Monitoring International Trends

**posted January 2014**

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:

* Results from studies of new recombinant factors eight and nine, including long-acting products (pages 2 to 4).
* Update on development of an RNAi therapeutic (targeting antithrombin) for the treatment of bleeding disorders (page 4).
* Approval by the United States Food and Drug Administration (FDA) of Baxter's FEIBA, on the basis of a Phase III trial, for prophylaxis in patients with haemophilia A or B who have developed inhibitors (page 6).
* Approval by the FDA of NovoNordisk’s Tretten (NovoThirteen in Australia) for prophylaxis in patients with congenital factor XIII (FXIII) A-subunit deficiency (page 6).
* The acquisition of Canadian plasma fractionator Cangene Corporation by US firm Emergent Biosolutions (page7).
* The decision by the UK’s House of Commons science and technology committee to open a parliamentary investigation into measures to improve the quality of screening of blood and organ donors (page 9).
* The finding of a French study that blood transfusions raise the risk of thrombosis in patients with acute coronary syndromes (page 11).
* Funding for a US study of whether the age of transfused red blood cells received by critically ill children affects the risk of new or progressive multiple organ failure (page 11).
* A study of Danish blood donors which confirmed “iron deficiency as an important problem, especially among menstruating women donating frequently” (page 11).
* The creation by German scientists of artificial bone marrow (page 14).
* The expectation that the Penrose Inquiry into Scotland’s HIV-contaminated blood products will report in March (page 15).
* The resurgence of H7N9 flu in China (page 16).
* The continuing incidence of Middle East Respiratory Syndrome (novel coronavirus), MERS-Cov (page 18).

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# 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.*

### Haemophilia treatments/Clotting factors

* 1. UC Davis researchers led a phase III clinical trial which confirmed that Biogen Idec’s new recombinant factor IX (rFIXFc) decreases the number of injections needed to maintain effective clotting for haemophilia B patients[[1]](#footnote-1). This new product, Alprolix, fuses clotting factor IX with an immunoglobulin (antibody) molecule, which prevents the body from rapidly metabolizing the hybrid protein. rFIXFc can be administered once a week, or even every two weeks, rather than every other (or every third) day. Improved convenience for patients is also expected to increase compliance.
	2. A phase III study of a recombinant Factor VIII Fc fusion protein showed that a prolonged half-life was associated with low bleeding rates in patients with severe hemophilia A[[2]](#footnote-2). The regimen decreased injection frequency compared with recombinant Factor VIII. No patients developed inhibitors.
	3. Biogen Idec presented data from its haemophilia clinical development and research programs at the 55th Annual Meeting of the American Society of Hematology (ASH), in New Orleans in December[[3]](#footnote-3). This included the new, interim data from phase III studies in paediatric populations evaluating the long-lasting rFVIII Fc fusion protein candidate, Eloctate, for haemophilia A and rFIX Fc fusion protein candidate, Alprolix, for haemophilia B. At the time of the meeting regulatory applications for Eloctate and Alprolix were under review in several countries including the US, Canada and Australia.
	4. Baxter International filed an application with the FDA for a paediatric indication for its recombinant factor IX (Rixubis) to treat haemophilia B. The application relied on a Phase II/III clinical trial, which assessed the efficacy and safety of Rixubis in 23 previously-treated male patients under twelve, with severe or moderately severe haemophilia B. The FDA approved Rixubis for adults last year, and Baxter filed for marketing approval in Europe in November.
	5. Baxter International submitted a biologics license application (BLA) to the US Food and Drug Administration (FDA) for the approval of OBI-1, a recombinant porcine sequence factor VIII, in patients with acquired haemophilia A[[4]](#footnote-4). Phase II/III data supporting the submission was presented at the American Society of Hematology's (ASH) 55th Annual Meeting in New Orleans. These “showed that all patients in the trial experienced a positive response to treatment with OBI-1 within 24 hours of initiation of care,'' said Rebecca Kruse-Jarres, Associate Professor of Medicine and Pediatrics, Tulane University. ''These are promising results for a patient population that would benefit from a treatment option that provides temporary FVIII replacement and measurement of FVIII levels.'' Two of the eighteen patients in the study developed anti-porcine inhibitors to OBI-1. OBI-1 has orphan-drug designation for acquired haemophilia A by the FDA[[5]](#footnote-5). The application also has a fast-track designation[[6]](#footnote-6). Baxter acquired OBI-1 in March from Inspiration BioPharmaceuticals and Ipsen Pharma.
	6. Alnylam Pharmaceuticals presented new pre-clinical data for ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin (AT) for the treatment of haemophilia and rare bleeding disorders, at the 55th Annual Meeting of ASH[[7]](#footnote-7). Repeat administration of ALN-AT3 was found to be well tolerated in haemophilia A mice, with no adverse findings up to dose levels 200 times greater than levels required to achieve 50 per cent AT knockdown. The new studies also showed that ALN-AT3 administration achieved complete correction of the activated Partial Thromboplastin Time (aPTT)[[8]](#footnote-8) in haemophilia A mice. Alnylam expects to begin a Phase I trial with ALN-AT3 early in 2014. Sanofi is spending $US 700million for a 12 per cent stake in Alnylam.

### Sickle Cell treatments

* 1. At the 55th Annual Meeting of ASH, Acceleron and Celgene reported new interim clinical data from their phase II trial of Sotatercept in beta-thalassemia[[9]](#footnote-9). Dose-dependent increases in haemoglobin were demonstrated in non-transfusion dependent patients. Sotatercept has been granted orphan drug status by the FDA for the treatment of beta-thalassemia.
	2. Also at the ASH meeting NKT Therapeutics presented as a poster its initial clinical trial results for its monoclonal antibody, NKTT120, designed to suppress the chronic inflammation associated with sickle cell disease. The company said interim results from an ongoing phase 1 safety and dose escalation study in adults with stable disease showed complete and specific depletion of invariant Natural Killer T (iNKT) cells from the peripheral blood. No significant adverse events were reported.
	3. Again at the ASH meeting, Sangamo presented preclinical data from its therapy program for the treatment and possible cure of beta-thalassemia and sickle cell disease[[10]](#footnote-10). Sangamo uses its proprietary zinc finger nuclease (ZFN) gene-editing technology to increase the expression of foetal gamma-globulin in adult red blood cells. The first Phase I trial in transfusion-dependent patients will be conducted by two teams. The leader of one team, Mark Walters, Director of Blood and Marrow Transplantation at Children's Hospital & Research Center Oakland, said "The modification process is extremely efficient and scalable. We look forward to conducting a clinical study that employs Sangamo's technology in a patient's own stem cells to potentially provide a safer approach than current therapies, and eliminate the need for life-long medications and red blood cell transfusions that are currently the standard of care for these disorders."

