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Perspective
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The EHA Research Roadmap: Transfusion Medicine

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In 2016, the European Hematology Association (EHA) published the EHA Roadmap for European Hematology Research¹ aiming to highlight achievements in the diagnostics and treatment of blood disorders, and to better inform European policy makers and other stakeholders about the urgent clinical and scientific needs and priorities in the field of hematology. Each section was coordinated by 1–2 section editors who were leading international experts in the field. In the 5 years that have followed, advances in the field of hematology have been plentiful. As such, EHA is pleased to present an updated Research Roadmap, now including eleven sections, each of which will be published separately. The updated EHA Research Roadmap identifies the most urgent priorities in hematology research and clinical science, therefore supporting a more informed, focused, and ideally a more funded future for European hematology research. The 11 EHA Research Roadmap sections include Normal Hematopoiesis; Malignant Lymphoid Diseases; Malignant Myeloid Diseases; Anemias and Related Diseases; Platelet Disorders; Blood Coagulation and Hemostatic Disorders; Transfusion Medicine; Infections in Hematology; Hematopoietic Stem Cell Transplantation; CAR-T and Other Cell-based Immune Therapies; and Gene Therapy.

We dedicate this paper in honor of Anneke Brand, who was a wonderful colleague and mentor to so many in European transfusion medicine.

TRANSFUSION MEDICINE

Transfusion medicine is a broad discipline, encompassing not just use of blood components, but many areas of donor recruitment and safeguarding, apheresis, and novel cellular therapies. This roadmap provides a framework for discussion of research priorities in transfusion medicine moving forward. Although one could highlight many future research

areas of direct relevance to donor and patient care, important themes remain centered on minimizing risks to patients and donors, and for the development of stratified or personalized transfusion strategies. It is clear that wide-scale genetic typing of donors and patients can now be delivered at low-cost, and the introduction of these technologies heralds a new era for transfusion medicine, which has been grounded in serological tests.

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Summary of main research and policy priorities

- Continued need for evidence for safe and effective use of blood components, including how donor/donation characteristics impact on outcomes after transfusion.
- Strategies for addressing prevention and management of alloimmunization, and the role of genotyping of donors and patients for matching.
- Defining evidence-informed indications for therapeutic apheresis and use of immunoglobulins, including dose and formulations alongside addressing self-sufficiency at a European level.
- Initiatives on safety and hemovigilance should specifically include donor vigilance of blood, plasma, and cell donation.
- Research in new areas of cellular therapies and the place of ex vivo generation and storage of blood cells.

USE OF BLOOD COMPONENTS

Introduction

The most commonly transfused blood component remains red blood cells (RBCs), followed by plasma and platelets. After the first Roadmap, the evidence base for transfusion therapy continues to expand with an increasing number of randomized trials, as highlighted by the European Frankfurt consensus conference.² The randomized trials of red cell transfusion typically compare giving more or fewer transfusions, at higher and lower hemoglobin (Hb) concentration thresholds, termed liberal and restrictive transfusion policies, respectively. In the main, most studies continue to show no harm when applying a more restrictive red cell transfusion policy compared to more liberal policy to maintain a higher Hb concentration posttransfusion. However, subgroups of patients may benefit from more liberal transfusions. A European trial, REALITY,³ is the largest randomized trial comparing a restrictive versus a liberal blood transfusion strategy in myocardial infarction patients with anemia, and results indicated noninferiority. Only one large trial with 300 patients has been conducted in patients with hematological diseases, which again reported no benefits for a liberal red cell policy in adult patients undergoing HSCT.⁴ Further analyses of all randomized trials may reveal a more precise definition of the benefits of restricted and liberal use for particular patient and age groups. Transfusion is potentially life-saving in major bleeding. The use of whole blood, providing all components of blood, and the role of cold stored platelets, which may have added functionality, continue to be important areas of research interest.

