciences.com)

[21] *One Year Data from A Phase 2b Trial Of AMT-061 (AAV5-Padua hFIX Variant), An Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B (ORAL10); Clearance of Vector DNA Following Systemic Administration of AAV5-hFIX Or AAV5-hFIX Padua In Patients with Severe or Moderate-Severe Hemophilia B (Poster 89); Stable FIX Expression and*

iii. **Takeda had a direct interest in nine presentations[22] (**one oral) concerning bleeding disorders,
iv. **Octapharma sponsored a symposium in which its product Nuwiq featured[23]; and**
v. **Freeline presented further data from its Phase I/IIB-AMAZE trial of its gene therapy**, FLT180a, for haemophilia B.

- **Researchers reported[24] that specific genetic changes may account for a larger proportion than previously thought of children with severe haemophilia B who develop inhibitors against coagulation factor IX replacement therapy.**
  i. Haemophilia B, a deficiency in the production of coagulation factor IX protein, results from mutations in the F9 gene. Between 30 and 40 per cent of haemophilia B patients have the severe form (defined as one per cent or less of factor IX activity). It is mostly these patients with the severe form of the

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Durable Reductions in Bleeding and Factor IX Consumption for Up To 4 Years Following AMT-060 Gene Therapy in Adults with Severe or Moderate-Severe Hemophilia B (Poster 100); Prevalence and Affinity/Avidity Assessment of Pre-Existing NABS Against AAV1, 2, 5 And 8 Analyzed In the Serum Of 300 Healthy Donors (Poster 54); Seroprevalence Of Pre-Existing NABS Against AAV1, 2, 5, 6 And 8 in the South African Hemophilia B Patient Population (Poster 116); Evaluation of A Blood Coagulation Factor IX Variant That Functions Independently of Factor Viii as An Alternative Treatment of Hemophilia A; and *Gene Therapy for People with Haemophilia B (PWHB): Development of A Cost-Effectiveness Model Framework (Poster 154)*

[22] *"Incidence and Prevalence of Diagnosed and Undiagnosed Hemophilia A and Hemophilia B in the United Kingdom, Germany, France, Italy, and Spain"* (abstract P050) reports that the estimated percentage of undiagnosed cases in EU5 countries ranged from 16–47 per cent for hemophilia A and 34–65 per cent for haemophilia B. The diagnosis rates varied with disease severity, and the highest rates were typically observed for severe disease; *"Management of Menorrhagia in a Phase 3, Post-Hoc, Open-Label Study of rVWF in patients with severe VWD"* (abstract P218) shows the haemostatic efficacy rating of vWVF in patients being treated with it; *"AHEAD International and German studies: 6-year interim effectiveness and safety outcomes in patients with hemophilia A receiving antihemophilic factor (recombinant) in a real-world setting"* (abstract P115) focusses on the long-term effectiveness and tolerability of rAHF, regardless of disease severity, in two study populations. AHEAD is one of the largest long-term real-world studies on haemophilia, conducted in 22 countries around the world; in *"Immunogenicity Profile of Rurioctocog Alfa Pegol in Previously Treated Patients with Severe Congenital Hemophilia A: Findings from 6 Clinical Trials"* (abstract P187), researchers analyzed the association of PEGylated TAK-660 and the risk of developing FVIII inhibitors and persistent antibody response; *"Safety and Effectiveness of Activated Prothrombin Complex Concentrate (aPCC) Monotherapy in Patients with Hemophilia and Inhibitors (PwHI) Undergoing Surgery: A Systematic Review and Meta-Analysis*" (abstract P114) shows the rate of adverse events in patients treated with aPCC monotherapy in a surgical setting, as well as its haemostatic effectiveness in different surgical procedures; and in *"Rurioctocog Alfa Pegol PK-guided prophylaxis targeting two FVIII Trough Levels in Severe Hemophilia A Patients (PROPEL Phase 3 Study): Impact of Patient FVIII Half-Life on Consumption and Efficacy Outcomes"* (abstract OR09), researchers carried out a post hoc analysis to evaluate the relationship between patient FVIII half-life and efficacy and consumption of prophylactic rurioctocog alfa pegol (TAK-660). The abstract describes the impact of FVIII half-life on the amount and frequency of TAK-660 doses needed to achieve target FVIII troughs. Wolfhard Erdlenbruch, Vice President and Head of Global Medical Affairs Hematology at Takeda, commented: "We cannot assume that one regimen or one dosing strategy is going to be suitable for all patients – that's because although these patients may be living with the same condition, the variation in their individual pharmacokinetics, for example, may mean they respond to the same treatment differently. With this in mind, Takeda is always finding new ways to make sure treatments for our patients are as tailored to their individual needs as possible."

