Monitoring International Trends

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The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could potentially put financial or other pressures on the Australian sector.

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

- ❖ Reports from the American Heart Association Scientific Sessions in November, including an update on CSL112. This is made from plasma CSL currently discards and is designed to reduce the high incidence of early recurrent cardiovascular events seen in patients after a myocardial infarction (Section 1).
- ❖ Reports from the American Society of Haematology Annual Meeting in December, with some emphasis on sickle cell anaemia and beta-thalassemia (Section 1).
- ❖ Ten patients with severe haemophilia B have remained free of the bleeding disorder for as long as three years as a result of gene therapy (Section 1).
- ❖ Oregon State University engineers have identified a means of rapidly preparing frozen red blood cells for transfusion, using a membrane-based microfluidic device (Section 1).
- ❖ Bayer submitted an application for marketing authorization to the European Medicines Agency for BAY 81-8973, its upgrade of Kogenate (Section 2).
- ❖ Baxter submitted a biologics license application to the US Food and Drug Administration (FDA) for BAX 855, its extended half-life recombinant factor VIII based on Advate (Section 2).
- ❖ Grifols has received FDA approval to proceed with a new plasma installation in North Carolina. This will increase Grifol's annual plasma fractionation capacity by 6 million litres (Section 3).
- ❖ CSL expects to launch early in 2016 its long-acting treatment for haemophilia B (Section 3).
- ❖ Tests, treatments and vaccines are being tried for Ebola Virus Disease (Section 7).

Contents

1. Products

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

Discussions at the American Heart Association Scientific Sessions in Chicago in November

a) Two reports[1] enhanced understanding of how CSL112, a novel formulation of apolipoprotein A-1 (apoA-1), may reduce the high incidence of early recurrent cardiovascular events seen in patients after a myocardial infarction. These early recurrent cardiovascular events are associated with high morbidity and mortality. CSL has now announced the launch of AEGIS-I, a Phase IIb clinical study of CSL112, administered as a short series of weekly infusions. This Phase Iib trial will involve 1200 patients round the world, including Australia. CSL112 is made from plasma that CSL currently discards.

b) Boehringer Ingelheim reported that Phase I study sub-analyses showed its idarucizumab reverses the effects of dabigatran[2] on fibrin formation in healthy volunteers. Idarucizumab is a humanized antibody fragment which restores wound-site formation of fibrin, the main component of a blood clot.

[1] Andreas Gille, CSL Head of Clinical and Translational Science Strategy, presented a poster titled, *CSL112 enhances cholesterol efflux equally in patients with high and low HDL functionality*. Svetlana Didichenko, CSL Senior Scientist,presented *Mechanism of HDL remodelling induced by CSL112.*

[2] the active ingredient in Pradaxa (dabigatran etexilate mesylate)

c) Portola Pharmaceuticals, Bristol-Myers Squibb and Pfizer announced results from the first part of the Phase III ANNEXA-A[3] studies. Andexanet alfa produced rapid and nearly complete reversal of the anticoagulant effect of *Eliquis* (apixaban) in healthy volunteers ages 50-75.
d) Omni Bio Pharmaceutical presented Phase 1/II clinical data for plasma-derived alpha-1 antitrypsin, demonstrating its ability to inhibit the inflammatory response in patients with acute ST-elevation myocardial infarction ("STEMI"), the most severe type of heart attack[4]. The company said these clinical findings further highlighted the potential value of Omni Bio's first-in-class recombinant AAT candidate, AAT-Fc. The recombinant AAT-Fc could offer several potential advantages over current plasma-derived products, including superior potency, longer half-life, improved safety and easy-to-administer subcutaneous dosing, as well as significantly enhanced manufacturing scalability.