Despite historical precedence and biological plausibility, repeated clinical trials have shown lack of effectiveness for convalescent plasma in unselected patients with COVID-19, although further studies may identify a role for convalescent plasma in specific groups of patients, for example in immunocompromised patients, without anti-SARS-COV2 antibodies; these results enable health care resources to be better allocated to other areas of patient need during a pandemic.⁵

Proposed research

Many clinical settings for use of blood continue to be defined by variation in practice beyond that explained by case-mix, reflecting an inadequate evidence base. The degree to which the optimal Hb transfusion threshold and target for transfusion should be modified for subgroups of patients or those with specific risk factors (eg, elderly, coronary disease) still remains unclear. Therefore, there is a need for further trials of red cell transfusions in nonbleeding patients in clinical settings where there are currently no adequately powered randomized controlled trials data, for example patients with cardiovascular disease, brain injury, and hematological malignancies including

especially chronic transfusion-dependent anemias such as myelodysplasia.⁶ Better diagnostic tests and biomarkers identifying transfusion needs remain an area of research need. The Hb concentration is still used to define the need for red cell transfusions, calculate the dose of RBCs required, and monitor the response to transfusion or alternative treatment. However, Hb is a surrogate marker, and research should address better-targeted or physiological measures of oxygen requirements that can identify specific patient needs and personalize transfusion interventions.

There remains a lack of evidence to guide prophylactic use of platelet and plasma transfusions, to cover invasive/surgical procedures. Of concern is the finding from trials of platelet transfusions in neonates, and intracerebral bleeding in adult patients on antiplatelet agents, which reported evidence of harm with use of platelets.^{7,8} The mechanism by which platelets might be responsible for adverse effects in these trials is unclear, but platelets have well recognized roles beyond coagulation and hemostasis. Research to tackle the safety of prophylaxis will require efficiently designed studies to identify predictive risk factors for negative effects of platelet transfusions. These topics may be addressed by analysis of real-world data, such as through registries, and large clinical datasets drawing on information captured by electronic medical record systems.⁹

Anticipated impact of the research

Research will continue to refine the optimal and evidence-informed use of blood components. New methodological approaches to trial design, incorporating routine data, will be an increasing area of active interest in transfusion medicine. Indeed, a common feature of many hospital IT systems is limited ability for researchers to access and analyze comprehensive real-world data through electronic medical record systems, yet such approaches could significantly enhance the delivery of research. Cost-effectiveness is an increasingly important objective for research given the costs (alongside unwanted effects) of unnecessary transfusions.

PLASMA-DERIVED AND RECOMBINANT HUMAN PLASMA PROTEINS

Introduction

Plasma is a source of many proteins for medicinal use. Intravenous immunoglobulins (IVIGs), a pooled normal IgG from the plasma of several thousand healthy donors, are used for the treatment of hypogammaglobulinemia, autoimmune, and inflammatory conditions. The recent mechanistic studies performed by European researchers show that IVIG could exert anti-inflammatory effects by inducing autophagy in inflammatory immune cells and by inducing IL-4 in human basophils through direct interaction with FcεRI bound IgE.¹⁰⁻¹²

Proposed research

A better understanding of the (cost-) effectiveness of IVIG continues to be needed. IVIG infusion by intravenous route requires trained personnel, hospital admission and also leads to loss of working days. To address these issues, alternative IgG formulations for subcutaneous administration (SCIG) have been developed, and may have roles beyond well-established uses in patients with primary immunodeficiencies, for example, to treat autoimmune and inflammatory diseases and at lower dosages.¹³⁻¹⁵ Recent studies have highlighted possible benefits that early initiation of IgM-enriched immunoglobulin therapy may reduce the risk of mortality and duration of mechanical ventilation in subpopulations of sepsis patients.^{16,17}

There is interest in the application of therapeutic molecules as alternatives to IVIG to overcome its potential limitations of supply and cost. Analogous to IVIG, a pooled normal IgA from plasma of several thousand healthy donors has been explored

in experimental models of autoimmune diseases and have yielded promising results, which require further evaluation.^{18,19} In addition, rozanolixizumab, an antihuman FcRn monoclonal antibody, and efgartigimod, an IgG1 Fc fragment, have been investigated to promote catabolism of autoantibodies.^{20,21} The phase I randomized, double-blind, placebo-controlled, dose-escalating study showed that rozanolixizumab and efgartigimod reduce the concentrations of circulating IgG. Furthermore, a phase 2 study of efgartigimod in generalized myasthenia gravis and primary immune thrombocytopenia demonstrated promising therapeutic benefits.^{22,23} Data from these studies warrant further investigation of FcRn antagonists as a novel therapeutic approach to treat autoimmune diseases.