[23] "*Unravelling the challenges of haemophilia A: Efficacy, immunogenicity and inhibitor management with Nuwiq® (simoctocog alfa)*" was chaired by Maria Elisa Mancuso (Ospedale Maggiore Policlinico, Milan, Italy).

[24] Christoph Male et al., "Inhibitor Incidence In An Unselected Cohort Of Previously Untreated Patients With Severe Haemophilia B: A PedNet Study," in *Haematologica*, January 2020. **doi:**10.3324/haematol.2019.239160

disease who have an immune response to factor replacement therapy — developing inhibitors which lead to treatment resistance.

ii. In the present study, researchers used selected data[25] from the PedNet registry to evaluate the frequency of inhibitor development and allergic reactions in children with severe haemophilia B, and the impact of mutations in the F9 gene on the risk of developing inhibitors. They analysed demographic and clinical details of 154 untreated children with severe haemophilia B. A high proportion of the children were Caucasian. Around half of them had a family history of haemophilia. They started preventive treatment at a median age of 9.6 months, and 77 per cent were followed until 50 days of treatment, 75 per cent until 75 days, 68 per cent until 150 days, and 43 per cent until 500 days of treatment.

iii. During the study 14 children developed factor IX inhibitors, at a median of 11 days of treatment and when they were almost two years old. Seven exhibited significantly high levels. A family history of factor IX inhibitors was significantly more frequent among children positive for inhibitors than those who were not.

iv. The researchers reported that further analysis confirmed "previous reports suggesting a strong association between absent endogenous [factor IX] protein due to gross and complete gene deletions and inhibitor development."

- ASC Therapeutics has orphan drug designation from the FDA for its gene therapy ASC-618 for haemophilia A. It plans to file an Investigational New Drug Application in the fourth quarter of 2020, and to begin a clinical trial in the first quarter of 2021.

Treating beta thalassemia and sickle cell disease

- **FORMA Therapeutics' announced[26] that its experimental therapy for sickle cell disease (FT-4202), showed a favourable safety and pharmacokinetic profile in healthy volunteers in a Phase 1 clinical trial.** The company said patient recruitment was open for the second part of the trial (NCT03815695). Trial findings were reported at the 2019 American Society of Hematology (ASH) Annual Meeting in Orlando, Florida, in an oral presentation, "Phase 1 Single (SAD) and Multiple Ascending Dose (MAD) Studies of the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of FT-4202, an Allosteric Activator of Pyruvate Kinase-R, in Healthy and Sickle Cell Disease Subjects".

Treating other conditions

- **A prospective study[27] has found that human "fibrinogen concentrate was efficacious for on-demand treatment of bleeding and as surgical prophylaxis**, with a favourable safety profile, in patients with congenital afibrinogenemia".
- A study reports[28] that a **new diagnostic tool for people with hereditary angioedema** (HAE) and normal C1 inhibitor activity **potentially gives physicians the first method for properly diagnosing the condition.**

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[25] The PedNet registry (NCT02979119) includes children born with all types of haemophilia across 18 countries from 1 January, 2000 to 1 January, 2020.

[26] See press release.

[27] Toshko Lissitchkov, Flora Peyvandi et al., "Fibrinogen concentrate for treatment of bleeding and surgical prophylaxis in congenital fibrinogen deficiency patients", *Journal of Thrombosis and Haemostasis,* first published 29 December 2019. https://doi.org/10.1111/jth.14727

[28] Blas Larrauri, "sgp120 and the contact system in hereditary angioedema: A diagnostic tool in HAE with normal C1 inhibitor," *Molecular Immunology.* Volume 119, March 2020, pp27-34.

- Intellia Therapeutics reported preclinical results in support of its **gene therapy candidate** for hereditary angioedema[29].
- **KalVista Pharmaceuticals provided an update[30] on its franchise of oral plasma kallikrein inhibitors for treatment of hereditary angioedema**. KalVista has undertaken patient, physician and payer research to identify perceived needs in the market. Oral therapy is seen as the highest unmet need for both on-demand and prophylactic usage, but patients said they were not prepared to accept significantly reduced efficacy for the convenience of oral therapy. Twice-daily dosing compared with once-daily dosing was not seen as a disincentive[31]. KalVista will investigate twice-daily dosing in the planned Phase II trial of KVD824 as an oral prophylactic treatment.
- **Akari Therapeutics** reported positive interim results for its **Phase III paroxysmal nocturnal haemoglobinuria (PNH) CAPSTONE study** involving complement inhibitor naïve, transfusion-dependent PNH patients. All patients dosed with nomacopan met the primary endpoint of transfusion independence.