### Other

* 1. Kamada has completed the pivotal phase II/III clinical trial in Europe and Canada of inhaled Alpha-1 Antitrypsin (AAT) therapy for the treatment of Alpha-1 Antitrypsin Deficiency (AATD or Inherited Emphysema). Kamada expects to report top-line results in the first quarter of 2014 and to submit a marketing authorization application (MAA) for the European Medicines Authority (EMA) in the second half of 2014. Kamada has approval from the FDA for a phase II clinical trial with inhaled AAT for AATD.
	2. Octapharma in December announced the enrolment of the first two patients in its GAM-27 Phase II/III clinical trial for the treatment of relapsing multiple sclerosis (RMS). This will trial intravenous immunoglobulin (Octagam 5%), to determine the overall clinical benefit of a lower annualised relapse rate in patients where first-line treatment is not suitable. Using a combination of functional genomic and protein expression tests on a blood sample, a special assay panel was developed to classify patients into predicted responders or non-responders.
	3. Immunomedics announced that its monoclonal antibody veltuzumab, administered subcutaneously, yielded an overall objective response rate of 49 per cent in 47 patients with relapsed immune thrombocytopenia (ITP), including 15 patients who experienced a complete response. For the 23 patients who responded to treatment, the median time to relapse from their initial veltuzumab dose was 9.2 months, with 11 patients maintaining their response for more than a year.
	4. [St. Teresa Medical of](http://www.stteresamedical.com/) Minnesota is commercializing a haemostatic technology platform called [FASTCLOT](http://www.stteresamedical.com/technology.php) which uses an [electrospun nano-fibre dextran matrix carrier](http://www.thefutureisnear.org/student_research/current_research/documents/drugencapsulation/xq21.pdf) along with fibrin producing proteins such as [thrombin](http://www.rcsb.org/pdb/101/motm.do?momID=25) and [fibrinogen](http://www.nlm.nih.gov/medlineplus/ency/article/003650.htm). The carrier dissolves in contact with fluid, releasing the clot forming proteins at the bleeding site. FASTCLOT products leave nothing behind in the patient’s body. St Teresa Medical is developing products for both surgery ([SURGICLOT) and trauma (WRAPCLOT)](http://www.stteresamedical.com/applications.php), for both civilian and military markets.
	5. Data presented on December 9th by CSL Behring at the 55th Annual Meeting of ASH showed Kcentra (Prothrombin Complex Concentrate [Human]) was superior to plasma, the current standard of care in the US, in adult patients taking vitamin K antagonist (VKA) therapy such as warfarin who needed warfarin reversal prior to an urgent surgery or invasive procedure. Kcentra, a non-activated 4-factor prothrombin complex concentrate, was approved by the FDA in April 2013 for the urgent reversal of warfarin therapy in adult patients with acute major bleeding but was not at that time FDA-approved for use in patients on VKA therapy requiring an urgent surgery or invasive procedure. This approval followed later (see page 6).
	6. Shire therapeutics announced that patients with inflammatory bowel disease and iron deficiency anaemia showed positive results from their ST10, an orally dosed form of ferric iron, in a phase III trial. The company CEO describes the drug “as the only effective, low-dose oral iron-replacement therapy without the significant GI (gastro-intestinal) side effects of ferrous iron or the high risks associated with intravenous administration of iron”**.**
	7. Researchers in Boston, led by [Jeffrey Karp](http://www.karplab.net/)[[11]](#footnote-11) and [Pedro del Nido](http://www.ctsnet.org/home/pdelnido)[[12]](#footnote-12) have developed and tested a new type of surgical glue. It is not toxic, adheres well to wet tissue, repels blood and water, and is strong and elastic enough to bind major blood vessels even when under the pressure of flowing blood. The team has shown that the material can seal the carotid artery and stick to the heart wall during surgery in pigs[[13]](#footnote-13).

# 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

* 1. The FDA approved Baxter's FEIBA [Anti-Inhibitor Coagulant Complex] for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A or B who have developed inhibitors. The approval was based on a Phase III trial, FEIBA PROOF, in which treatment with a FEIBA prophylactic regimen showed a 72 percent reduction in median annual bleed rate compared with treatment on-demand.
	2. The FDA approved CSL Behring’s Kcentra (Prothrombin Complex Concentrate [Human]) for an additional indication - urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (e.g., warfarin) therapy in adult patients needing urgent surgery or other invasive procedure. The product had received FDA approval in April 2013 for the urgent reversal of warfarin therapy in adult patients with acute major bleeding.
	3. The European Medicines Agency (EMA) has expanded the administration options for CSL Behring’s Hizentra (human normal immunoglobulin, subcutaneous, 20 per cent liquid) to include fortnightly dosing. Hizentra was approved in 2011 as once weekly subcutaneous immunoglobulin (SCIg) replacement therapy for adults and children with primary immunodeficiency[[14]](#footnote-14) to treat existing or chronic infections and prevent new infections.
	4. Baxter submitted an amended biologics license application to the FDA to re-start the review process for HyQvia [Immune Globulin Infusion 10 per cent (human) with Recombinant Human Hyaluronidase] subcutaneous infusion for the treatment of adult patients with primary immunodeficiency[[15]](#footnote-15). The FDA requested additional preclinical data from Baxter and Halozyme in 2012. The companies expect a six-month review period. HyQvia was launched in a number of European countries in the second half of 2013.
	5. The FDA approved NovoNordisk’s Tretten (coagulation factor XIII A-subunit [recombinant]) for the routine prophylaxis of bleeding in people with congenital factor XIII (FXIII) A-subunit deficiency. The company said that in clinical trials Tretten demonstrated safety and efficacy, offering patients once-monthly dosing with a short infusion time. Tretten is approved in Australia as NovoThirteen.
	6. The EMA's Committee on Human Medicinal Products (CHMP), on December 19 endorsed [recommendations](http://www.medscape.com/viewarticle/817398) from the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concerning two second-generation factor VIII products marketed by Bayer – Kogenate Bayer and Helixate NexGen. The CHMP [agreed](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Kogenate_Bayer_Helixate_NexGen_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500158680.pdf) with the PRAC that the benefits of the products continue to outweigh the risks in previously untreated patients with haemophilia A but accepted the PRAC recommendation that the product information for these medicines should be updated to reflect the results from the RODIN study. This Research of Determinants of Inhibitor Development (RODIN)/PedNet study raised concerns about a potentially increased risk for factor VIII inhibitor development with full-length second-generation factor VIII products like Kogenate Bayer and Helixate NexGen, compared with a third-generation recombinant product[[16]](#footnote-16). These findings had led to the review by the PRAC in March 2013.

