



Who Owns Hematopoietic Stem Cells? Some Fundamental Legal Stakes for the Manufacture of Cultured Red Blood Cells

Jean Mercier Ythier*

Research Centre for Economics and Law, Sorbonne University, France

Abstract

Significant R&D investment is currently being made in the design of cost-effective devices for the manufacture of red blood cells (RBCs) from hematopoietic stem cells. If successful, such techniques will permit the for-profit manufacture of homologous transfusion products for alloimmunized patients, at a supply price comparable to the cost of the phenotyped transfusion units currently in use. Stem cell lines from scarce phenotypes of universal donors will gain substantial economic value as basic assets of this new bio-industry. This paper addresses a number of issues related to this predictable consequence of the development of an RBC industry. The main strands of case law and legal literature related to cell line patents are reviewed and their applicability to putative RBC manufacturing is discussed. I examine the various conceivable patterns of compensation for stem cell donors, from full-market compensation to full-free (i.e., uncompensated) donation, and discuss their respective relevance for the collection of suitable cell lines and for the development of the industry.

Keywords

Transfusion medicine, Cultured RBCs, Blood donation, Monetary compensation

Introduction

The proof of principle for the transfusion of *in vitro* generated red blood cells (RBCs) was established in 2011 [1]: A total of 10^6 hematopoietic stem cells (HSCs) from an adult donor were collected by apheresis, subsequently expanded and differentiated to 10^{10} RBCs, which were finally transfused back to the donor, with results exactly comparable to standard autologous transfusion, in terms of the quality and the functionality of the cultured RBCs transfused.

Since this breakthrough, research has focused on the development of cell engineering techniques for the mass manufacturing of RBCs from HSCs for transfusion purposes. [2] identified two main challenges on the agenda over the next two or three years, for the development of an economically sustainable technology: (i) the achievement of a biotechnological breakthrough, namely, the development of dedicated stirred bioreactors capable of reaching culture concentrations in the range from 5×10^7 to 2×10^8 cells/mL; and (ii) the achievement of a breakthrough in cost effectiveness, through the control of the cost of the media and growth factors consumed in culture. The objective, for the time being, is to mar-

ket cultured RBCs at a price of about \$3,000 per unit. This is compatible with their utilization in transfusion in the difficult cases encountered in the treatment of rare phenotypes, of patients suffering from hemoglobinopathies such as thalassemia or sickle-cell disease, and of poly-transfused patients with poly-immunization [2].

Schnitzler, et al. [3] reviewed a number of additional technical challenges that need to be addressed for the achievement of cost-effective scale-up in cell therapy industry. These include, notably, the development of chemically-defined (i.e, animal-product free) media appropriate for the cultivation of cells for therapeutic use, and the design of processes for the downstream purification and cryopreservation of cells that would meet the

***Corresponding author:** Jean Mercier Ythier, Research Centre for Economics and Law, Panthéon-Assas, Sorbonne University, Place du Panthéon, 75005 Paris, France, E-mail: jean.mercier-ythier@orange.fr

Received: December 15, 2016; **Accepted:** March 03, 2017;
Published online: March 07, 2017

Citation: Mercier Ythier J (2017) Who Owns Hematopoietic Stem Cells? Some Fundamental Legal Stakes for the Manufacture of Cultured Red Blood Cells. J Transplant Surg 1(1):1-7

(yet-to-be defined) regulatory and safety standards of the field^a.

In this article, I examine some fundamental legal stakes associated with RBC manufacturing. A basic legal condition for the emergence of a cultured RBC industry is the possibility for the industrial operator to file patents for the HSC lines used for RBC production. I argue that the development of the industry will, in the long run, result in unpaid HSC donation and derived HSC lines of high market value. I discuss the problem of social acceptability that may result from this situation, and the conceivable solutions.

The main thesis of the paper is supported by useful insights provided by the current functioning of plasma industries. The putative RBC industry and the manufacturing of plasma products belong to two technologically distinct components of healthcare industries: the sector of cell therapy industries and the pharmaceutical sector respectively [4]. These two sectors -would-both operate in the field of blood transfusion, which is shaped, to a large extent, by the norm of voluntary unpaid donations. I use these facts and a number of present characteristics of the plasma industry to build plausible predictions about the future legal and economic features of RBC manufacturing.