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) finalized six guidance documents on gene therapy development (including one relating to haemophilia[32])** and issued a new draft guidance on interpreting the sameness of gene therapies under the orphan drug regulations[33].
- **Pharmacosmos Therapeutics received FDA approval for its ferric derisomaltose (Monoferric) 100 mg/mL for the treatment of adult patients with iron deficiency** who have an intolerance or have had unsatisfactory response to oral iron or patients who have non-haemodialysis dependent chronic kidney disease.
- On 3 February, **BioCryst submitted a Japanese New Drug Application for Berotralstat,** for the prevention of hereditary angioedema attacks. This followed a New Drug Application submitted to the FDA in December. An application will shortly be made in Europe.

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[29] In animal models, the therapy lowers kallikrein activity which is expected to reduce angioedema attacks in patients. Updates on a number of programs were released at Keystone Symposia's Engineering the Genome, 8-12 February in Alberta. The title of the presentation was "*In Vivo* Liver Delivery of CRISPR/Cas9 Using Lipid Nanoparticles Enables Gene Knockout Across Multiple Targets and Species."

[30] Andrew Crockett, CEO of KalVista, said: "Based upon the progress of the ongoing KVD900 Phase II clinical trial, we expect to announce data from that trial in the second quarter of this year," said "We are also pleased to announce the selection of KVD824 for development as an oral prophylactic treatment for HAE (hereditary angioedema). Based on preclinical formulation work conducted, we see evidence that KVD824 can achieve the properties we believe necessary for high efficacy as a twice-daily treatment for prevention of HAE attacks. After completing additional clinical work to optimize the exposure profile, we plan to commence a Phase II clinical trial in the second half of this year. KVD824 could be an excellent companion to KVD900's profile as an on-demand therapy to together serve all of the needs of HAE patients."

[31] Kalvista will investigate twice-daily dosing in the planned Phase II trial of KVD824 as an oral prophylactic treatment.

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-hemophilia

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations

- On 11 February, **the FDA granted CSL Behring's Privigen**® (Immune Globulin Intravenous (Human) 10 per cent Liquid) **orphan-drug designation as an investigational therapy in the treatment of systemic sclerosis** (SSc)[34].
- **The FDA** in mid-January **granted Fast Track designation to bomedemstat (IMG-7289; Imago BioSciences) for the treatment of essential thrombocythemia**, a myeloproliferative disorder characterized by high platelet counts.
- **The FDA granted avatrombopag (Doptelet) Orphan Drug Designation for the potential treatment of chemotherapy-induced thrombocytopenia** (CIT). Enrolment for the Phase III clinical trial for avatrombopag as a treatment of CIT is ongoing. Doptelet is an oral thrombopoietin receptor agonist administered with food. It is already FDA approved for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure[35] and thrombocytopenia in adult patients with chronic immune thrombocytopenia[36] (ITP) who have had an insufficient response to a previous treatment.

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.

- **CSL CEO Paul Perreault said on 12 February he was confident the company would enjoy "a few more years" of very strong global demand for immunoglobulin products**. The company had just revealed an 11 per cent increase in half-year earnings and increased its full-year profit outlook by 3 per cent to between $US 2.11 billion and $US 2.17 billion, which would represent growth of 10 to 13 per cent over 2019.
- **CSL is working with University of Queensland researchers to develop a vaccine for Covid-19,** the new coronavirus.
- The Global Board of Directors of the Plasma Protein Therapeutics Association (**PPTA**) **elected Karen Etchberger of CSL Behring as its Chair**, effective January 2020. Dr. Etchberger will serve a three-year term.
- **The Octapharma Group in 2019 experienced strong growth in operating income[37].** The Group's immunoglobulin portfolio performed particularly well year -on -year.
- **Cellphire[38] announced that the US Army Medical Research Acquisition Activity (USAMRAA) has awarded the company a 6.5-year contract valued at $US 29.25 million (including all options) to develop an FDA-licensed dimethyl sulfoxide (DMSO) Cryopreserved Platelets (CPP) product** to improve battlefield management of severe haemorrhage due to combat trauma. Cellphire will undertake all research, development, manufacturing, and regulatory activities. The platelets will be able to be stored for 2 years. The US Government has developed CPP through a

[34] This is a chronic and potentially life-threatening autoimmune disorder characterized by a build-up of scar tissue (fibrosis) in the skin and other organs. It impacts about 100,000 people in the US. There have not been any FDA-approved, disease-modifying treatments.
[35] also European Medicines Agency approved for this indication
[36] Chronic ITP is an autoimmune bleeding disorder characterised by low number of platelets
[37] https://www.businesswire.com/news/home/20200214005230/en/Octapharma-Group-Delivered-Strong-Growth-Sales-Operating and www.octapharma.com
[38] www.cellphire.com

Phase I dose escalation study. Cellphire will complete a Phase II clinical trial to demonstrate efficacy in cardiac surgery.