# 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.*

* 1. Cerus Corporation submitted the fourth and final module for its Premarket Approval (PMA) application to the FDA the Intercept Blood System for plasma.
	2. ProMetic BioProduction’s plasma purification facility in Laval, Quebec completed the first commercial-scale production run. ProMetic says its plasma protein purification system allows for the targeting and removal of multiple high-value proteins from a single plasma sample using its mimetic ligand adsorbent technology, which incurs lower losses than does the Cohn precipitation process.
	3. Octapharma in April 2013 submitted a BLA to the FDA for human prothrombin complex concentrate for the urgent reversal of Vitamin K antagonist (e.g., warfarin) therapy in adults requiring urgent surgery or invasive procedures. The product is already approved in a number of countries as Octaplex, and in Australia as Pronativ. Octapharma has now entered into an agreement with Pfizer under which Pfizer will exclusively be responsible for marketing and commercialization in the US while Octapharma retains rights elsewhere.
	4. Canadian plasma fractionator Cangene Corporation signed a definitive agreement under which Emergent BioSolutions of Rockville, Maryland will acquire Cangene in an all-cash transaction valued at $US 222 million. Cangene shareholders will receive $US3.24 per share. The purchase price represents a premium of approximately 27 per cent on Cangene's closing stock price on December 10, 2013 and 45 per cent on Cangene's 90-day volume weighted average stock price. The acquisition is subject to a number of customary conditions including the approval of at least two-thirds of the votes of Cangene common shareholders, as well as court and regulatory approvals.
	5. Biotest AG of Germany and US firm EpiVax, of Providence, Rhode Island, announced a collaborative research agreement to develop a novel, non-immunogenic FVIII. The plan is to alter the coagulation in such a way that the immune system of haemophilia A patients may not respond by developing inhibitory antibodies. It is expected that suppression of immunogenicity will be achieved through integration of EpiVax’ Tregitope[[17]](#footnote-17), an immune-modulating technology, with the FVIII.
	6. Therapure Biopharma of Onatario and Denmark’s Upfront Chromatography have entered into an agreement for Therapure to acquire the assets and associated business related to human plasma fractionation from Upfront. Upfront has developed a proprietary protein purification technology, based on Expanded Bed Adsorption (EBA) chromatography. Therapure will continue development and marketing this technology under the new trademark PlasmaCap EBA. The CEO of Therapure said: “With PlasmaCap EBA, Therapure now possesses a technology to capture therapeutic plasma proteins that is highly efficient and less damaging to the end product compared to conventional methods of fractionation. Ultimately PlasmaCap EBA allows for a more cost-effective process to manufacture plasma proteins.”
	7. **CSL has granted US firm Janssen Biotech a licence to develop and commercialise CSL362, a monoclonal antibody for acute myeloid leukaemia, which is** an aggressive form of cancer affecting the blood and bone marrow.
	8. Biogen Idec and Sangamo BioSciences announced an exclusive collaboration and license agreement on the development of therapeutics for haemoglobinopathies, inherited conditions arising from the abnormal structure or underproduction of haemoglobin. Biogen Idec will be able to enhance its expertise in non-malignant haematology with Sangamo's proprietary zinc finger nuclease (ZFN) genome-editing technology platform to develop treatments for sickle cell disease and beta-thalassemia. (Sangamo’s ZFN technology is also mentioned on page 4).
	9. The Vall d'Hebron Research Institute in Barcelona (VHRI) has entered an agreement with Grifols to promote a centre of excellence for research and education for alpha-1-antitrypsin deficiency.
	10. The US Department of Defense through its Defense Advanced Research Projects Agency (DARPA) awarded Pfizer a $US 7.7 million contract to determine whether it might be possible to "identify and subsequently induce the production of protective antibodies to an emerging pathogen directly in an infected or exposed individual". This would be a departure from the usual method of developing immunity: extracting a pathogen, isolating its antigen, and using that antigen to create a vaccine *in vitro*. This vaccine is then injected into a patient to stimulate his or her immune system to repel subsequent attacks by the pathogen. DARPA’s hoped-for *in vivo* method would reduce the time between the discovery of a pathogen and the ability to deal with it. This current research contract ends in December 2016.
	11. Industry and stock market analysts have been writing about the competition on the horizon for [Baxter](http://analysis.morningstar.com/analystreport/ar.aspx?t=BAX&region=USA&culture=en-US)'s profitable haemophilia A product, Advate and what it could mean for the company. Baxter's BioScience division accounts for less than half of the firm's sales, but more than half of its profits. Advate dominates the US market for recombinant FVIII but is behind Bayer's Kogenate in Europe. Biogen Idec plans in 2014 to launch a long-acting product with a once-weekly dosing schedule. Novo Nordisk has a long-acting FVIII in late-stage development. Baxter has speeded up development of its own long-acting factor VIII BAX855, hoping for a 2015 launch. In addition, HyQvia, a long-acting subcutaneous version of Baxter's immunoglobulin product Gammagard has regulatory approval in Europe and Baxter hopes for a US launch in 2014.

# 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

* 1. In the US in 2011, hospital stays cost a cumulative $US 387.3 billion, approximately $US 10,000 per stay, according to the [Agency for Healthcare Research and Quality](https://www.hcup-us.ahrq.gov/reports/statbriefs/sb168-Hospital-Costs-United-States-2011.pdf). Mean hospital cost per stay varied from $US 4,500 for children under one year of age to $US 12,600 for those aged 65 to 84.
	2. An article in the *Journal of the American Medical Association[[18]](#footnote-18)* entitled "The Anatomy of Health Care in the United States" examined why the system is comparatively expensive, why its quality compares unfavourably with that in other developed countries[[19]](#footnote-19), and why chronic illness management in all age groups is the key to improvement. The article concluded that US underperformance across a range of diseases arises from fragmentation, the lack of organizational strategy in individual systems, and financial incentives that encourage procedures rather than comprehensive longitudinal care.
	3. The [Department of Health and Human Services](file:///%5C%5CCBRINTFS01.nba.local%5Ctopics%5Cdepartment-of-health-and-human-services%5C) reported[[20]](#footnote-20) that national blood transfusions fell to 13.8 million units in 2010, about 8 per cent fewer than in 2008. Blood collections were down by 9 percent, with 15.7 million units collected. Dr. Darrell Triulzi, medical director for the Institute for Transfusion Medicine in Pittsburgh and a former president of the American Association of Blood Banks, told The Associated Press that blood centres are shifting “from a collect-as-much-as-you-can mentality to a collect-to-need mentality”. He said the industry is “still learning how to do that well.”
	4. The American Society of Hematology (ASH) issued a list of five haematologic tests and/or procedures that should be discontinued, or at least used less frequently[[21]](#footnote-21). The list was published in the journal *B*lood. The recommendation concerning red blood cell transfusion is to use the smallest effective dose.
	5. The Centers for Disease Control and Prevention (CDC) reported that the number of cases of primary and secondary syphilis in the US increased 11.1 per cent in 2012. Men-particularly gay and bisexual men-accounted for the spike. Gonorrhoea increased 4 per cent in 2012, mostly among men.
	6. In 2007 the share of the US in global biomedical research spending was 51 per cent. By 2012 this had fallen to 45 per cent. While the National Institutes of Health had suffered some reduction in purchasing power, it was primarily reduced industry funding driving the decline in the US share[[22]](#footnote-22).

### Other countries

* 1. The United Arab Emirates will host the 34th International Congress of the International Society of Blood Transfusion (ISBT) in September 2016 at the Dubai International Convention and Exhibition Centre. The 2014 meeting will be held in Seoul, in the Republic of Korea.
	2. In the UK, the House of Commons science and technology committee decided to open a parliamentary investigation into measures to improve the quality of screening of blood and organ donors. Amongst other experts, Dr [Roland Salmon](http://www.irishtimes.com/search/search-7.1213540?tag_person=Roland%20Salmon&article=true) had told MPs the danger of variant CJD “becoming a self-sustaining epidemic”–because of the ever-increasing number of infected carriers–“has to remain a significant concern”.
	3. Biotest Farmaceutica Ltda., Brazil, a totally-owned subsidiary of Biotest AG, has received marketing approval for Albiomin (human albumin). Albumin production is doubling from 21 to 42 tons in Dreieich, Germany. Biotest is currently represented on the Brazilian market with its hyperimmunoglobulin Hepatect for prophylaxis of hepatitis B infections, in particular re-infections after liver transplantation. It also sells Megalotect, its hyperimmunoglobulin for the prophylaxis of cytomegalovirus infection for patients undergoing an immuno-suppressive therapy. Brazil is the fifth largest country in the world by population (around 200 million), which continues to grow. It has a large transplant market and a high incidence of hepatitis B.
	4. The Vietnam Health Ministry's Institute of Vaccines and Medical Biologicals says it has successfully produced vaccines against H1N1 and H5N1 flu and that production is underway, funded by the World Health Organization (WHO). The Institute is now conducting trials of another vaccine for the H7N9 flu virus.
	5. The Organisation of Economic Co-operation and Development (OECD), in its annual ‘Health at a Glance’ 2013 report says that Australians have access to a high quality health care system. Life expectancy at birth is 82 years, almost two years above the average life expectancy of the 34 OECD countries. Australia consistently rates among the top five countries in terms of survival after being diagnosed with cancer or after suffering heart attacks. Australians spend 8.9 per cent of their GDP on health compared with an OECD average of 9.3 per cent. However, Australia has among the highest rates of adult obesity in the world at 28.3 per cent, behind the US at 36.5 per cent, Mexico at 32.4 per cent and New Zealand at 28.4 per cent. The UK is 24.8 per cent and Ireland 23 per cent. Australia also reports comparatively high numbers of adverse events during hospitalisation. The incidence of a foreign body being accidentally left in after a surgical procedure is 8.6 per 100 000 hospital discharges, compared with the OECD average of five reports.