The paper is organized as follows. Section 2 describes a number of facts sustaining voluntary unpaid donation as the dominant norm in blood transfusion at present. Section 3 describes the structural features of blood transfusion as an economic sector, including exceptions to the rule of voluntary unpaid donation exhibited by paid plasma donation in the USA and by paid blood donations in Germany. Section 4 develops the main thesis of the paper from the elements presented in the previous sections.

Voluntary Unpaid Donation as a Standard of Good Practice for Blood Donation

Well-established blood donation organizations are the product of a long history, which started in the early Twentieth Century [5]. Their main characteristic features, which have been stable since the 1970s, are two-fold: (i) They are, in the main, gift economies; and (ii) these gift economies succeed in solving, for the time being, the quantitative and qualitative issues of mass blood provision. Exclusive reliance on voluntary unpaid donations imposed itself progressively as the relevant norm for the collection of whole blood, suitable for obtaining a suffi-

^aThe main focus of Schnitzler, et al. is the bioprocessing of human mesenchymal/stromal cells (hMSCs), but much of their analysis applies to HSCs as well. A distinctive feature (and constraint) of RBC manufacturing in the field of bioprocessing techniques covered by their article is the large number of cells involved. The RBC transfusion unit contains 2.1012 cells, that is, a number of cells close to 104 times the largest indication they consider (of 250 million cells per dose).

cient, stable supply, with a low risk of transfusion-related transmissible infections [6]. The generalization of this norm was slow and is still in progress. The USA's pioneering blood organization still resorted extensively to paid collection in the early 1970s, and this fact was at the origin of a famous controversy between Richard Titmuss [7] and Kenneth Arrow [8] regarding paid and unpaid collection, in terms of the quantity and quality of the blood collected. The USA stopped paid collection in the second half of the 1970s. The World Health Organization (2016) reports that: "74 countries collect more than 90% of their blood supply from voluntary unpaid blood donations (39 high-income countries, 26 middle-income countries and 9 low-income countries). This includes 62 countries with more than 99% of their blood supply from voluntary unpaid blood donors" [6]. These countries account for more than half of total donations globally.

Established collection organizations routinely provide sufficient quantities of safe blood components at manageable costs. This overall success of the blood donation economy stands in sharp contrast to the state of rationing that characterizes other important sectors of transplant medicine (principally kidney, liver, lung and heart transplants [9]).

The US national blood collection and utilization report [10] shows a permanent surplus of whole blood and RBC collections, relative to whole blood and RBC transfusions. In the USA, the supply of screened whole blood and RBC was 14.5 million units in 2011, exceeding whole blood and RBCs transfusions by a margin of 5.2%, corresponding to a surplus of more than 750 000 units, which was mainly allocated to the production and transfusion of plasma and platelets concentrates. Similarly, more than 3 million units of whole blood and RBC were collected in France in 2011, providing 2.4 million RBC transfusion units (i.e., 78% of the total number of transfusions)^b [11]. Shortages of blood products are rare in normal circumstances in established blood donation systems. For example, only 3.3% of US hospitals reported postponing elective surgery due to blood inventory shortages in 2011 for a median of two days, with only 433 patients affected.

^bOne notes a significant difference between the French and the US transfusion practices, namely, the US medical system produces and utilizes plasma more intensively than the French (it is more "plasma intensive", so to speak), while RBC concentrates are more intensively produced and utilized in French practice than in the USA. Notably, the average number of RBC units transfused per patient is less than three in the USA (2.7 in 2008), and larger than five in France (5.5 in 2010). The ratio of plasma units transfused to the total number of RBC, platelets and plasma units transfused was about 13% in France in 2010, and 21% in the USA in 2008. Reciprocally, the ratio of RBC units transfused to the total number of RBC, platelets and plasma units transfused was 78% in France in 2010, and 69% in the USA in 2008. The rate of utilization of platelets components is comparable in the two systems, accounting for about 10% of the total number of RBC, platelets and plasma units transfused in both. These facts may be partly explained by the cost of plasma components, which is much lower in the USA than in France, for reasons detailed in section 3-2 below.

This state of relative abundance is also reflected in the low cost of blood component units. For example, in 2011, the average amount paid for a unit of RBCs in the USA was \$225, €184 euros (about \$193) in France, £125 (about \$158) in the UK^c.