Anticipated impact of the research

Better evidence from good quality comparative studies would define more appropriate use of IVIg for replacement, and define the role of novel plasma derived and synthetic therapeutic molecules for autoimmune and inflammatory diseases.

APHERESIS

Introduction

Apheresis procedures are a resource intensive intervention applied for diverse indications. The American Society for Apheresis (ASFA) provides an evidence-based synthesis of indications for hospital practice, but for many indications, the optimal role of apheresis therapy is not established. Some indications for apheresis appear more common practice in Europe, for example the use of adsorption columns for IgG-removal in case of HLA- or ABO-antibodies in organ transplant recipients or for lipid binding in combination with plasma separation devices.

Apheresis procedures are commonly used in donor practice, for example plasmapheresis for the collection of plasma as a source for polyvalent immunoglobulins for intravenous (IVIg) or subcutaneous (SCIg) use. Apheresis collection of platelets is practiced in many blood services, although the nature of the clinical benefit and adverse transfusion reaction profile compared to whole blood-derived platelets has not been demonstrated. European plasma-collection from nonremunerated donors is not sufficient to meet demands, and strategies are required to promote and expand the nonremunerated donor population alongside appropriate surveillance of donor safeguarding.

The collection of progenitor hemopoietic cells or immune cells for autologous and allogeneic use is a significant growth area. Of >50,000 hematopoietic stem cell transplants (HSCTs) performed worldwide each year, over 70% are obtained by blood stem cell apheresis. Apheresis procedures support the collection of mononuclear cells (CD3+ T-cells) for donor lymphocyte infusion after HSCT. Ex vivo processing of the collected leukocytes for cellular therapies is underpinning novel potent anticancer treatment or antiviral vaccination therapy.

Proposed research

There remains an ongoing need to contribute to evidence base indications for therapeutic apheresis. The establishment of a global standardized surveillance system for related stem cell donor care comparable to care for unrelated volunteer donors is in development, as a joint effort of the World Marrow Donor Association and EBMT. The safety of new stem cell mobilization drugs (eg, biosimilars and CXCR4 agonists) requires pan-European collaboration.²⁴

The request for CD3+ immune cells for the cellular therapies is increasing, but many aspects of production and processing remain poorly defined for optimal practice. Manufacturing and processing need to be studied alongside trials to evaluate

benefits in recipients and require attention to the potential risks for the donor including procedure-related stress. Other developments are the need of cells from volunteer donors to improve processes, and to develop allogeneic chimeric antigen receptor T cells (CAR-T).

For plasma and platelet donation from unrelated donors, safety of donors remains paramount. Further study risks include repeated exposure to citrate and protein removal, which may impact on risks for osteoporosis and hypogammaglobulinemia in the long term. There is a need to address European self-sufficiency of plasma collection.

Anticipated impact of the research

New cellular treatments will be an area of expansion. Although short-term adverse effects of patient as well as donor apheresis are considered minimal, long-term effects of many procedures applied in healthy (volunteer, nonremunerated) donors are less well studied. The proposed research subjects can provide the European community with information about the risk and safety issues for donors, and promote policies for greater protection of nonremunerated donors.

IMMUNOLOGICAL TRANSFUSION COMPLICATIONS (ALLOIMMUNIZATION/TRIM/HEMOVIGILANCE)

Introduction

Blood transfusions are biological interventions. A new encounter with a cognitive antigen by transfusion, pregnancy, or transplantation can cause morbidity and mortality. The overall prevalence of alloimmunization across Europe is unknown and varies between patient categories and according to the numerous antigens expressed on blood cells and blood substances. Molecular genotyping of most blood cell antigens is now possible,^{25,26} and cost-efficient genotyping of donors are real advances happening now in transfusion practice. Taken together, the next 5 years will see a paradigm shift in matching abilities for transfusion practice.