# Safety and patient blood management

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

### Appropriate transfusion

* 1. A review published in the *Annals of Internal Medicine[[23]](#footnote-23)* reports that the effects of liberal transfusion protocols on outcomes in heart disease patients with anaemia are mixed. Devan Kansagara, from Portland Veterans Affairs Medical Center in Oregon, and colleagues conducted a systematic literature review to identify trials of blood transfusions, iron, or erythropoiesis-stimulating agents in adults with anaemia and congestive heart failure or coronary heart disease. They also assessed observational studies of transfusion. They found that, considering combined risk, liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols. Nevertheless, in a small trial of patients with acute coronary syndrome, mortality rates were decreased with liberal transfusion. Three trials suggested intravenous iron might improve short-term exercise tolerance and quality of life in patients with heart failure. Seventeen trials of erythropoiesis-stimulating agents did not identify consistent benefits and suggested that the therapy might be associated with harms such as venous thromboembolism. The researchers concluded large trials were needed.
	2. Researchers from New York's NYU Langone Medical Center analyzed blood stock use from over 750 aortic valve replacements. They found that where data about potential complications was analyzed before surgery, less donor blood stock was usually required during the procedure so that clinicians could safely have less blood on standby.
	3. A French study[[24]](#footnote-24) concluded that blood transfusions raise the risk of thrombosis in patients with acute coronary syndromes (ACS). Dr Johanne Silvain[[25]](#footnote-25) and colleagues[[26]](#footnote-26) found increased platelet reactivity, while moderate, was sufficient to be considered an ischemic risk. They suggested that “the risk/benefit of transfusion should be weighed on an individual basis in ACS patients until a randomized controlled trial on conservative vs. liberal treatment of anemic ACS patients clarifies this issue.”

### Age and storage of units for transfusion

* 1. Dr. Philip Spinella, associate professor of paediatrics at Washington University Medical School, and director of the paediatric Blood Research Programhas received a $US 7.8 million grant from the National Institutes of Health to study whether the age of transfused red blood cells in critically ill children affects the risk of new or progressive multiple organ failure. Dr. Marisa Tucci of Sainte-Justine Hospital in Montreal will be his co-investigator. Most children transfused in the US are given the oldest available blood, the standard blood banking practice. Average storage time is 17-21 days, and range is 2 to 42 days. However, certain paediatric patients, at some hospitals, are given the freshest products: babies less than six months old, children having cardiac surgery, and some children with sickle cell anaemia. In Spinella's five-year study, 1538 critically ill children, from 3 days to 16 years of age, will be divided randomly into two groups. One group will receive red blood cells stored less than a week. The other group will follow the standard transfusion protocol. Those who would already receive fresh red blood cell transfusions will not be included in the study. About thirty US and Canadian hospitals will participate. The Canadian Institutes of Health Research will fund Canada-based costs. Only blood bank personnel will know which patients have received fresh vs. standard red blood cells. The label indicating length of storage will be obscured in the blood bank; neither patient nor doctor knows which kind of blood is given. This is the first large double-blind investigation involving children in paediatric intensive care units.
	2. New research suggests that, although red blood cells may be collected in solutions containing glucose to extend their shelf-life, these solutions may be adversely affecting both the patients who are transfused and the stored blood. Adverse effects of blood transfusions could be the result of high levels of glucose in the storage fluid. This may be up to ten times the normal bloodstream glucose level. Adverse effects on the red blood cells could mean ineffectiveness in transfusion. [Dana Spence](http://www.chemistry.msu.edu/faculty-research/faculty-details/params/group/spenceda/) of Michigan State University said: “By reducing the glucose levels, we saw that the red blood cells were able to release increased amounts of ATP [adenosine triphosphate] which, in turn, can stimulate nitric oxide in other cell types”. Nitric oxide is essential to blood flow and low nitric oxide bioavailability is a recognised problem associated with transfusion. The team is now investigating *in vivo* the survival of red blood cells after transfusion.

### Treating iron deficiency

* 1. A study of Danish blood donors[[27]](#footnote-27) confirmed “iron deficiency as an important problem, especially among menstruating women donating frequently. The risk of iron depletion was largely explained by sex, menopausal status, and donation frequency. Other factors, including dietary and supplemental iron intake, had a much weaker effect on the risk of iron depletion.”
	2. Acceleron Pharmawill receive a $US 7 million [milestone](http://www.4-traders.com/ACCELERON-PHARMA-INC-14297719/news/Acceleron-Pharma-Inc--Acceleron-Earns-7-Million-Milestone-Payment-for-Celgenes-Initiation-of-Sota-17623450/) payment from Celgene for the initiation of a Phase II clinical trial of sotatercept in patients on dialysis with end stage renal disease. Acceleron is also eligible to receive future milestones of up to $US 360 million for the sotatercept program. The drug increases haemoglobin levels and the mass of red cells, but is not erythropoietin-based. Its target is a protein, activin receptor type IIA. Sotatercept aims to regulate the differentiation and maturation of the precursor cells that will turn into red blood cells. By blocking signaling by Activin A, sotatercept stimulates bone formation.
	3. Scientists from Dana-Farber/Boston Children's Cancer and Blood Disorders Center told the 55th Annual Meeting of the American Society of Hematology that some babies treated for a bone marrow failure disorder, called diamond blackfan anaemia, may actually have been misdiagnosed, and in reality be affected by a very rare anaemia syndrome that has a different disease course and treatment. Genetic analysis of DNA from 175 [patients](http://medicalxpress.com/tags/patients/) thought to have diamond blackfan anaemia found eight who showed hallmarks of Pearson marrow pancreas syndrome. Suneet Agarwal, a paediatric haematologist/oncologist at Dana-Farber/Boston Children's said: "Some patients with diamond blackfan will respond to steroids, but there's no reason to give steroids to someone with Pearson Syndrome, and they could make things worse". A specific laboratory test for Pearson’s can identify a characteristic abnormality in the infant's DNA and Agarwal says this test "should be performed in the initial genetic evaluation of all patients with congenital anaemia…. Most patients with diamond blackfan anemia require blood transfusions into adulthood. If you're going to do a (bone marrow) transplant in a patient with diamond blackfan, outcomes are better if you do it early……Because patients with Pearson syndrome can get over their blood defect as young children, and because bone marrow transplantation does not cure the other problems in their bodies, the decision to proceed with transplant is more difficult”.