Discussions at the American Society of Hematology Annual Meeting in San Francisco in December

e) Novo Nordisk announced a new analysis of Phase III data demonstrating people with haemophilia A who had the highest annualised bleeding rate during initial treatment with Novoeight (Antihaemophilic Factor [Recombinant]) showed the largest reduction in bleeding over the duration of treatment. There was no confirmed inhibitor development in 213 previously treated patients. The most common adverse reactions seen in the study were injection site reactions, increased hepatic enzymes, and fever[5].
f) Biogen Idec presented data supporting its approved haemophilia therapies, Eloctate and Alprolix[6].
g) Sangamo BioSciences presented new preclinical data from its proprietary programs for the treatment of lysosomal storage disorders and its Shire-partnered haemophilia program. The data demonstrated broad application of the ZFN[7] mediated genome-editing approach to therapeutics for these disorders[8].

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[3] Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors – Apixaban

[4] 1Alpha-1 antitrypsin (AAT) to quench the acute inflammatory response in ST-segment elevation acute myocardial infarction. ClinicalTrials.gov identifier: NCT01936896

[5] Amongst the eleven abstracts Novo Nordisk presented were *Changes in annualised bleeding rate over time and relationship with dosing of turoctocog alfa during the guardian programme* (Poster #2850); *Safety, efficacy, and pharmacokinetics of nonacog beta pegol (N9-GP) in prophylaxis and treatment of bleeding episodes in previously treated pediatric haemophilia B patients* (Poster #1513); *Safety and efficacy of nonacog beta pegol (N9-GP) for prophylaxis and treatment of bleeding episodes in previously treated patients with haemophilia B: Results from an extension trial* (Poster #2846); *Impact of Glanzmann's Thrombasthenia: Perceptions from US patients and parents* (Poster #4853); and *Unmet needs in diagnosis and treatment of Glanzmann's Thrombasthenia: Perceptions of US hematologists and nurses* (Poster #2179).

[6] The company presented seven abstracts. All data abstracts can be found on the ASH website at http://www.hematology.org/Meetings/Annual-Meeting/; full-text abstracts were published December 5 in the online archives of *Blood*, the journal of ASH. Biogen's key abstracts were *Safety, Efficacy, and Pharmacokinetics of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Previously-Treated Children with Severe Hemophilia A (Kids-ALONG)* – Poster #1494 ; *Predicting FVIII Activity in Patients Who Use Recombinant FVIII Fc Fusion Protein for Prophylaxis and Treatment of Bleeding Episodes* – Poster #1522; and *Predicting FIX Activity in Prophylaxis Patients Using Recombinant FIX Fc Fusion Protein for Treatment of Bleeding Episodes* – Poster #2842.

[7] Zinc finger nuclease

[8] *Taking it to the Clinic: Genome Editing for Blood Disorders* was given by Sangamo senior scientist, Fyodor Urnov, as part of the session *"Fixing the Broken Helix: Genome Editing for Disease Correction."* Other presentations by Sangamao were *NY-ESO-1 Single Edited T Cells to Treat Multiple Myeloma without Inducing GvHD (*Abstract #308*); HPRT As a Selectable Safe Harbor for*

h) A study of ten clinical trials involving dabigatran, rivaroxaban, and apixaban suggested that payers in the US would see a reduction in overall medical costs if patients switched to newer oral anticoagulants[9]. The authors reviewed recent clinical trials for new oral anticoagulants and compared event rates for patients taking these newer therapies for nonvalvular atrial fibrillation and venous thromboembolism to those taking standard therapy or placebo[10].
i) American Regent, a subsidiary of Luitpold Pharmaceuticals (a Daiichi Sankyo Group company), announced new data from two studies involving oral and intravenous iron replacement therapy in patients with iron deficiency anaemia[11].
j) Researchers reported on patient and caregiver perspectives on adherence to iron chelation therapy, which is used to manage iron overload in patients with sickle cell disease and other anaemias who have repeat transfusions[12].
k) A study based at the University of Wisconsin claimed to provide the first evidence that blood transfusion improves health-related quality of life for children with sickle cell disease[13].
l) A Phase III study of oral L-Glutamine therapy for sickle cell anaemia and sickle beta thalassemia suggested the treatment reduced pain crises and other events[14].
m) NKT Therapeutics presented positive Phase 1 clinical data for its lead compound NKTT120 in patients with sickle cell disease, as well as supportive data in a preclinical model of that condition.
n) Capnia's poster presentation described positive proof-of-concept data for the company's CoSense ETCO Monitor in patients with sickle cell anaemia, a disorder in which patients have chronic haemolysis. CoSense is a portable, non-invasive device that measures carbon monoxide in the exhaled breath and therefore the rate of haemolysis. CoSense is currently FDA cleared and CE marked[15].
o) Acetylon Pharmaceuticals announced positive preclinical data further detailing the mechanism of action and potential therapeutic use of selective HDAC1/2 inhibitors in the treatment of sickle cell disease and beta-thalassemia[16].