- **The European Commission has approved Rigel Pharmaceuticals' fostamatinib disodium hexahydrate (known as Tavalisse in the US) for the treatment of chronic immune thrombocytopenia (ITP) in adults who are refractory to other treatments**. Grifols has exclusive rights to fostamatinib in chronic ITP, as well as any potential future indications, in Europe and Turkey. The launch is expected in the second quarter of this year.
- **Freeline reported data on its gene therapy programmes for Fabry Disease and Gaucher Disease** at the 16th annual WORLD*Symposium* in Florida[39].
- Andy Plump, **Takeda's head of R&D, was reported[40] to have said in an interview with the *Boston Business Journal*: "I think the likelihood is that our hemophilia A gene therapy is not going to be a competitor in the market…** But I don't think you need to be a frontrunner in a field to really be effective. In fact, I think, sometimes in the world we live in, being the frontrunner can have disadvantages." Takeda is developing gene therapy TAK-754 for haemophilia A. It is currently in a Phase I study. TAK-748 is in preclinical studies for treatment of haemophilia B. Last September, Takeda published the results of a Phase II study of TAK-620 (maribavir) for cytomegalovirus (CMV)[41].
- **Roche has extended its collaboration** with French firm Inotrem **on a plasma test for septic shock[42].**
- **GC Green Cross is undertaking Phase II and III clinical trials on HepaBig-Gin (GC1102), a recombinant hepatitis B immunoglobulin.** The company says the drug has higher antibody purity and better viral suppression than blood plasma-based products so it can reduce drug administration time. Last year GC Green Cross started a Phase I trial of its haemophilia antibody treatment (MG1113). This can be given to both type-A and -B haemophilia patients.
- **Novo Nordisk's financial report** for the period 1 January 2019 to 31 December 2019 **showed an increase 11 per cent in operating profit for the year in Danish kroner** (6 per cent at constant exchange rates).
- On 10 February, **Novo Nordisk announced that ESPEROCT® [antihemophilic factor (recombinant), glycopegylated-exei] is now available in the US** for the treatment of adults and children with haemophilia A. ESPEROCT® is a recombinant extended half-life factor VIII replacement therapy used to prevent or reduce the number of bleeding episodes, to treat and control bleeding, and to manage bleeding during surgery in people with haemophilia A.
- **Sun Pharmaceutical Industries** Ltd announced that one of its wholly owned subsidiaries had **entered into exclusive licensing and supply agreements** with Rockwell Medical Inc. **to commercialize Rockwell's Triferic**, an iron replacement and haemoglobin maintenance drug, **for treating anaemia in haemodialysis patients in India.**

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[39] Orlando, 10-13 February 2020. https://www.pharmiweb.com/press-release/2020-02-12/freeline-presents-data-on-its-aav-based-gene-therapies-for-fabry-disease-and-gaucher-disease-at-the-16th-annual-worldsymposium

[40] https://www.biospace.com/article/takeda-r-and-d-head-doesn-t-see-a-blockbuster-in-its-hemophilia-a-gene-therapy-but-does-see-big-things-coming/

[41] https://www.globaldata.com/potential-first-in-class-cmv-therapeutic-tak-620-set-to-reach-global-sales-of-7-1m-by-2027/ and
Johan Maertens et al., "Maribavir for Pre-emptive Treatment of Cytomegalovirus Reactivation", September 19, 2019 *N Engl J Med* 2019; 381:1136-1147 DOI: 10.1056/NEJMoa1714656

[42] https://www.fiercebiotech.com/medtech/roche-inotrem-extend-collaboration-blood-test-for-septic-shock

- **Acpeth[43] has begun commercial manufacture of Bluebird bio's gene therapy Zyntelgo, after health insurance companies in Germany agreed to a pricing structure.** Bluebird bio received marketing approval for Zyntelgo[44] for the European market in June of last year. To treat patients 12 years and older with transfusion-dependent β-thalassemia (TDT), Bluebird has had to create qualified treatment centres, the first being at the University Hospital of Heidelberg.
- **BioMarin** Pharmaceutical's CEO Jean-Jacques Bienaimé told the J.P Morgan Healthcare Conference in January that the company was **considering a price of $US2 million to $US3 million for its haemophilia gene therapy, Valrox**, if the treatment is approved.
- **AbbVie** in mid-January **received conditional approval in Europe for its Allergan merger**.