For selection of HLA compatible stem cell and organ transplants, Europe has established registries that cooperate, including research networks to characterize the genetic HLA diversity of populations with impact on both, public health and fundamental research (Allele Frequency Net Database).²⁷ Eurotransplant offers over 25 years an acceptable mismatch program for heavily immunized patients, which is regularly updated. Until 2021 over 1700 highly sensitized patients received a compatible renal graft with good graft survival.^{28,29} A feasible goal is to extend these European initiatives to other settings including compatibility of classic blood components used for transfusion. Recent work has defined the determination of fetal blood groups from maternal blood to avoid unnecessary treatment.

Proposed research

Broad research goals can be summarized as addressing: (1) epidemiology; (2) prevention; (3) reversal of immunity; and (4) new strategies for mitigation of severe alloimmune reactions.

One major research focus will be to define which of the genetic information available for donors and patients needs to be considered for safe transfusion and transplantation. This requires integration of available technological platforms for testing new concepts of logistical assignment of blood products into clinical practice. A European platform has provided a signpost to implement "RBC blood match on a chip" with next-generation sequencing (NGS) approaches targeting HLA, HNA, HPA, and RBC genes.²⁶ This provides the information for improved matching, including epitope rather than antigen matching,²⁹ in the transfusion as well as transplantation setting.

EU wide registration of alloantibodies is important to recruit appropriate phenotypes for blood and stem cell donation (for instance, ethnic minorities) and for composition of

high-throughput RBC, HLA, HNA, and HPA typing platforms of donors and recipients. Surveillance of immune reactions towards manipulated blood products (eg, treated for pathogen reduction; genetically engineered) is needed to exclude immunogenic neoantigen formation. Registration of patients suffering severe clinical reactions versus patients with no or minor symptoms from a comparable mismatch, will lead to personalized medicine taking into account acceptable mismatches and risk factors, both, in patient and products/grafts. In parallel, a joint nomenclature for consistent and safe reporting of alleles has been devised as well as databases of blood group variants to support NGS and other genotyping interpretation. A large database listing of rare blood group donors for international use is already coordinated by the International Blood Group Reference Laboratory in Bristol, and for highly immunized patients frozen rare blood is banked at several European centers. To be included on microarrays or targeted in NGS, the molecular genetic bases of circa 40 of the 370 defined RBC antigens must be completed to predict the full phenotype, and to match for selected cases of incompatibility between the donor and patient.

Despite all measures, some patients still get immunized (eg, during pregnancy). Studies of genetic and environmental/innate factors for T- and B-cell activation, memory³⁰ and antibody persistence in humans must elucidate the complex pathophysiology of high- and low-responder individuals.³¹

New drugs and approaches are needed to mitigate overwhelming innate immune responses such as complement-activation and other sequels (cytokine storm) of antigen-antibody reactions. They may save lives and transplanted organs. New immune-treatments like CAR-T cells might even open the possibility to specifically eradicate B- and T cells underlying unwanted alloimmune reactions.

An important new field is to overcome immunogenicity of engineered allogeneic immune cells used to treat malignancies or autoimmune disorders to overcome the restricting of their use mainly to autologous settings, which is a limiting cost barrier.

Anticipated impact of the research

Wide-scale genetic typing of donors and patients can now be delivered at low-cost, and should enhance the move toward personalized transfusion therapy, but needs to be evaluated for benefit and cost-effectiveness in real life. The benefits include reducing (HLA, RBC, or HPA) alloimmunization in patients at high risk for the consequences of particular antibodies. All research programs require investments and support through bio-informatics systems for analyzing big-data.²⁶⁻²⁸

TRANSFUSION-TRANSMITTED INFECTIONS AND PATHOGEN REDUCTION OF BLOOD COMPONENTS

Introduction

Pathogen reduction technologies (PRTs) have been developed to further reduce the already very low risks of transfusion transmitted infections (TTIs), and allow quicker responses to emerging infectious threats. Another potential approach for the reduction of infectious risk from transfusion is to replace human blood components with alternatives or substitutes. These include recombinant coagulation factors, albumins, immunoglobulins and polyhemoglobin. Ex vivo cultured red blood cells and platelets are under development, as discussed in the next section.