Transgenesis (Abstract #4796); and Gene Editing of CCR5 in Hematopoietic Stem Cells in a Nonhuman Primate Model of HIV/AID (Abstract #4802)

[9] The study's lead author, Alpesh N. Amin, consults for Bristol-Myers Squibb (BMS), and for Pfizer, who are joint makers of apixaban; other presenters on the poster consult or are employed by BMS or Pfizer.

[10] Amin, AN, Bruno A, Trocio J, Lin J, Lingohr-Smith M. "Comparison of medical costs avoided when new oral anticoagulants are used for the treatment of patients with atrial fibrillation and venous thromboembolism in the US". *Blood*, 2014; 124 (21): Poster 2181.

[11] *Clinical Criteria for Transitioning from Oral to IV Iron Replacement Therapy in Patients with Iron Deficiency Anemia (Abstract #68597)* and *Evaluation of Serum Oxidative Stress Indices Following Intravenous Iron Delivery in Women with Iron Deficiency Anemia (Abstract #67979).* The full abstracts can be found at: http://www.hematology.org/Annual-Meeting

[12] Bal V, Cote I, Lasch K, Huang V. "Patient and caregivers perspectives of factors associated with adherence to and satisfaction with iron chelation therapy". *Blood*, 2014; 124 (21): Poster 2166.Reasons for adherence included an established routine for taking treatment, belief in positive effects of ICT on health and longevity, and support from trusted caregivers and clinicians.Reasons for nonadherence included not liking the taste or aftertaste or texture of the therapy, or its gastrointestinal side effects. Mealtime restrictions were also an issue. Several coping mechanisms were reported, such as efforts to mask the taste. The lead author and all but 1 co-author are employed by Novartis.

[13] Beverung LM, Strouse JJ, Hulbert ML, et al. Health-related quality of life in children with sickle-cell disease: impact of blood transfusion therapy. *Blood*, 2014; 124 (21): Poster 2167

[14] The lead study author was Yutaka Niihara, of Emmaus Medical, in Torrance, California,

[15] *Elevated End-Tidal Carbon Monoxide Concentration in Children with Sickle Cell Anemia (Abstract #: 1390)*

[16] *Pharmacological Inhibition of Histone Deacetylases 1 and 2 (HDAC1/2) Induces Fetal Hemoglobin (HbF) through Activation of Gata2 (oral presentation (Abstract #335)*

p) In a poster presentation (Abstract #4053), Dr Jane Little[17] and colleagues introduced a novel biochip aimed at improving outcomes for patients with sickle cell disease. This innovative biochip evaluates the biophysical properties of red blood cells in sickle cell patients. It has wide applicability and uses only small volumes of blood[18].
q) The recombinant fusion protein luspatercept increased haemoglobin levels in patients with non-transfusion-dependent beta-thalassemia, according to study results presented by Antonio G. Piga[19]. Celgene and Acceleron are jointly developing luspatercept.
r) Mast Therapeutics presented data from an *ex vivo* study of MST-188 (vepoloxamer). In the study conducted at Loyola University Medical Center, the supplementation of MST-188 to blood samples collected from healthy normal individuals, sickle cell anaemia patients and sepsis-associated coagulopathy patients resulted in significant decrease in thrombin generation and marked decrease of functioning microparticles[20].