5. Specific country events

- A study[45] found that the **risks faced by US bone marrow transplant patients have fallen** sharply.
- In Australia, the Medicare Services Advisory Committee **(MSAC) recommended funding of the monoclonal antibody emicizumab (Hemlibra)** via the National Blood Authority **for patients with moderate or severe haemophilia A without factor VIII inhibitors.** The Committee said in its advice to the Minister for Health that the application for funding "did not justify the expense of emicizumab for all patients, and this supportive advice was subject to pricing negotiations" with Roche.
- The post-Brexit headquarters of the European Medicines Agency (EMA) are now open in Amsterdam.
- Canadian Blood Services confirmed that 11 towns and cities in north-eastern Ontario (including Sudbury) will no longer have mobile blood donor events. A spokesperson said: **"Canadian Blood Services will be opening a proof-of-concept plasma donor centre in Sudbury. We will not be operating mobile donor events after Jan. 31.** The new plasma donor centre in Sudbury will offer longer, more flexible hours of operation to accommodate donors who may come to Sudbury on weekends or evenings. The equipment used to collect plasma is not as transportable as that for blood donations and therefore, mobiles will not be possible."
- At the same time, **Canadian Blood Services is hoping to attract 112,000 new donors in 2020.**
- **In India, the government will provide financial support** of up to Rs 15 lakh under its Rashtriya Arogaya Nidhi scheme **for one-time treatment of rare diseases**, according to its draft Rare Diseases Policy[46].

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[43] apceth Biopharma GmbH, a subsidiary of Hitachi Chemical Co., Ltd.

[44] Zynteglo is conditionally approved in the EU as a gene therapy for patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β^0/β^0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.
https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo
The product is subject to additional monitoring.

[45] GB McDonald et al., "Survival, non-relapse mortality, and relapse-related mortality after allogeneic hematopoietic cell transplantation: comparing 2003–2007 versus 2013–2017 cohorts." Ann Intern Med. 21 January, 2020;172:229-39. doi:10.7326/M19-2936
https://annals.org/aim/fullarticle/2759354/patient-outcomes-after-bone-marrow-transplant

[46] https://www.outlookindia.com/newsscroll/govt-proposes-to-treat-rare-disease-patients-at-onetime-treatment-cost-of-up-to-rs-15-lakh/1708153

6. Research not included elsewhere

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

- A new study has found that **global sepsis infections are twice as high as previous estimates** with sepsis responsible for 1 in 5 deaths[47].
- A survey concluded that **13 per cent of cancer cases globally in 2018 may have been attributable to infections**, the primary causes being *Helicobacter pylori*, human papillomavirus (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV). China accounted for 42 per cent of cancers caused by *H pylori* and for 69 per cent of those caused by HBV[48].
- A pilot study[49] has found that **a molecule synthesized by researchers at the University of Montreal has increased the possibility for wider use of banked umbilical cord blood as a source of stem cells** for patients who need a hematopoietic stem-cell transplant (HSCT).
- A study[50] by scientists at the University of Colorado Cancer Center found **a new way to encourage pluripotent stem cells (iPSCs) into making hematopoietic stem cells (HSCs)** by magnifying the *MLL* gene, a gene that can cause a form of childhood leukaemia.
- A study[51] found **people in Italy with hereditary angioedema** types 1 or 2 **are not at an increased risk of premature death relative to the general population, and that swelling that blocks the airway is not their main cause of death.**
- Scientists have developed **a capillary model which allows investigation of the dynamics of blood flow obstruction in real scale** and could be used to test new therapies for *P. falciparum* malaria[52].

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[47] Rudd KE, Johnson SC, Agesa KM, et al. "Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study**",** *Lancet.* 2020; (published online Jan 16.) https://doi.org/10.1016/S0140-6736(19)32989-7
Jordan A Pempker and Greg S Martin, "A global accounting of sepsis", *The Lancet,* VOLUME 395, ISSUE 10219, P168-170, JANUARY 18, 2020.
HTTPS://WWW.THELANCET.COM/JOURNALS/LANCET/ARTICLE/PIIS0140-6736(19)33065-X/FULLTEXT
https://edition.cnn.com/2020/01/16/health/sepsis-deaths-global-study/index.html

[48] Catherine de Martel et al., Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis *The Lancet Global Health*, Volume 8, Issue 2, PE180-E190. 1 February 2020. https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(19)30488-7/fulltext

[49] Sandra Cohen et al., "Hematopoietic stem cell transplantation using single UM171-expanded cord blood; a single-arm, phase 1-2 feasibility study" , *Lancet Haematol.* Published online 5 November, 2019. Abstract, Editorial https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(19)30202-9/fulltext