Finally, established blood donation organizations achieve satisfactory levels of safety: incidents associated with manageable risks of transfusion such as ABO incompatibility or infection transmission are rare, with frequencies smaller than 1 per 100,000 blood components transfused. For example, hemovigilance statistics show that there were 59 cases of post transfusion sepsis and 42 cases of acute hemolysis caused by ABO incompatibility in the USA in 2011, from a total number of almost 21 million components transfused [10]. Moreover, only a tiny fraction of these adverse transfusion reactions are fatal. In France, the incidence was 5 deaths per million components transfused over the decade 2000-2010 [11].

Resolution WHA63.12 of the World Health Organization [6] endorses this state of the art by urging “all Member States to develop national blood systems based on voluntary unpaid donation and work towards the goal of self-sufficiency”.

Donated Blood as a Common Resource for Transfusion Communities

In this section, I briefly examine the consequences of voluntary unpaid blood donations on the economic status of donated blood as a specific type of common resource. Also, I examine the challenge raised by the persistence of large markets or quasi-markets for plasma, and also the challenge raised, to a lesser extent, by paid blood donation in Germany.

Ownership rights in donated blood

Donated blood is a resource for transfusion medicine, in the technical sense, as a basic input for the provision of transfusion services, and also in the economic sense, as a useful item of positive monetary value (a “scarce” resource). The norm of voluntary unpaid donation translates into a number of specific characteristics of property rights over the resource, designed to ensure its availability for the general provision of transplant care services, and for such purposes only. These specific characteristics consist mainly of: (i) market ban and other basic restrictions on individuals’ property rights on their own bodies; (ii) the availability of the resource for general (i.e. anonymous) transfusion purposes; and (iii) a particular emphasis on the donor’s free and informed consent, as a condition of validity of donation. Let us briefly consider them in turn.

Legal bans on blood markets reflect a general move of rejection of market transactions on body parts and tissues in public opinion [12]. Legal bans on markets for bodies, body parts, fluids and tissues spread widely, if not universally, from the late 1980s, in the wake of progress in transplant medicine: For example, the National Organ Transplantation Act of 1984 in the USA was followed by the Human Organ Transplant Act of 1989 in the UK, France’s laws of bioethics from 1992-1994, India’s 1994 Transplantation of Human Organs Act, and, more recently, China’s ban on marketing of human tissues and organs in 2006, to cite only a few. A characteristic illustration of the general tendency to impose restrictions on individuals’ property rights over their own bodies (such as the ban on individuals’ sales of their body parts) is provided by the decision of the Supreme Court of California in the famous case *Moore v. Regents of the University of California*, 1990. John Moore was treated for hairy cell leukemia at the medical center of UCLA by Dr. David Golde. Golde used Moore’s tissues and fluids, excised during the treatment, to create the lucrative Mo cell line, without informing him of his projects and of the large financial benefits that could be expected from them. The court ruled that Moore had no right to any share in the profits made from his cells, on the basis that, notably: (i) he had no property rights on the tissues retrieved from his body; and (ii) the patented cell line developed by Golde and his team was factually and legally distinct from the tissues excised from Moore’s body.

A second characteristic feature of the legal apparatus constraining blood donation in mature organizations is their marked preference for anonymous gift-giving. Exceptions to the rule of anonymous blood donation must be duly motivated by medical reasons such as urgency or compatibility issues (as in the case of rare blood types for example). This type of rule may be interpreted as another type of restriction on individuals’ property, constraining their right to donate (constraining, more precisely, their right to choose the beneficiary of their donation). Such restrictions on individuals’ property rights are not specific to blood donation. They are widely applied to body parts, fluids and tissues in general. A characteristic illustration is provided by the case *The Washington University v. Dr. W. Catalona, et al.* 2006. Dr. Catalona had developed a large repository of biological samples for his research on prostate cancer at Washington University, and intended to take it with him when he left for a new position at Northwestern University. He had obtained the written agreement of 6,000 of his former patients for the transfer of their tissue samples to him at his new Institution. The court decided that the research participants’ continuing rights in connection with their donated samples were strictly “limited to their right to discontinue participation in research”, and that, conse-

^cConversions are made at the current exchange rates of \$1.05 for €1 and \$1.26 for £1 respectively.

quently, neither Dr. Catalona nor the research participants had “any ownership interests in the repository”, which belonged therefore to Washington University.