Products, devices and services

s) ADMA Biologics announced its lead product candidate, immunoglobulin RI-002 has demonstrated positive Phase III results and successfully achieved its primary endpoint of preventing serious bacterial infections such as bacterial pneumonia, osteomyelitis and bacterial sepsis in immune compromised (with primary immune deficiency disease or PIDD) patients. The Phase III US based trial enrolled 59 patients who received RI-002 for 12 months. Final data from the study will be reported during the first quarter of 2015. This will include secondary endpoints eg incidence of all infections (serious or otherwise), lost days of work or school, hospital admissions, emergency department visits and antibiotics prescribed. ADMA expects to submit its biological licence application during the first half of 2015[21].
t) Ten patients with severe haemophilia B have remained free of the bleeding disorder for as long as three years thanks to gene therapy, according to a new report in the *New England Journal of Medicine*. The study updates a 2011 report, in which six volunteers had been successfully treated at St. Jude Children's Research Hospital in Memphis, Tennessee with various doses of the treatment that uses a virus to insert genetic material into the liver. The four additional patients received the highest dose. The higher the dose of the engineered virus, the more factor IX the body produced. To engineer enough virus to treat the 10 patients required six months of work.
u) Researchers from MIT and Texas A&M University are developing biodegradable gelatin that once injected, helps with blood coagulation, cutting down on blood loss internally. Researchers hope that when tests are complete soldiers will carry preloaded syringes into the field.
v) Oregon State University engineers have identified a means of rapidly preparing frozen red blood cells for transfusion, using a membrane-based microfluidic device[22].

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[17] Director of the Adult Sickle Cell Anemia Center,University Hospitals Case Medical Center and Associate Professor at the School of Medicine.
[18] The biochip was developed by Umut Gurkan, assistant professor of mechanical and aerospace engineering at Case Western Reserve working in collaboration with a team.
[19] of the Azienda Ospedaliero-Universitaria San Luigi Gonzaga in Turin, Italy. (Abstract #53)
[20] The abstract entitled *Pro-coagulant Actions of Circulating Microparticles in Sickle Cell Anemia and Sepsis Associated Coagulopathy and their Modulation by a Triblock Polymer MST-188* was also published in the November 14, 2014 supplemental volume of the journal *Blood*. It is available on the company's website at http://www.masttherapeutics.com/technology/publications/
[21] ADMA's RI-002 is a plasma-derived, polyclonal, intravenous mmunoglobulin produced from human plasma containing naturally occurring polyclonal antibodies (e.g., Streptococcus *pneumoniae,* H. *influenza* type B, Cytomegalovirus (CMV), measles, tetanus, etc.) as well as standardized, high levels of antibodies to respiratory syncytial virus (RSV).
[22] The findings were reported in the journal *Biomicrofluidics.*

The reduction in preparation time from one hour to three minutes would make it more feasible to use frozen red cells in an emergency.

w) Welsh company EKF Diagnostics released its DiaSpect point-of-care haemoglobin analyzer. This provides nearly instant results, doesn't require pre-calibration, and performs a self-check between every reading.

x) Scientists from the University of California at Irvine have developed a new bloodstream infection test technology to speed up accurate diagnosis of ailments technology can detect bacteria in millilitres of blood without the need for cell culture.

2. Regulatory

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

Plasma and recombinant products

a) Bayer HealthCare submitted an application for marketing authorization to the European Medicines Agency (EMA) for BAY 81-8973, a full-length recombinant Factor VIII (rFVIII) compound for the treatment of haemophilia A in children and adults. It provides bleeding control when used for prophylaxis twice or three times per week, with standard dosages. Bayer will file for approval in other countries in the coming months. BAY 81-8973 is an upgrade to Kogenate that can be produced without the need for any human or animal components. Bayer is also working through Phase III on BAY 94-9027, a long-acting factor VIII replacement therapy that can be dosed as infrequently as once a week.

b) Baxter submitted a biologics license application to the US Food and Drug Administration (FDA) for BAX 855, an investigational extended half-life recombinant factor VIII treatment for haemophilia A based on Advate [Antihemophilic Factor (Recombinant)].

c) Grifols has received FDA approval to proceed with a new plasma installation in Clayton, North Carolina. The plant will increase Grifol's plasma fractionation capacity by 6 million litres of plasma a year, almost doubling its total global capacity.