### New oral anticoagulants

* 1. A meta-analysis[[28]](#footnote-28) has suggested that the oral anticoagulants-dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)-consistently reduced the risk of intracranial haemorrhage when used for stroke prevention in patients with nonvalvular atrial fibrillation. They considered the pooled results of five warfarin-controlled trials and one aspirin-controlled trial.
	2. Boehringer Ingelheim has launched two new global clinical trials of dabigatran (Pradaxa). One will evaluate the drug in patients with an embolic stroke of undetermined source, while the other evaluation will be in patients with nonvalvular atrial fibrillation who have undergone percutaneous coronary intervention (angioplasty). The company has also released data from a Phase I study that it says showed that an investigational fully humanized antibody fragment led to an immediate, complete and sustained reversal of the anticoagulation effect of dabigatran in 145 healthy volunteers, and that there were no adverse events. Reversal was dose-dependent[[29]](#footnote-29).
	3. The FDA’s Cardiovascular and Renal Drugs Advisory Committee voted to approve Merck’s vorapaxar, for use as an adjunctive therapy for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). The panel spent much of the day discussing the drug’s controversial history. One large trial, TRACER, was stopped because of high rates of serious bleeding. T[he TRA2P trial](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2961269-0/fulltext) was redesigned partway through. However the panel concluded that TRA2P had been able to show that vorapaxar was effective in a post-MI population in which patients with a history of stroke were excluded. One of the eleven members dissented from the decision.
	4. Portola Pharmaceuticals has accepted a further clinical collaboration agreement with Bristol-Myers Squibb and Pfizer to study Portola's investigational Factor Xa inhibitor reversal agent, andexanet alfa (PRT4445), with the oral Factor Xa inhibitor Eliquis (apixaban). The first agreement, in November 2012, concerned a Phase II proof-of-concept study whose results were presented at the 2013 Congress of the International Society on Thrombosis and Haemostasis, and were said to have demonstrated that andexanet alfa could produce an immediate and either temporary or sustained reversal of the anticoagulation activity of Eliquis. The second clinical collaboration agreement covers Phase III studies and any potential US and EU regulatory approval of andexanet alfa.

### Other

* 1. The annual clinical congress of the American College of Surgeons was told that cardiac and vascular surgery patients are at higher risk postoperatively for deep vein thrombosis than are general surgery patients. The retrospective analysis was undertaken by Dr. Faisal Aziz of the Pennsylvania State University (Hershey) Heart and Vascular Institute and his colleagues.
	2. Austrian researchers reported[[30]](#footnote-30) that morphine appears to slow and to diminish the anti-clotting action of Plavix (clopidogrel). Morphine was associated with delayed ability to thin a patient's blood by an average of two hours, and decreased blood levels of the drug by about half. It also seemed to diminish the effectiveness of clopidogrel in breaking up blood clots, although the study showed only association and not a cause-and-effect relationship. The study is of special relevance to emergency treatment of heart attack victims, where doctors are dealing with both intense pain and the necessity to break up/ prevent blood clots.

# 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.*

### Sickle cell disease

* 1. Doctors at The Children’s Hospital in Philadelphia are hoping to prevent some sickle cell disease by identifying cases before babies are born. Each such baby would be given healthy bone marrow cells from one parent, in the hope that these healthy cells will become the dominant cells in the baby. Animal tests have so far been successful. Human trials are yet to come.
	2. Foetal haemoglobin is not affected by the genetic defect in sickle cell disease, so haematology researchers at The Children's Hospital of Philadelphia have manipulated events in adult blood cells to produce the form of haemoglobin which is not usually present after the newborn stage. "Our study shows the power of a technique called forced chromatin looping in reprogramming gene expression in blood-forming cells," said haematology researcher Jeremy W. Rupon. The team worked first with blood-forming cells from adult mice, then with adult human red blood cells. They will continue their research with the aim of moving to clinical application.
	3. The Doris Duke Foundation is funding researchers at Case Western Reserve University in Cleveland, Ohio, to work on sickle cell disease. Led by [Umut Gurkan](http://www.case-bml.net/Members.htm), an assistant professor of mechanical and aerospace engineering, the team wants to be able to predict when sickle cell patients will suffer an acute crisis, and also to monitor the effectiveness of their treatment. They are designing a hand-held device with which patients can monitor their blood. A further award from the Center for Clinical Research and Technology at University Hospitals Case Medical Center will allow the adaptation of the technology to children as well as adults, in particular the diagnosis of newborns.

### Other.

* 1. Scientists from the Karlsruhe Institute of Technology, the Max Planck Institute for Intelligent Systems in Stuttgart and the University of Tubingen have recreated basic properties of bone marrow artificially. Using synthetic polymer they created a porous structure to mimic the spongy bone in the area of the hematopoietic bone marrow. They added isolated hematopoietic stem cells straight from umbilical cord blood and incubated them for several days. The cells proliferated.
	2. Three centres[[31]](#footnote-31) are testing a new stem cell treatment that may help heart attack patients regenerate dead heart muscle. The therapy comes from Capricor, a Los Angeles company. The cells are injected into the coronary artery, from which they are expected to migrate to the heart and encourage muscle regrowth. The Phase I trial (mainly evaluating safety) is complete. Phase II will examine efficacy in around 300 patients, receiving either the treatment or placebo. The trial is financed by a $US 19.7 million grant from the California Institute for Regenerative Medicine, or CIRM, the state's stem cell agency. Although the procedure can use autologous cells (taken from the patient), using donor cells is preferred because they can be banked in advance and used when needed, like a blood transfusion. They are also less expensive because of economies of scale. While embryonic stem cells can become nearly any cell in the body, these "adult" progenitor cells can differentiate only into heart cells.
	3. Researchers from Kyoto University’s Centre for iPS Cell Research and Application (CiRA) and other institutions have developed a technique using induced pluripotent stem (iPS) cells to engineer red blood cells in significant numbers, twenty times the number of red blood cells compared with an existing method using the same amount of culture fluid. The team was led by Koji Eto, a stem cell biology professor at CiRA[[32]](#footnote-32).
	4. Researchers have found a way around the inhibitor response in dogs treated for naturally occurring haemophilia A. With a plasmapheresis machine and a blood-enrichment technique, they isolated platelet precursor cells from three dogs with haemophilia A. They engineered the cells to incorporate a gene therapy vector that expresses factor VIII, and returned them to the dogs. The cells proliferated and produced new platelets, and increasing numbers expressed factor VIII. After 30 months, factor VIII was still being expressed in platelets in all three dogs. In the animal that expressed the most factor VIII in platelets, the bleeding was limited to just one serious event each year. Tim Nichols, professor of medicine and pathology at the University of North Carolina at Chapel Hill, said “now we want to explore the possibility of moving it into human clinical trials”. The therapy might initially be restricted to patients who develop inhibitors to their treatment.

# Legal actions and enquiries

*The NBA is interested in the implications for Australia of any proceedings against companies, governments and professional practitioners in relation to blood and blood products; or of relevant public enquiries.*

* 1. A widower has filed a wrongful death claim in Pennsylvania against Octapharma. He alleges his wife died in 2011 as a result of health complications relating to treatments for multiple sclerosis with Octagam. In July 2010, days after having one of her intravenous infusions, the patient was discovered with slurred speech and unable to move her upper and lower extremities. She was taken to Thomas Jefferson University Hospital in Philadelphia where she was admitted to the stroke unit. The lawsuit alleges that in August 2010 Octapharma voluntarily withdrew selected lots of Octagam as a result of an increased number of stroke events experienced by patients who had received infusions; it further alleges the patient had received Octagam from the lots that were selected for voluntary withdrawal. A month after the selective withdrawal Octapharma withdrew all Octagam in the US. The company in time determined that the cause of the strokes was procoagulant impurities associated with the manufacturing process.
	2. The long-running Penrose Inquiry into Scotland’s HIV-contaminated blood products is due to report in March. Coinciding with this is the opening of *Factor 9*, presented by Inverness theatre company Dogstar, based on the story of some of specific patients infected by the NHS with HIV and hepatitis C through "bad blood" products during the 1970s and 1980s. The play will open in Sweden at a Festival of Horror and Art, be seen in Denmark and Wales, and make a four-week tour of Scotland in April.
	3. The Michigan appeals court ruled that doctors could not be held liable for the death of a woman who for religious reasons turned down a blood transfusion after a kidney transplant. In a 3-0 decision, the court determined the "doctrine of avoidable consequences" applied. Judge [Mark Boonstra](file:///C%3A%5C%3FcontrollerName%3Dsearch%26action%3Dsearch%26channel%3Dnews%26search%3D1%26inlineLink%3D1%26query%3D%22Mark%2BBoonstra%22) said: "It is the essence of personal responsibility that the makers of decisions and choices, relative to their own lives, bear the consequences that flow from those decisions and choices”.