Proposed research

Any TTI may have important consequences in immunocompromised patients, but the risks and incidence of TTIs in hematological patients have not been fully investigated.^{32,33} Examples of potential TTIs include hepatitis E virus, parvovirus B19 and

cytomegalovirus. Approaches to increase blood safety may include additional donor and donation screening, vaccination of patients at risk (when possible), and pathogen reduction of blood components.³⁴ On the other hand, the expanding need of additional blood safety measures will likely increase the cost of producing blood components and burden already limited health resources. In addition, disproportionately stringent donor selection criteria can lead to detrimental deferral of blood donors with negligible or no risk. Adequate research may help in evidence-based decision-making related to above questions.

Several questions related to PRT of blood should be addressed.³⁵⁻³⁷ These questions that require further research include:

- To what extent do PRTs affect the platelet function?
- What is the clinical efficacy, quality, and safety of PR for RBCs?
- Do PRTs increase the immunogenicity of cellular blood products?
- How to decrease costs and evaluate the infectivity-reduction capacity of PRT?
- What are the differences in the clinical effectiveness, quality, and safety of blood products treated by different PRTs (with comparative studies)?
- How to achieve pathogen reduction efficacy of nonenveloped viruses and bacterial spores?

Due to intrinsic limitations of the various strategies and a lack of applicability to all pathogens and blood component types, PRTs are not always sufficient to prevent infectious blood from entering the blood supply.

Anticipated impact of the research

The proposed research will contribute to improving the quality of established commercial technologies for pathogen reduction of platelets and plasma A broader efficacy spectrum of PRTs, to include nonenveloped viruses and spores, will further reduce the frequency and severity of pathogen transmission with blood transfusions.

LABORATORY MANUFACTURED BLOOD CELLS FOR THERAPEUTIC USE

Introduction

Advances in our understanding of erythropoiesis and megakaryopoiesis enable us to generate in vitro cultured red blood cells (cRBCs) and cultured platelets (cPLTs) that could ultimately be used for transfusion purposes. These culture techniques are now being implemented for at scale production of these blood cells using bioreactors and offer the potential for reduced blood borne infections, but they are currently still very expensive to produce at the scale needed for transfusion therapy. While they are being manufactured, the cRBC and cPLT might be customized to reduce inherent risks such as alloimmunization against, for example, high-frequency blood group antigen, and also allow the generation of functionally enhanced cells expressing therapeutic molecules or containing drugs.

Currently, multiple research groups in Europe develop larger scale cultures to manufacture (small scale) transfusion products.³⁸⁻⁴⁵ These different laboratories use a range of different initial starting sources to generate the cRBC and cPLT products. These include hematopoietic stem cells from adult blood or cord blood,^{38-43,45,46} differentiated induced pluripotent stem cells (iPSCs) or forward programmed lines derived from GMP compliant sources,^{44,47,48} and more recently novel immortalized adult erythroblast cell lines,^{3,12,40,49} or transdifferentiated fibroblasts.⁵⁰ Bioreactors and shear force generating technology are being developed for the production of mature cPLT and cRBC free of genetic material.^{41,45,51-54}

Proposed research

Implementation of cRBC and cPLT products requires a collaborative multidisciplinary approach to render the process more cost effective, to optimize downstream purification/harvesting of the cells, and to develop a fully customized blood product designed to be accessible for safe use in as many patients as possible. In the initial stages of development, cRBC or cPLT has been derived from adult peripheral blood stem cells as this cellular source is most advanced,³⁸ and more clinical trials are in the preparation stage. These clinical trials take time as researchers move what is essentially a Research and Development product to a Good Manufacturing Practice (GMP) compliant product of a quality and safety suitable for use in humans.