Other

d) The FDA granted Cerus Corporation an Investigational Device Exemption for its INTERCEPT Blood System which will be used to treat the plasma of Ebola survivors for transfusion to patients infected with Ebola.

e) The US Senate passed a bill to add Ebola to the FDA Priority Review Voucher Program Act.

f) The US National Heart, Lung, and Blood Institute (NHLBI) announced that a clinical trial of hydroxyurea in children with sickle cell anaemia had been stopped a year early because it had been shown to be a safe and effective treatment for managing the disease and reducing the risk of stroke. The research, at 25 centres across the US and Canada, compared monthly blood transfusions with daily hydroxyurea pills with respect to the velocity of blood flow to the brain.

g) The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 9 to 1 to recommend approval of once-daily edoxaban 60 mg dosing regimen for the reduction in risk of stroke and systemic embolic events in patients with non-valvular atrial fibrillation.

h) The US Department of Health and Human Services proposed regulations to implement reporting requirements for clinical trials that are subject to Title VIII of the *Food and Drug Administration Amendments Act of 2007 (FDAAA).* This clarifies requirements for clinical researchers to register trials and submit summary trial results to ClinicalTrials.gov, a publicly accessible database operated by the National Library of Medicine, part of the National Institutes of Health (NIH). The required

summary results will now include trials of unapproved, unlicensed, and uncleared products.

i) The FDA has developed *Drug Trials Snapshots* to provide information about who participated in the clinical trials for new FDA approved drugs: their sex, age, race and ethnicity. *Snapshots* also includes information on how the study was designed, results of the efficacy and safety studies and, if known, differences in efficacy and side effects among sex, race and age (subgroups)[23].

3. Market structure and company news

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

a) CSL shares rose after CSL announced that it expected to launch early in 2016 a new drug to treat haemophilia B. Regulatory approval would be sought in the US and Europe. Chief Scientific Officer Andrew Cuthbertson said the drug exhibited a half-life 5.3 times longer than patients were accustomed to, and was effective in seven-day, 10-day and 14-day treatments. He said it had an "excellent" safety profile, with no adverse events reported during trials.
b) Expression Therapeutics and biomedical contract research group ABL announced they will collaborate to develop improvements in manufacturing recombinant factor VIII replacement therapy to reduce costs and reach new markets. ABL will perform cell line development studies. Express Therapeutics has previously used bioengineered FVIII transgene technology in preclinical gene therapy animal studies.
c) Spark Therapeutics, a gene therapy company, announced that it has entered into a global collaboration with Pfizer for the development and potential commercialization of *SPK-FIX*, a program advancing proprietary, bio-engineered adeno-associated virus (AAV) vectors for the potential treatment of haemophilia B.
d) Shares of Bluebird Bio rose after the company said its experimental gene therapy, LentiGlobin BB305, helped four patients with beta thalassemia major no longer need regular blood transfusions.
e) Inovio Pharmaceuticals, the University of Pennsylvania and MedImmune will collaborate on monoclonal antibody-based infectious disease treatments under a $US 12.2 million award from the US Defense Advanced Research Projects Agency (DARPA).

4. Country-specific events

The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia's visitors and immigrants come.

United States

a) A study has shown that bed bugs are capable of transmitting Chagas disease.
b) Researchers examined the correlation of sickle cell trait with deep vein thrombosis and pulmonary embolism in middle-aged African-Americans participating in the Atherosclerosis Risk in Communities Study. They found that after adjustment for age, sex, ancestry, hormone replacement therapy (women), body mass index, diabetes,

[23] For more about the drug trials snapshots: www.fda.gov/Drugs/NewsEvents/ucm424178.htm

and estimated glomerular filtration rate, the hazard ratio for venous thromboembolism for participants with sickle cell trait versus those without sickle cell trait was 1.50.

c) The emergence of a mutated flu virus not covered by the seasonal flu vaccination[24] has caused the Centers for Disease Control and Prevention (CDC) to issue a national health advisory urging caregivers to prescribe the antiviral medications Tamiflu and Relenza to suspected flu patients, even before they've been confirmed to have the virus.

Canada

d) Canadian Plasma Resources, the private firm trying to open plasma clinics in Ontario using paid donors, is leaving the province because of the Ontario government's opposition to payment for donors.