# 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).*

### Mosquito-borne diseases: dengue, chikungunya and malaria

* 1. Panama government authorities have asked media to reduce their reporting of the country’s dengue epidemic because of the effect on tourism.
	2. French Polynesia has been experiencing twin epidemics- dengue and the zika virus. The latter is similar to dengue fever, chikungunya, yellow fever and Japanese encephalitis.
	3. Fiji’s outbreak of dengue is not the DENV 1 strain most usually seen there, but DENV 3 which has not been seen for around two decades, so a large proportion of the population is susceptible.
	4. A run of dry weather helped slow the spread of dengue in Cairns.
	5. Texas has had its first outbreak of dengue since 2005.
	6. Scientists at the University of Hawaii at Manoa have found that the FDA approved InBios dengue virus IgM ELISA kit detects anti-dengue virus IgM antibodies in under five hours[[33]](#footnote-33).
	7. There is a significant outbreak of chikungunya in the Caribbean. US health officials are concerned that infected travellers returning home can introduce the virus into local Aedes aegypti and Aedes albopictus populations when bitten by the mosquitoes.
	8. Chikungunya, which was thought to have been eradicated from Singapore, appears to have become endemic again. In the Philippines, the number of cases in 2013 was three times the number in 2012.
	9. In Western Australia the number of people diagnosed with chikungunya in the year to December 16 was 54, with most contracting it in Bali.
	10. GlaxoSmithKline and Medicines for Malaria Venture have received from the FDA breakthrough therapy designation for tafenoquine, an investigational drug for treating *Plasmodium vivax* malaria and preventing relapse. This designation is designed to speed development and reduce review times for drugs for life-threatening conditions.
	11. A team from Nanyang Technological University in Singapore has found a way to block access to red cells by the malaria parasite and hopes this can lead to development of an effective vaccine.
	12. The Bill Gates-backed antibody therapeutics developer Visterra has acquired an exclusive license to a family of four early-stage monoclonal antibodies that target dengue virus. They were discovered at MIT, using protein engineering approaches.

**Influenza: strains, spread, prevention and treatment**

### H7N9

* 1. By 20 January 204 human cases of avian influenza A (H7N9) had been confirmed on the Chinese mainland, including Zhejiang (77 cases), Shanghai (40 cases), Jiangsu (30 cases), Guangdong (23 cases), Fujian (12 cases), Jiangxi (six cases), Anhui and Henan (four cases each), Beijing, Hunan and Shandong (two cases each), and Hebei and Guizhou (one case each).
	2. On 18 January a medical worker in a Shanghai hospital died from H7N9, fuelling concern that the strain may be spreading from person to person.
	3. A patient in Hong Kong (who had travelled to the mainland) died on 13 January. His close contacts had earlier been quarantined and given Tamiflu and his other contacts were under medical surveillance. Hong Kong borders Guangdong province and Hong Kong's secretary for food and health on 12 January called on people in Hong Kong not to visit markets in Guangdong or the eastern mainland when they visited their relatives during the Lunar New Year holiday.
	4. On 5 January, Xinhua reported that samples of goose flesh taken from a Guangzhou market tested positive for H7N9 flu.
	5. On 30 December Hong Kong had its first H7N9 death.
	6. A study published in the *Proceedings of the National Academy of Sciences*[[34]](#footnote-34) suggested ethnic differences in the ability to mount an immune response to the H7N9 virus. This is due to genetic differences in a protein complex involved in cell-mediated immune responses. Professor Peter Doherty said the findings were supported by experience during the 1918-19 influenza pandemic, when 100 per cent adult mortality was seen in some remote Alaskan villages; and between ten and twenty per cent of Indigenous Australians died, compared with fewer than one per cent of non-Indigenous Australians. Similarly, during the 2009 H1N1 outbreak, 16 per cent of hospitalized Australians were Indigenous. Katherine Kedzierska[[35]](#footnote-35) explained that “The genetic susceptibility of Indigenous Australian and Alaskans would have resulted from isolation of indigenous populations from the viruses like influenza. The indigenous populations were not subjected to evolutionary pressures caused by the viruses over the centuries”.

### H10N8

* 1. A woman in Nanchang died of this strain in December. She was known to have been in contact with live poultry. The strain was detected in water birds in China in 2007. Its transmission mode is not known, and the possibility of human-to-human transmission is thought to be low. Its symptoms are severe pneumonia and respiratory failure. WHO described this death as “worrisome”.
	2. Taiwan responded to news of this death by issuing a travel alert for the Chinese province of Jiangxi. Taiwan had already banned the slaughter of poultry at traditional markets.

### H5N1

* 1. A resident of Alberta, Canada, died of the avian flu strain H5N1, following a visit to Beijing. This was not only the first known H5N1 death in North America, it was also the first known case of H5N1 infection imported by a traveller into a country where the virus was not present in the poultry. WHO advised that while it is difficult to transmit the virus from person to person, when people do become infected, the mortality rate is about 60 per cent.
	2. WHO confirmed that between 2003 and 2013 inclusive there were 648 human cases of H5N1 infection in 15 countries, and 384 deaths. If the H5N1 virus were to mutate and become easily transmissible between humans, the consequences for public health could be very serious.
	3. In mid-January, Vietnam reported its first H5N1 death for 2014.
	4. On December 18, 2014, 56 researchers wrote to the President of the European Commission asking that the Commission convene a meeting to discuss the risks of continuing research in which viruses are mutated to increase their transmissibility between mammals. This debate had begun with earlier “gain-of-function” studies with the H5N1 virus[[36]](#footnote-36).
	5. UK scientists[[37]](#footnote-37) have developed a new flu test using gold particles. They found that a gold solution changes colour in the presence of the flu virus, and the colour it changes to differs according to the strain. The test can distinguish between human and avian flu, and it could be used to fight superbugs in hospitals and even to detect toxins like ricin used in bioterrorism. “We are now looking for a diagnostics company to help us bring it to market,” said the researchers[[38]](#footnote-38).

### H9N2

* 1. A 7 year old boy in Hunan and an 86 year old man in Shenzhen were taken ill with avian flu H9N2. The boy had been in contact with poultry. He was treated in the local hospital and recovered. The man had no recent poultry contact, consumption of undercooked poultry, or contact with patients. He was treated in Hong Kong. The number of flu strains in circulation, including H10N8, may signal a higher risk of virus mutation and genetic swapping, said one expert. He said "Biosecurity measures and regulatory controls on the mainland have not caught up with increasing poultry numbers” as traders packed more birds into limited-space wet markets. Hong Kong in 2008 banned wet markets from keeping live poultry overnight. The H9N2 infection rate had been 5 per cent to 6 per cent but fell below 1 per cent after the ban.