Future developments of this product will utilize iPSC, forward programming or immortalized cell lines (eg, Bel-A).⁴⁰ These offer the potential of more attractive sustainable sources of cRBC or cPLC that can easily be stored and banked for use. Another clear advantage of these starting sources is that we can either generate them from rare donors with attractive blood groups phenotypes,⁴⁹ or engineer specific cellular phenotypes that can generate for instance HLA-deficient cPLT.⁵¹

The key challenges for the field remain GMP-compliant production of iPSC or immortalized lines that reliably produce higher yields of mature definitive hematopoietic cells (for iPSCs), and that maintain a stable karyotype during extended culture. A well-defined cell culture media and reliable reagent supply are also critical for expansion and differentiation of stem cells or iPSC or cell lines. Another key issue is to develop scalable bioreactors and operating protocols, and new filtration/isolation methodology to harvest large numbers of cRBC or cPLT efficiently with minimal loss of product. A major obstacle for the field is to enable cultures to grow at high cell density to manufacture the vast quantities of cells needed on an industrial scale, cost effectively. To date, most optimization has focused on growth factors and hormones. The new challenge is to understand and modulate cell metabolism and cell signaling pathways at a depth of knowledge required to facilitate efficient high-density cultures and conditions for making sure red cells grow and enucleate efficiently, and megakaryocytes efficiently shed hundreds of cPLT per megakaryocyte.

Anticipated impact of the research

Ultimately the research in efficient production and engineering of cRBC and cPLTs will deliver (1) better care for patients suffering from chronic anemia, particularly with patients with alloimmune antibodies or those with rare blood groups who are difficult to source blood for (2) innovation in cellular therapies targeted drug delivery as red cells, particularly offer the possibility to transfuse bespoke medicines safely encapsulated the red cell membrane to produce medicines that could last for the red cells natural lifetime of up to 120 days⁵⁵ (3) engineering blood cells to surpass shelf life or enhance beyond the scope of what's possible with current standard donor derived products, for example that store even longer or have enhanced therapeutic function and (4) a follow on effect in the production and infrastructure for support of other cellular therapies, for example culture conditions, novel bioreactors, new/more efficient harvesting techniques, and novel culture media recipes that enhance expansion cells.

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REFERENCES

- Engert A, Balduini C, Brand A, et al. The European Hematology Association Roadmap for European Hematology Research: a consensus document. *Haematologica*. 2016;101:115–208.
- Mueller MM, Van Remoortel H, Meybohm P, et al; ICC PBM Frankfurt 2018 Group. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA*. 2019;321:983–997.
- Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA*. 2021;325:552–560.
- Tay J, Allan DS, Chatelain E, et al. Liberal versus restrictive red blood cell transfusion thresholds in hematopoietic cell transplantation: a randomized, open label, phase III, noninferiority trial. *J Clin Oncol*. 2020;38:1463–1473.
- Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. 2021;384:610–618.
- Carson JL, Stanworth SJ, Alexander JH, et al. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. *Am Heart J*. 2018;200:96–101.
- Curley A, Stanworth SJ, Willoughby K, et al. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med*. 2019;380:242–251.
- Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomized, open-label, phase 3 trial. *Lancet*. 2016;387:2605–2613.
- Bodilsen J, Mariager T, Vestergaard HH, et al. Association of lumbar puncture with spinal hematoma in patients with and without coagulopathy. *JAMA*. 2020;324:1419–1428.
- Das M, Karnam A, Stephen-Victor E, et al. Intravenous immunoglobulin mediates anti-inflammatory effects in peripheral blood mononuclear cells by inducing autophagy. *Cell Death Dis*. 2020;11:50.
- Galeotti C, Stephen-Victor E, Karnam A, et al. Intravenous immunoglobulin induces IL-4 in human basophils by signaling through surface-bound IgE. *J Allergy Clin Immunol*. 2019;144:524–535.e8.
- Galeotti C, Kaveri SV, Bayry J. Intravenous immunoglobulin immunotherapy for coronavirus disease-19 (COVID-19). *Clin Transl Immunology*. 2020;9:e1198.
- Al-Zuhairy A, Jakobsen J, Andersen H, et al. Randomized trial of facilitated subcutaneous immunoglobulin in multifocal motor neuropathy. *Eur J Neurol*. 2019;26:1289–1e82.
- Sala TP, Crave JC, Duracinsky M, et al. Efficacy and patient satisfaction in the use of subcutaneous immunoglobulin immunotherapy for the treatment of auto-immune neuromuscular diseases. *Autoimmun Rev*. 2018;17:873–881.
- Berger M, Harbo T, Cornblath DR, et al. IgPro20, the polyneuropathy and treatment with Hizentra® study (PATH), and the treatment of chronic inflammatory demyelinating polyradiculoneuropathy with subcutaneous IgG. *Immunotherapy*. 2018;10:919–933.
- Carlone G, Torelli L, Maestro A, et al. Pentaglobin® efficacy in reducing the incidence of sepsis and transplant-related mortality in pediatric patients undergoing hematopoietic stem cell transplantation: a retrospective study. *J Clin Med*. 2020;9:E1592.
- Cui J, Wei X, Lv H, et al. The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis. *Ann Intensive Care*. 2019;9:27.
- Saha C, Das M, Patil V, et al. Monomeric immunoglobulin A from plasma inhibits human Th17 responses in vitro independent of FcαRI and DC-SIGN. *Front Immunol*. 2017;8:275.
- Rossato E, Ben Mkaddem S, Kanamaru Y, et al. Reversal of arthritis by human monomeric IgA through the receptor-mediated SH2 domain-containing phosphatase 1 inhibitory pathway. *Arthritis Rheumatol*. 2015;67:1766–1777.