[50] Weiwei Yang et al., "Enhancing Hematopoiesis from Murine Embryonic Stem Cells through MLL1-Induced Activation of a Rac/Rho/Integrin Signaling Axis", *Stem Cell Reports*, Volume 14, Issue 2, pp285-289, 11 February 2020. DOI: 10.1016/j.stemcr.2019.12.009

[51] F Perego et al.," Life expectancy in Italian patients with hereditary angioedema due to C1 inhibitor deficiency," in *The Journal of Allergy and Clinical Immunology: In Practice*. 16 January 2020 pii: S2213-2198(20)30046-5. doi: 10.1016/j.jaip.2020.01.007

[52] Christopher Arakawa et al., "Biophysical and biomolecular interactions of malaria-infected erythrocytes in engineered human capillaries**",** *Science Advances*. 17 Jan 2020: Vol. 6, no. 3, eaay7243 DOI: 10.1126/sciadv.aay7243 https://advances.sciencemag.org/content/6/3/eaay7243

- **Physicists from McMaster University have developed red blood cells that can be used to distribute drugs round the body to target infections or treat diseases**[53]. The modified cells can circulate for some weeks and target bacteria, tumours or organs. Maikel Rheinstädter[54] said: "We call these super-human red blood cells. We think that they could work as the perfect stealth drug carriers which can outsmart our immune system." The researchers have developed a way to open the red blood cell, modify its cell wall, and then substitute a drug molecule for the original contents. The cell is returned to the body by injection. The hybrid cell behaves normally, but its now-sticky surface allows, for example, attachment to bacteria where it will open and release its load of antibiotics. Sebastian Himbert[55] said: "We have combined synthetic material with biological material and created a new structure, which has never been done before in this way. The entire process is very efficient and can be completed in one day in the lab". Researchers believe targeted delivery could reduce dosages of the potent drugs used in cancer and Alzheimer's disease.
- Scientists report[56] that a **stroke appears to create a sticky situation inside the blood vessels of the brain that can worsen damage** later.
- Researchers in France have been working on a means of **replacing damaged blood vessels by knitting new vessels** with a collagen-based extracellular matrix[57].
- A study[58] has shown how **thrombin triggers blood platelets to release transforming growth factor-beta 1 (TGF-b1), which is known for promoting disease progression in breast, prostate, colorectal and other cancers, and for suppressing immune-system responses to cancer**[59].

[53] Sebastian Himbert, Matthew J. Blacker, Alexander Kihm, Quinn Pauli, Adree Khondker, Kevin Yang, Sheilan Sinjari, Mitchell Johnson, Janos Juhasz, Christian Wagner, Harald D. H. Stöver and Maikel C. Rheinstädter , "Hybrid erythrocyte liposomes: functionalized red blood cell membranes for molecule encapsulation", *Advanced Biosystems 2020* https://doi.org/10.1002/adbi.201900185

[54] a senior advisor on the study and professor in the Department of Physics & Astronomy at McMaster

[55] lead author and a graduate student in the Department of Physics & Astronomy at McMaster.

[56] Zsolt Bagi et al., 'Extracellular vesicle integrins act as a nexus for platelet adhesion in cerebral micro-vessels', *Scientific Reports* volume 9, Article number: 15847 (2019) https://www.nature.com/articles/s41598-019-52127-3

[57] Laure Magnan et al., "Human textiles: A cell-synthesized yarn as a truly "bio" material for tissue engineering applications", 15 March 2020, *Acta Biomateriali* Volume 105 https://doi.org/10.1016/j.actbio.2020.01.037

[58] led by researchers at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

[59] Alessandra Metelli, Bill X. Wu, Brian Riesenberg, Silvia Guglietta, John D. Huck, Catherine Mills, Anqi Li, Saleh Rachidi, Carsten Krieg, Mark P. Rubinstein, Daniel T. Gewirth, Shaoli Sun, Michael B. Lilly, Amy H. Wahlquist, David P. Carbone, Yiping Yang, Bei Liu, Zihai Li. "Thrombin contributes to cancer immune evasion via proteolysis of platelet-bound GARP to activate LTGF-β", *Science Translational Medicine*, 2020; 12 (525): eaay4860 DOI: 10.1126/scitranslmed.aay4860