United Kingdom

e) The government rejected recommendations from the House of Commons Science and Technology Committee that further research and screening was necessary to prevent the spread of vCJD.

f) A UK study found that for older patients with diabetes, the prevalence of anaemia is 59 percent, with determinants including older age and longer duration of diabetes[25].

5. Safety and patient blood management

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

a) Research suggests longer surgery times increase the risk of developing blood clots[26].

b) A study by Harry Buller from the University of Amsterdam and colleagues found that reducing Factor XI levels with a second-generation antisense oligonucleotide (FXI-ASO) is effective for preventing venous thromboembolism after total knee arthroplasty[27].

c) A Swiss study suggests that for elderly patients on anticoagulant therapy, a high level of physical activity is associated with a decreased risk of major bleeding[28].

d) Preliminary data from a clinical trial showed that treatment for 30 months with dual antiplatelet blood-thinning therapy[29] decreased the risk of heart attacks and clot formation in stents, but there was an increased overall risk of death compared with 12 months of treatment[30]. The FDA said it would communicate its final conclusions and recommendations when its evaluation is complete, but meanwhile health care professionals should not change the way they prescribed these drugs at that time and patients should not stop taking these drugs at that time because doing so may result in an increased risk of heart attacks, blood clots, strokes, and other major cardiovascular problems. Healthcare professionals and patients were encouraged to

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[24] Testing has found that 52 percent of more than 1,100 H3N2 virus samples were found to be antigenetically different, or "drifted," from the H3N2 virus used in this year's flu vaccine, the CDC said.

[25] The research, by Katie Trevest from Rotherham General Hospital, and colleagues, was published in the October issue of *Clinical Diabetes*.

[26] See *JAMA Surgery, online December 3rd.*

[27] See the *New England Journal of Medicine*, 7 December. The study was funded by Isis Pharmaceuticals, the manufacturer of FXI-ASO.

[28] online 18 November in the *Journal of Thrombosis and Haemostasis, senior author Pascal M. Frey*

[29] consisting of aspirin plus either clopidogrel (Plavix) or prasugrel (Effient), following implantation of drug-eluting coronary stents. These stents are small, medicine-coated tubes inserted into narrowed arteries in the heart to keep them open and maintain blood flow to the heart.

[30] The Dual Antiplatelet Therapy (DAPT) trial was published in the *New England Journal of Medicine* on November 16, 2014

report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program.

e) Researchers from South Korea have reported to the 2014 Kidney Week meeting in the US that severe anaemia is independently associated with prolonged bleeding time in patients with chronic kidney disease.
f) In a study published in Nature's *Journal of Perinatology*, Eric Mallow and Mary Fox, both of Johns Hopkins, write about the chemical DEHP: The "daily intake of DEHP for critically ill preterm infants is on the order of 4,000 and 160,000 times higher than desired to avoid reproductive and hepatic toxicities, respectively." In other words, sick preemies are regularly exposed to levels of DEHP—in breathing tubes, feeding tubes, catheters, intravenous lines, and blood storage bags—that are thousands of times higher than have been deemed safe for infants. In the US this plastic chemical is banned from baby toys.
g) Researchers found that people with atrial fibrillation who take common painkillers might significantly increase their risk for bleeding and blood clots. That risk appears even higher for patients who take a blood thinner along with one of these nonsteroidal anti-inflammatory painkiller drugs (NSAIDs), which include aspirin, ibuprofen, naproxen and celecoxib (Celebrex)."If you add NSAIDs on top of blood-thinning medication, you double the risk of bleeding," said lead researcher Dr. Gunnar Gislason, from the Danish Heart Foundation in Copenhagen[31].