20. Kiessling P, Lledo-Garcia R, Watanabe S, et al. The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: a randomized phase 1 study. *Sci Transl Med*. 2017;9:eaan1208.
21. Ulrichs P, Guglietta A, Dreier T, et al. Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. *J Clin Invest*. 2018;128:4372–4386.
22. Howard JF Jr, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology*. 2019;92:e2661–e2673.
23. Newland AC, Sánchez-González B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. *Am J Hematol*. 2020;95:178–187.
24. Cho A, Jantschitsch C, Knobler R. Extracorporeal photopheresis-an overview. *Front Med (Lausanne)*. 2018;5:236.
25. Quill E. Medicine. Blood-matching goes genetic. *Science*. 2008;319:1478–1479.
26. Gleadall NS, Veldhuisen B, Gollub J, et al. Development and validation of a universal blood donor genotyping platform: a multinational prospective study. *Blood Adv*. 2020;4:3495–3506.
27. Sanchez-Mazas A, Vidan-Jeras B, Nunes JM, et al. Strategies to work with HLA data in human populations for histocompatibility, clinical transplantation, epidemiology and population genetics: HLA-NET methodological recommendations. *Int J Immunogenet*. 2012;39:459–72; quiz 473.
28. Tambur AR, Claas FH. HLA epitopes as viewed by antibodies: what is it all about? *Am J Transplant*. 2015;15:1148–1154.
29. Heidt S, Haasnoot GW, van de Linden-van Oevelen MJH, Claas FHJ. Highly sensitized patients are well-served by receiving a compatible organ offer based on acceptable mismatches. *Front Immunol*. 2021;12:687254.
30. Wehmeier C, Karahan GE, Krop J, et al. Donor-specific B cell memory in alloimmunized kidney transplant recipients: first clinical application of a novel method. *Transplantation*. 2020;104:1026–1032.
31. Hönger G, Niemann M, Schawalder L, et al. Toward defining the immunogenicity of HLA epitopes: impact of HLA class I eplets on antibody formation during pregnancy. *HLA*. 2020;96:589–600.
32. Ainley LI, Hewitt PE. Haematology patients and the risk of transfusion transmitted infection. *Br J Haematol*. 2018;180:473–483.
33. de Niet A, Zaaier HL, ten Berge I, et al. Chronic hepatitis E after solid organ transplantation. *Neth J Med*. 2012;70:261–266.
34. Dodd RY. Emerging pathogens and their implications for the blood supply and transfusion transmitted infections. *Br J Haematol*. 2012;159:135–142.
35. Stanworth SJ, Killick S, McQuilten ZK, et al. Red cell transfusion in outpatients with myelodysplastic syndromes: a feasibility and exploratory randomised trial. *Br J Haematol*. 2020;189:279–290.
36. Rebullá P. The long and winding road to pathogen reduction of platelets, red blood cells and whole blood. *Br J Haematol*. 2019;186:655–667.
37. McCullough J, Alter HJ, Ness PM. Interpretation of pathogen load in relationship to infectivity and pathogen reduction efficacy. *Transfusion*. 2019;59:1132–1146.
38. Giarratana MC, Rouard H, Dumont A, et al. Proof of principle for transfusion of in vitro-generated red blood cells. *Blood*. 2011;118:5071–5079.