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

- **The European Medicines Agency (EMA) has agreed that Emergent BioSolutions should proceed with its proposed development plan for its chikungunya virus-like particle (CHIKV VLP) vaccine candidate**. Emergent proposed conducting a safety and immunogenicity Phase III trial using Serum Neutralizing Antibodies (SNA) as an immune correlate of protection to predict clinical benefit of the vaccine candidate. The vaccine is currently being investigated in a Phase II parallel-group, dose-finding study of approx. 430 healthy adults at three US sites.
- **Researchers have genetically engineered mosquitoes to be resistant to all four types of dengue[60].** They cannot be infected by or spread the virus. Omar Akbari, from the University of California, San Diego, said in a journal news release[61]: "The most important aspect of this study is the fact that we engineered mosquitoes to be refractory to all major serotypes of dengue virus. This may serve as a genetic tool to control dengue in the wild in the future."
- Early results from an ongoing project led by scientists from the Walter Reed Army Institute of Research have been published[62]. In a Phase 1 trial, **scientists found that an antibody (MZ4) had a positive effect on both the Zika virus and the dengue virus.** This suggests MZ4 could eventually play a role in a universal vaccine that would be able to work against the Zika virus and dengue.
- **A Phase I clinical trial**[63] sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) and **testing the safety and effectiveness of a monoclonal antibody[64] against malaria** began enrolling healthy adult volunteers at the National Institutes of Health Clinical Center in Bethesda, Maryland.

Influenza

- The US Food and Drug Administration (FDA) approved **the first adjuvanted, cell-based vaccine to provide active immunization against the influenza A virus**

[60] Anna Buchman, Omar S Akbari et al., "Broad dengue neutralization in mosquitoes expressing an engineered antibody", *PLOS Pathogens*, 16 January 2020 https://journals.plos.org/plospathogens/article?id=10.1371%2Fjournal.ppat.1008103
[61] *PLOS Pathogens*, news release, 16 January, 2020
[62] Vincent Dussept et al., "Potent Zika and dengue cross-neutralizing antibodies induced by Zika vaccination in a dengue-experienced donor", 3 February 2020, *Nature Medicine*. DOI: 10.1038/s41591-019-0746-2
[63] information about the study is available at clinicaltrials.gov using the identifier NCT04206332
[64] NK Kisalu *et al.* A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite. *Nature Medicine* DOI: 10.1038/nm.4512 (2018). https://www.nature.com/articles/nm.4512

H5N1 strain. Seqiris' vaccine Audenz is for use in people aged 6 months and older. It can be rapidly deployed and can be stockpiled for administration to first responders in a pandemic. Support for the development of Audenz was provided by the Biomedical Advanced Research and Development Authority (BARD).

- **Highly pathogenic bird flu (H5N6 and H5N1) have broken out in poultry in two Chinese provinces near Hubei.** These are two of the four strains that, while not easily infecting humans at the moment, have done so, have caused human deaths, and have shown possibility for human to human transmission[65].

Ebola virus disease

- **The World Health Organization on 13 February extended its global health emergency status for the Ebola outbreak in the Democratic Republic of Congo**, concerned that allowing the declaration to lapse might negatively affect response effort. WHO Director-General Tedros Adhanom Ghebreyesus told the media in Geneva: "As long as there is a single case of Ebola in an area as insecure and unstable as eastern DRC, the potential remains for a much larger epidemic."
- A recently published study[66] employed pharmacokinetics to evaluate an experimental treatment called TKM-130803 during the 2015 outbreak of Ebola in Sierra Leone[67].

MERS-CoV

- A study from the US National Institute of Allergy and Infectious Diseases (NIAID) found that **the experimental antiviral remdesivir successfully prevented disease in rhesus macaques infected with Middle East respiratory syndrome coronavirus** (MERS-CoV)[68]. Gilead tested remdesivir in Ebola with little success.
- **Vaccitech and its partner, the University of Oxford's Jenner Institute, in December 2019 began Phase I clinical trial of a vaccine against the Middle East Respiratory Syndrome Coronavirus** (MERS-CoV). Vaccitech retains commercial rights to this vaccine. The ChAdOx1 MERS vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the MERS Spike protein antigen.
- **Initial results have been published[69] for a Phase I first-in-human clinical trial of a DNA vaccine**, GLS-5300 MERS-CoV Vaccine.

New coronavirus first identified in Wuhan, China (Covid-19)

- UK public health specialist **Dr John Ashton said that WHO "failed to declare a global public health emergency in a timely way"**[70]. By the time the emergency was

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[65] https://infosurhoy.com/top-stories/bird-flu-breaks-out-in-two-chinese-provinces-near-coronaviruss-epicentre/

[66] Janet T. Scott et al. "Pharmacokinetics of TKM-130803 in Sierra Leonean patients with Ebola virus disease: plasma concentrations exceed target levels, with drug accumulation in the most severe patients", *EBioMedicine* (2020). DOI: 10.1016/j.ebiom.2019.102601

[67] The research was a collaboration of scientists from Sierra Leone and the Universities of Glasgow, Oxford, Cambridge and the Liverpool School of Tropical Medicine.