6. Research

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) At the University of California at Santa Barbara, researchers in the Department of Chemical Engineering and at the Center for Bioengineering have created nanoparticles that mimic the shape, flexibility and surface biology of the body's own platelets. This accelerates natural healing processes while opening the door to therapies and treatments that can be customized to specific patient needs.
b) A Japanese study found higher serum ferritin levels are associated with all-cause, cardiovascular, and infection-related mortality among patients on haemodialysis[32].
c) University of California researchers led by Donald Kohn have pioneered a stem cell gene therapy cure for children born with adenosine deaminase-deficient severe combined immunodeficiency (SCID), sometimes known as "Bubble Baby" disease, a life-threatening condition that if not treated can be fatal within the first year of life.
d) Scientists led from the Miller School of Medicine's Department of Medicine and Diabetes Research Institute have found that young capillary vessels can rejuvenate aged pancreatic islets. This suggests that targeting inflammation and fibrosis in the small blood vessels of the islet may offer new treatment options for diabetes[33].
e) Research has found a significant correlation between African Americans with sickle-cell trait and their likelihood of having or developing chronic kidney disease[34].

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[31] Gunnar Gislason, Danish Heart Foundation, Copenhagen, Denmark; Gregg Fonarow, professor, cardiology, University of California, Los Angeles; Nov. 18, 2014, *Annals of Internal Medicine*
[32] By Yukio Maruyama, of the Jikei University School of Medicine in Tokyo, and colleagues and presented in the US at the 2014 Kidney Week meeting.
[33] See *Proceedings of the National Academy of Sciences*. Team leaders include Alejandro Caicedo
[34] See the Journal of the American Medical Association, *JAMA*. Authors of the study were Rakhi Naik of Johns Hopkins University in Baltimore and Vimal Derebail of the University of North Carolina at Chapel Hill.

f) Dutch researchers[35] using meta-analysis identified predictors of chronic childhood immune thrombocytopenia: female gender, older age at presentation and the presence of antinuclear antibodies. They also observed a considerable protective effect of intravenous immunoglobulin alone against chronic immune thrombocytopenia.
g) Scientists from Johns Hopkins Medicine found a receptor on blood vessels that causes the vessel to relax in response to light, offering potential for treating vascular diseases. Scientists also discovered a previously unknown mechanism by which blood vessel function is regulated through light of a specific wavelength[36].

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, and the tick-borne babesiosis and Lyme disease).

Ebola virus disease

a) Sierra Leone has overtaken Liberia as the country with the highest number of Ebola cases in the current outbreak. Health officials discovered scores of bodies in a remote area. Without these, official records by 12 December were of 7987 cases in Sierra Leone since the outbreak began.
b) An African-led scientific team in collaboration with US based Clinical Research Management, and the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) announced the assembly of the Global Emerging Pathogens Therapy/Treatment (GET) Consortium. The group is pooling resources to assess the efficacy of immune plasma collected from survivors of Ebola in West Africa.
c) A rapid (15 minute) test for Ebola virus infection is being tried at a treatment center in Guinea. The trial, led by researchers at the Pasteur Institute in Dakar, Senegal, is funded by the Wellcome Trust and the UK government.
d) Molecular diagnostics company Cepheid has received a grant of up to $US 3.3 million from private foundations to develop a diagnostic test for Ebola.
e) Merck has acquired the exclusive rights to NewLink Genetics' Ebola vaccine. A clinical trial of the vaccine in Geneva was suspended as a precaution after some subjects complained of joint pains in their hands and feet. The trial is expected to resume on 5 January if the symptoms prove to be benign and temporary.
f) Integral Molecular has been awarded a $US 3.5 million contract to study the human antibody response to Ebola virus and hepatitis C virus. The award is from the National Institute of Allergy and Infectious Diseases (NIAID, part NIH).
g) Fujifilm Holdings Corp hopes its influenza drug Avigan will be approved by international government bodies to treat Ebola. Clinical test results are expected by the end of this year
h) Brincidofovir, an experimental antiviral drug made by Chimerix of Durham in North Carolina, is being trialled in West Africa in an Ebola treatment centre run by

[35] including Katja M.J. Heitink-Pollé**,** of University Medical Center Utrecht and Wilhelmina Children's Hospital
[36] See the *Proceedings of the National Academy of Sciences,* senior author Dan Berkowitz of the Johns Hopkins University departments of Anesthesiology and Critical Care Medicine, and Biomedical Engineering.