### Seasonal influenza including H1N1

* 1. North America’s predominant flu strain in the current winter appears to be the 2009 H1N1 pandemic strain popularly known as “swine flu”. It has been sickening and killing young adults, and people 49 to 64. Europe has had three strains of flu circulating.
	2. The European Commission reported that of the 18 European Union member states who provided vaccination statistics for older age groups for 2011-12, only the Netherlands met the target of 75 per cent coverage.
	3. Japanese researchers have reported[[39]](#footnote-39) an H1N1 cluster resistant to oseltamivir (Tamiflu) and peramivir. The viruses were however sensitive to zanamivir (Relenza) and laninamivir, two other neuraminidase inhibitors.
	4. Visterra’s lead experimental flu drug VIS410 will be trialled in humans. It is not a vaccine, because it provides antibodies to fight the flu rather than encouraging the body to produce them.

### MERS-CoV

* 1. At January 3, 2014 WHO had been informed of a total of 177 laboratory-confirmed cases of infection with MERS-CoV, including 74 deaths[[40]](#footnote-40). Although camels are currently regarded as a probable reservoir for the disease, it has demonstrated human-to-human transmissibility. It also has a high [mortality rate](http://topics.sacbee.com/mortality%2Brate/) (42 per cent) and was called "a threat to the entire world" by Dr. Margaret Chan, the Director-General of WHO at the 66th World Health Assembly in Geneva.  In the US the Obama administration designated MERS-CoV a threat to public health and national security, and authorized the fast-tracking of approvals of tests and treatments for MERS-CoV.
	2. A health worker who treated the first MERS case in Dubai contracted the disease.
	3. Oman reported its second MERS case at the beginning of January.

### Other diseases: occurrence, prevention and treatment

* 1. A Canadian team led by Deborah Nicoll-Griffith of the Merck Frosst Centre for Therapeutic Research in Kirkland, Quebec, has developed a class of compounds which may help eradicate Chagas disease[[41]](#footnote-41). The current standard of care, benznidazole, has significant activity against the invading parasite during the acute phase, but is less effective in the chronic phase.
	2. Six biosecurity experts have strongly supported[[42]](#footnote-42) the omission of key genetic information from the October *Journal of Infectious Diseases* report of a newly identified *Clostridium botulinum* toxin. The six are either current or former members of the US National Science Advisory Board for Biosecurity. The toxin’s genetic sequence data has reportedly been withheld until an antitoxin can be developed.
	3. Two men who underwent routine bone marrow transplants in Boston, and who appeared to have become free of human immunodeficiency virus (HIV) after around eight months of antiretroviral therapy, have now tested positive for the virus again. A study[[43]](#footnote-43) has recently found T memory stem cells appear to hide a (HIV) viral reservoir long after treatment.
	4. British and Swedish researchers have found that patients with "superbug" types of tuberculosis (TB) could in future be treated with undifferentiated cells taken from their own particular bone marrow.
	5. That the blood of patients affected by sporadic and the new variant of Creuztfeldt-Jakob disease (CJD) shows the presence of infectivity was established by scientists from the French National Institute for Agricultural Research and the French National Veterinary School and European partners. Results so far[[44]](#footnote-44) support the concern that CJD might be transmitted (from people incubating the disease) by blood transfusion and blood derived products.
1. Jerry S. Powell et al., “Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B”, *N Engl J Med* 2013; 369:2313-2323 [December 12, 2013](http://www.nejm.org/toc/nejm/369/24/) DOI: 10.1056/NEJMoa1305074 [↑](#footnote-ref-1)
2. ##  [Mahlangu J.et al, “Recombinant Factor VIII Fc fusion protein effective in severe hemophilia A”,](http://bloodjournal.hematologylibrary.org/content/early/2013/11/13/blood-2013-10-529974.abstract%22%20%5Ct%20%22blank)

### *[Blood.](http://bloodjournal.hematologylibrary.org/content/early/2013/11/13/blood-2013-10-529974.abstract%22%20%5Ct%20%22blank)* [2013;doi:10.1182/blood-2013-10-529974.](http://bloodjournal.hematologylibrary.org/content/early/2013/11/13/blood-2013-10-529974.abstract%22%20%5Ct%20%22blank)

 [↑](#footnote-ref-2)
3. “Pharmacokinetics of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Pediatric Subjects with Hemophilia A: An Interim Analysis of the Kids A-LONG Study” -Poster #3609;

 “Dosing Long-Lasting Recombinant Factor VIII Fc Fusion Protein: Experience in the A-LONG Study” -Poster #3598;

“The Bleeding Tendency In Relation To Predicted FVIII Activity Levels In Severe Hemophilia A Patients Treated With Recombinant Factor VIII Fc Fusion Protein” -Poster #3590;

 “Association of Bleeding Tendency with Time Under Target FIX Activity Levels in Severe Hemophilia B Patients Treated with Recombinant Factor IX Fc Fusion Protein”- Poster #2349;

“Pharmacokinetics, Safety and Efficacy of Long-lasting Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Adolescent Subjects with Hemophilia B: A Subgroup Analysis of the B-LONG Study” -Poster #2350;

 “Pharmacokinetics of Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Pediatric Subjects with Hemophilia B: An Interim Analysis of the Kids B-LONG Study” -Poster #3599 [↑](#footnote-ref-3)
4. Acquired haemophilia A is a rare and potentially life-threatening bleeding disorder which occurs equally in both males and females and which usually affects older adults. Patients typically experience subcutaneous, deep tissue, and post-surgical bleeding. The comorbidities in this population provide challenges in the treatment of serious bleeding episodes. [↑](#footnote-ref-4)
5. Orphan-drug designation is given to drugs and biologics intended to treat rare diseases. [↑](#footnote-ref-5)
6. which is intended to expedite the review process of drug candidates with the potential to fulfil an unmet medical need [↑](#footnote-ref-6)
7. "Expanded Therapeutic Index of Antithrombin Silencing and Correction of APTT in a Hemophilia A Mouse Model" [↑](#footnote-ref-7)
8. an ex vivo measure of blood coagulation that is significantly prolonged in haemophilia [↑](#footnote-ref-8)
9. The poster containing relevant data is available on the Acceleron website in the publications section. [↑](#footnote-ref-9)
10. Sangamo abstracts at ASH pertinent to the company's programs in haemoglobinopathies included:
Using Forced Chromatin Looping to Overcome Developmental Silencing of Embryonic and Fetal Beta-Type Globin Genes in Adult Erythroid Cells” -Abstract#433;

“Targeted Gene Modification in Hematopoietic Stem Cells: A Potential Treatment For Thalassemia and Sickle Cell Anemia” -Abstract#434;