[68] E de Wit, *et al.*" Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection". *Proceedings of the National Academy of Sciences*. *PNAS* DOI: doi/10.1073/pnas.1922083117. https://www.pnas.org/content/early/2020/02/12/1922083117

[69] Xuejuan Shen et al., "Vaccine against Middle East respiratory syndrome coronavirus", *The Lancet Infectious Diseases,* October 2019 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30476-1/fulltext

[70] https://www.byronnews.com.au/news/who-accused-of-coronavirus-cover-up/3945744/

declared on 30 January the virus had spread beyond China. The UN agency said it did not declare a global emergency until it had evidence of human-to-human transmission outside China.

- **China has been using convalescent plasma to treat some Covid-19 patients.** Virologist Dr Jacob John commented: "Best time to give convalescent plasma containing antibodies is before disease develops. In the case of COVID-19, by the time pneumonia is diagnosed it is too late"[71].
- **Israeli firm Enlivex says Allocetra, its cell-based therapy developed to treat immune system over-reaction, may assist in combating complications caused by Covid-19[72].** The drug yielded positive results in six sepsis patients with multiple dysfunctional organs in a 2019 Phase Ib trial. The company said the therapy cannot vaccinate against or destroy the coronavirus, but it might offer hope to Covid-19 patients suffering from multiple organ failure by "returning over-reactive immune systems from a state of cytokine storm to equilibrium".
- **Gilead suggested using its antiviral remdesivir as a treatment.** A US patient was the first to receive it on a compassionate use basis[73].
- **AbbieVie has suggested its HIV drug Kaletra as a front-line treatment.**
- **There are numerous projects worldwide to develop a vaccine against Covid-19.** They include:
  i) CureVac, aiming to develop an mRNA coronavirus vaccine
  ii) Moderna, which is progressing its cytomegalovirus vaccine,[74] has now added a coronavirus vaccine to its pipeline with some funding from the Coalition for Epidemic Preparedness Innovations (CEPI)
  iii) Johnson & Johnson which has teamed up with the U.S. Biomedical Advanced Research and Development Authority (BARDA)
  iv) Inovio Pharmaceuticals has some CEPI funding
  v) As mentioned earlier, CSL is working with University of Queensland researchers to develop a vaccine**.**
- **South Korea has published online the travel logs of patients who developed Covid-19, so others can check if their paths have crossed[75].** Other governments have also used tracking systems for similar purposes. Hong Kong has used electronic wristbands to monitor patients in home quarantine. Taiwan has used mobile phone signals for monitoring home quarantine, though this could be readily circumvented.

[71] https://www.thehindu.com/sci-tech/science/convalescent-plasma-therapy-tested-on-critically-ill-covid-19-patients/article30830585.ece; http://www.xinhuanet.com/english/2020-02/14/c_138783616.htm; and John Mair-Jenkins et al., "The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis", *Journal of Infectious Diseases*, January 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264590/

[72] https://www.enlivex.com/ and https://m.jpost.com/HEALTH-SCIENCE/Israeli-company-ready-to-assist-coronavirus-victims-with-novel-drug-617777

[73] Michelle L Holshue et al, "First Case of Novel Coronavirus in the United States" New England Journal of Medicine, 5 March 2020, https://www.nejm.org/doi/full/10.1056/NEJMoa2001191

[74] Enrolment is proceeding in its Phase 2 clinical trial

[75] https://www.wsj.com/articles/south-korea-tracks-virus-patients-travelsand-publishes-them-online-11581858000

Other diseases

- **Researchers[76] have detected the presence of chronic wasting disease (CWD) prions in semen** and sexual tissues of prion-infected whitetail deer bucks[77].
- George Saade[78] reported at the Society for Maternal-Fetal Medicine annual meeting that **women with cytomegalovirus (CMV) randomized to receive hyperimmune globulin during pregnancy were more likely to develop placental syndrome**[79] than those assigned to placebo.

[76] from the University of Texas Health Science Center at Houston, Colorado State University and USDA/APHIS Veterinary Services

[77] Carlos Kramm et al., "In Vitro detection of Chronic Wasting Disease (CWD) prions in semen and reproductive tissues of white tailed deer bucks (*Odocoileus virginianus*)," *PLOS ONE* https://doi.org/10.1371/journal.pone.0226560

[78] of the University of Texas Medical Branch in Galveston.

[79] which includes preeclampsia, gestational hypertension, and small for gestational age infants