Médecins Sans Frontières (MSF), in the hope that it can be submitted for regulatory approval in that use.

i) Microdermis Corporation announced that its new antiseptic product, Provodine, which incorporates a novel drug-dermal delivery system, will be deployed by the US Army in West Africa in the fight against Ebola. Testing by USAMRIID demonstrated that Provodine provides superior antiseptic protection within 30 seconds of exposure with a > 99 per cent kill-rate against Ebola virus particles.The antiseptic skin product, is being applied as a final "molecular barrier" to viral exposure for healthcare workers and emergency responders using traditional layers of protective equipment. Skin coverage has been an issue in the fight against Ebola, with many antiseptic products contra-indicated for eye, mucosal surfaces (nose and mouth), ear and genitals, but Provodine is said to be safe to use on the most sensitive areas of the body.
j) Aethlon Medical hopes the use of its Hemopurifier device can be expanded to the treatment of Ebola, after it was used in treating a German patient who survived despite multiple organ failure**.** US clinical trials for use of the device in hepatitis C will be underway by the end of this year.

Mosquito-borne diseases

k) The head of surveillance at French Polynesia's Ministry of Health says chikungunya has spread throughout the territory.
l) Viennese company Themis Bioscience announced final results of its Phase I clinical trial of its chikungunya vaccine. It said the vaccine was well tolerated and safe and induced neutralizing antibodies in all 42 subjects.
m) Scientists from the Australian National University, working with other research groups nationally and internationally, have identified a number of molecules capable of disabling a molecular salt pump on the surface of the malaria parasite. With its pump disabled, the parasite fills up with salt, swells and bursts.
n) A new malaria drug developed by researchers from St. Jude's Children's Research Hospital in the US appears to trick the immune system into destroying 80 per cent of malaria parasites within 24 hours; and after 48 hours, no traces of the parasite are ever detectable again in patients. Laboratory results in mice suggest the drug works by inciting the body's immune system into destroying red blood cells that have been infected with malaria parasites without actually killing the healthy cells.

Influenza: strains, spread, prevention and treatment

o) Hundreds of thousands of birds in the Netherlands were culled after the H5N8 strain was identified, the strain that had earlier led to the culling of 30,000 turkeys in Germany. Avian flu was also found on a duck breeding farm in Yorkshire.
p) After bird flu was detected on poultry farms in British Columbia, the southern half of the province was designated an avian flu control zone. A number of overseas customers placed trade restrictions on all Canadian poultry.
q) Five subtypes of highly pathogenic avian flu have been notified by China to the World Organisation of Animal Health: H5N1, H5N3, H5N8, H5N6 and H5N2.
r) Russia is requiring poultry farms to carry out testing for bird flu.
s) Egypt continues to have human deaths from H5N1.
t) Researchers at NIAID in Bethesda, Maryland have found some types of avian flu can cause more severe disease in humans than others and should be watched carefully to prevent spread of disease[37]. Avian flu viruses of the subtypes H6, H7 or H10 might be expected to lead to severe infections in humans. In 2013 and 2014, approximately 400 cases of avian flu H7N9 infections were reported in China, along with cases of H10N8 and H6N1 subtypes.

[37] See the American Society for Microbiology journal *mBio,* senior study author Jeffery K. Taubenberger

MERS-CoV (Middle-East Respiratory Syndrome Coronavirus)

t) One or two people are being reported with MERS daily; the Saudi Arabian government is low key on the issue, advising citizens to wear a gown and mask when dealing with sick camels, and to boil camel milk before drinking.

u) Organic-Vaccines applied to the World Health Organization (WHO) for compassionate use of the company's MERS-CoV vaccine. Organic-Vaccines will file for an authorization from WHO for compassionate use of its monoclonal antibodies, to combat the recurrent mortality of Mers-CoV and be prepared for a potential outbreak in springtime.

Other diseases: occurrence, prevention and treatment

v) Research from the University of Arizona found that yeast cells can sometimes reverse the protein misfolding and clumping associated with diseases such as Alzheimer's.

w) Western Australia has issued a measles alert after a man returning from Bali moved widely around Perth while infectious.

x) A powdered measles vaccine has been found to be safe[38].

[38] See the November 28 issue of the journal *Vaccine,*