“Zinc Finger Nucleases Targeting the Beta-Globin Locus Drive Efficient Correction of the Sickle Mutation in CD34+ Cell”s -Abstract#2904; and
“Autologous Hematopoietic Stem/Progenitor Cell (HSPC) Therapy for Monogenic Blood Disorders: Scalable, cGMP-Compliant Process for Generating Highly Efficient Genome Edited HSPC” -Abstract#4213
 [↑](#footnote-ref-10)
11. a bioengineer at the Brigham and Women's Hospital in Boston [↑](#footnote-ref-11)
12. a cardiac surgeon at Boston Children’s Hospital [↑](#footnote-ref-12)
13. N. Lang et al. “A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects” *Science Translational Medicine*,10.1126/scitranslmed.3006557, 2014. [↑](#footnote-ref-13)
14. Primary Immunodeficiency Disease (PID) is not a single condition but a group of more than 1500 disorders that are caused by an absent or dysfunctional immune system. [↑](#footnote-ref-14)
15. The immunoglobulin provides the therapeutic effect and the recombinant human hyaluronidase facilitates the dispersion and absorption of the immunoglobulin administered subcutaneously, increasing its bioavailability. [↑](#footnote-ref-15)
16. Samantha C Gouw, et al., “Factor VIII Products and Inhibitor Development in Severe Hemophilia A” N Engl J Med 2013; 368:231-239[January 17, 2013](http://www.nejm.org/toc/nejm/368/3/)DOI: 10.1056/NEJMoa1208024 [↑](#footnote-ref-16)
17. Tregitopes are linear sequences of amino acids contained within the framework of the common serum protein, immunoglobulin G. Tregitopes act as a natural immune system ‘off switch’. [↑](#footnote-ref-17)
18. November 2013 [↑](#footnote-ref-18)
19. In the US, median "Years of Potential Life Lost" are much higher for several types of conditions when compared with the same measure for the other [33 countries](http://www.oecd.org/general/listofoecdmembercountries-ratificationoftheconventionontheoecd.htm) in the Organization for Economic Cooperation and Development. "Years of Potential Life Lost" are at least twice or three times as great as the OECD median in respiratory system disorders, blood/blood-forming organ disorders, musculoskeletal/connective tissue disorders, endocrine/nutritional/metabolic diseases, genitourinary disorders, infectious and parasitic diseases and skin/subcutaneous tissue disorders. [↑](#footnote-ref-19)
20. *2011 National Blood Collection and Utilization Survey Report* [↑](#footnote-ref-20)
21. The development of the list was part of the *Choosing Wisely* campaign led by the American Board of Internal Medicine Foundation during which a number of specialist societies have issued lists of practices which should stop. [↑](#footnote-ref-21)
22. *New England Journal of Medicine*, Vol. 370, No. 1, pp., Jan. 2, 2014 [↑](#footnote-ref-22)
23. on December 3, 2014 [↑](#footnote-ref-23)
24. published online December 18, 2013 in the *Journal of the American College of Cardiology*. [Rao SV. *J Am Coll Cardiol.* 2013;doi:10.1016/j.jacc.2013.11.028](http://content.onlinejacc.org/article.aspx?articleid=1789397) and [Silvain J. *J Am Coll Cardiol.* 2013;doi:10.1016/j.jacc.2013.11.029.](http://content.onlinejacc.org/article.aspx?articleid=1789398) [↑](#footnote-ref-24)
25. of Université Pierre et Marie Curie and Hôpital Pitié-Salpêtrière, Paris [↑](#footnote-ref-25)
26. In the second *Impact of Transfusion of Red Blood Cell on Platelet Activation and Aggregation Studied with Flow Cytometry Use and Light Transmission Aggregometry (TRANSFUSION-2)* study [↑](#footnote-ref-26)
27. Andreas Stribolt Rigas et al., “Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study*”, Transfusion,* doi: 10.1111/trf.12518 [↑](#footnote-ref-27)
28. by Saurav Chatterjee, of Brown University in Providence, Rhode Island, and colleagues in the December 2014 issue of [JAMA Neurology](http://archneur.jamanetwork.com/article.aspx?articleid=1788609). [↑](#footnote-ref-28)
29. The most sensitive indicator of dabigatran’s anticoagulant effect was thrombin time. Reversal was complete and sustained in all participants who received the 4-g dose and in seven of nine participants who received the 2-g dose. Reversal was not sustained in those who received the 1-g dose. [↑](#footnote-ref-29)
30. online December 4, 2013, in the *Journal of the American College of Cardiology*. [↑](#footnote-ref-30)
31. Cedars-Sinai Heart Institute, the Minneapolis Heart Institute Foundation and Scripps Health [↑](#footnote-ref-31)
32. The team's findings were published in the journal *Stem Cell Reports* on December 6. [↑](#footnote-ref-32)
33. The study was published in the *Journal of Clinical Microbiology*, [↑](#footnote-ref-33)
34. [Sergio Quiñones-Parra](http://www.pnas.org/search?author1=Sergio+Qui%C3%B1ones-Parra&sortspec=date&submit=Submit), [Emma Grant](http://www.pnas.org/search?author1=Emma+Grant&sortspec=date&submit=Submit), [Liyen Loh](http://www.pnas.org/search?author1=Liyen+Loh&sortspec=date&submit=Submit), [Thi H. O. Nguyen](http://www.pnas.org/search?author1=Thi+H.+O.+Nguyen&sortspec=date&submit=Submit), [Kristy-Anne Campbell](http://www.pnas.org/search?author1=Kristy-Anne+Campbell&sortspec=date&submit=Submit), [Steven Y. C. Tong](http://www.pnas.org/search?author1=Steven+Y.+C.+Tong&sortspec=date&submit=Submit), [Adrian Miller](http://www.pnas.org/search?author1=Adrian+Miller&sortspec=date&submit=Submit), [Peter C. Doherty](http://www.pnas.org/search?author1=Peter+C.+Doherty&sortspec=date&submit=Submit), [Dhanasekaran Vijaykrishna](http://www.pnas.org/search?author1=Dhanasekaran+Vijaykrishna&sortspec=date&submit=Submit), [Jamie Rossjohn](http://www.pnas.org/search?author1=Jamie+Rossjohn&sortspec=date&submit=Submit) , [Stephanie Gras](http://www.pnas.org/search?author1=Stephanie+Gras&sortspec=date&submit=Submit), and [Katherine Kedzierska](http://www.pnas.org/search?author1=Katherine+Kedzierska&sortspec=date&submit=Submit), “Preexisting CD8+ T-cell immunity to the H7N9 influenza A virus varies across ethnicities”, doi: 10.1073/pnas.1322229111 [↑](#footnote-ref-34)
35. Of the Department of Microbiology and Immunology at the University of Melbourne [↑](#footnote-ref-35)
36. In 2011, when a Dutch researcher was criticised for genetically manipulating the H5N1 strain so it could be transmitted by airborne particles between ferrets, the Dutch government used its export regulations to bar publication of full results. In October 2013 the European Society for Virology wrote to the European Commission supporting wide dissemination of research findings. [↑](#footnote-ref-36)
37. Professor Rob Field from the John Innes Centre and Professor David Russell from the University of East Anglia [↑](#footnote-ref-37)
38. Results were published in *Organic & Biomolecular Chemistry* [↑](#footnote-ref-38)
39. January 9, in Eurosurveillance [↑](#footnote-ref-39)
40. By 1 January, Saudi Arabia’s case count was 141, with 57 deaths. [↑](#footnote-ref-40)
41. The research was published online ahead of print in Antimicrobial Agents and Chemotherapy. [↑](#footnote-ref-41)
42. Casadevall A, Enquist L, Imperiale MJ, et al. “Redaction of sensitive data in the publication of dual use research of concern*”. mBio* 2014;5(1) (Early online publication Dec 31, 2013) [↑](#footnote-ref-42)
43. [published online](http://www.nature.com/nm/journal/vaop/ncurrent/full/nm.3445.html) January 12 in *Nature Medicine,* corresponding author Mathias Lichterfeld, from the Division of Infectious Diseases, Massachusetts General Hospital. [↑](#footnote-ref-43)
44. published in the journal *Emerging Infectious Diseases* on 11 December 2013 [↑](#footnote-ref-44)