39. Migliaccio AR, Whittsett C, Papayannopoulou T, et al. The potential of stem cells as an in vitro source of red blood cells for transfusion. *Cell Stem Cell*. 2012;10:115–119.
40. Trakarnsanga K, Griffiths RE, Wilson MC, et al. An immortalized adult human erythroid line facilitates sustainable and scalable generation of functional red cells. *Nat Commun*. 2017;8:14750.
41. Do Sacramento V, Mallo L, Freund M, et al. Functional properties of human platelets derived in vitro from CD34+ cells. *Sci Rep*. 2020;10:914.
42. Mittra J, Tait J, Mastroeni M, et al. Identifying viable regulatory and innovation pathways for regenerative medicine: a case study of cultured red blood cells. *N Biotechnol*. 2015;32:180–190.
43. Heshusius S, Heideveld E, Burger P, et al. Large-scale in vitro production of red blood cells from human peripheral blood mononuclear cells. *Blood Adv*. 2019;3:3337–3350.
44. Moreau T, Evans AL, Vasquez L, et al. Corrigendum: large-scale production of megakaryocytes from human pluripotent stem cells by chemically defined forward programming. *Nat Commun*. 2017;8:15076.
45. Kupzig S, Parsons SF, Curnow E, et al. Superior survival of ex vivo cultured human reticulocytes following transfusion into mice. *Haematologica*. 2017;102:476–483.
46. Griffiths RE, Kupzig S, Cogan N, et al. Maturing reticulocytes internalize plasma membrane in glycoprotein A-containing vesicles that fuse with autophagosomes before exocytosis. *Blood*. 2012;119:6296–6306.
47. Lopez-Yrigoyen M, Yang CT, Fidanza A, et al. Genetic programming of macrophages generates an in vitro model for the human erythroid island niche. *Nat Commun*. 2019;10:881.
48. Bernecker C, Ackermann M, Lachmann N, et al. Enhanced ex vivo generation of erythroid cells from human induced pluripotent stem cells in a simplified cell culture system with low cytokine support. *Stem Cells Dev*. 2019;28:1540–1551.
49. Hawksworth J, Satchwell TJ, Meinders M, et al. Enhancement of red blood cell transfusion compatibility using CRISPR-mediated erythroblast gene editing. *EMBO Mol Med*. 2018;10:e8454.
50. Capellera-García S, Pulecio J, Dhulipala K, et al. Defining the minimal factors required for erythropoiesis through direct lineage conversion. *Cell Rep*. 2016;15:2550–2562.
51. Blin A, Le Goff A, Magniez A, et al. Microfluidic model of the platelet-generating organ: beyond bone marrow biomimetics. *Sci Rep*. 2016;6:21700.
52. Prudent M, Stauber F, Rapin A, et al. Small-scale perfusion bioreactor of red blood cells for dynamic studies of cellular pathways: proof-of-concept. *Front Mol Biosci*. 2016;3:11.
53. Bayley R, Ahmed F, Glen K, et al. The productivity limit of manufacturing blood cell therapy in scalable stirred bioreactors. *J Tissue Eng Regen Med*. 2018;12:e368–e378.
54. Moura PL, Hawley BR, Mankelov TJ, et al. Non-muscle myosin II drives vesicle loss during human reticulocyte maturation. *Haematologica*. 2018;103:1997–2007.
55. Meinders M, Shoemark D, Dobbe JGG, et al. Expression and retention of thymidine phosphorylase in cultured reticulocytes as a novel treatment for MNGIE. *Mol Ther Methods Clin Dev*. 2020;17:822–830.