The third characteristic of the legal regulation of blood donation that should be emphasized here concerns the principle of free, prior and informed consent of donors. The first two features considered above support the concept of a pool of donated blood as a common resource for the community of the beneficiaries of transfusion care services, under the control of the healthcare units in charge of its collection, transformation and final distribution to the patients. The quality of consent, assessed in terms of the freedom and appropriate information of donors, balances the construct as the main barrier against an unappealing appropriation of blood resources by the healthcare system. This third feature, like the former two, applies to the whole field of body parts, tissues and fluids, as the *Moore* and *Catalona* cases above show. In the *Moore* case, the court recalled that the physician must “disclose personal interests unrelated to his patient’s health, whether research or economic, that may affect his medical judgment” in order to get the patient’s informed consent. In the *Catalona* case, the court considered that the written consent signed by 6,000 patients of Dr. Catalona was not valid because it failed to meet a number of requirements for an appropriate information of donors, and, more interestingly perhaps, also because it “failed to minimize the possibility of undue influence” by “implying that consent to transfer was necessary for continuing medical care”.

Monetary compensation and quasi-markets for donated blood products

The regulation of compensation is an important condition for the quality of donors’ consent. Monetary compensation, in particular, may be viewed as a form of undue influence, if it acts as incentives to donate, that is, if it constitutes a determinant motive of donation for a significant number of donors. Compensation is commonly practiced in live donations of bodily materials, and consists mainly of: (i) The reimbursement of spending incurred because of donation, such as travel expenses; (ii) the monetary or in-kind compensations for the non-financial costs of donation, including the donor’s inconvenience or discomfort; and (iii) the payment of a wage for the time spent on donation (to distinguish from payments of the donor’s health insurance, if any). The third component (wage payment, which is generally implicit in practice) is the critical point to consider in order to decide whether the donation should be classified as a market transaction or not, practically if not legally. If the compensation exceeds the value of the time spent on donation, computed from the hourly wage rates of standard

job markets, then donation should be viewed as a sale. Notably, this happens in two important practical cases in blood donation organizations: plasma donations in the USA and blood and plasma donations in Germany. These will be discussed briefly below.

About 14 million units of plasma were produced in the USA in 2011, for transfusion (6 million) and for the manufacture of plasma protein products (8 million) [10]. The US supply currently covers about 60% of the world supply, and 70% come from paid donors [13]. Paid plasma donation is performed by plasmapheresis, takes one to two hours, and is commonly remunerated in the range of \$20 to \$50 per sitting, an amount comparable to the US average hourly wage⁴. These facts convey clear indications that US paid donated plasma makes, *de facto*, a large market of millions of units purchased at prices indexed by and large on the average hourly wage of the US job market.

The German experience provides similar indications, although on a smaller scale. About 75% of blood donations in Germany are collected by the German Red Cross on a voluntary and unpaid basis, but the remaining 25% are collected by state agencies (20%) and private sites (5%) that offer monetary compensation. [14] report that the standard compensation for whole blood donation is €25, and may rise up to €60 for plasma donation. They note that the corresponding implicit wages are comparable to the German average hourly wage. Also, they show econometric evidence that the German supply of donated blood responds positively to monetary incentives, in terms of both the total number of donors and the number of donations per donor per year.

Neither the American nor the German experiences exhibit significant differences between paid and unpaid donations, in terms of the safety of the resulting blood products. That is, these experiences suggest that monetary incentives may substantially increase the quantities of donated blood without altering their quality, which seems to contradict some of the main conclusions of Titmuss’s famous study [7].

More evidence for the effects of financial incentives on blood donations comes from the comparison of the costs of red blood cells and plasma components in the USA, Germany and France. French blood donations are provided by voluntary unpaid donors exclusively. In 2011 the cost of a unit of fresh frozen plasma in France was about €97 (≈\$102). This was almost twice the average cost of the same component in the USA (≈\$59). Likewise, the 2011 French cost of a unit of red blood cells concentrate was €184 (≈\$193). This is comparable to the

⁴The US average hourly earnings of production and nonsupervisory employees on private nonfarm payrolls was \$21.80 on December 2016: <https://www.bls.gov/news.release/empsit.t24.htm>

average cost of the same component in the USA (\approx \$225), where it is provided on the same voluntary unpaid basis, but it was more than twice the cost of this same component in Germany ($\text{€}85\approx$ \$89). These facts suggest that the ethical requirement that blood donation be unpaid does have a financial cost, by doubling, roughly, the monetary cost of blood collection, relative to the cost of collection that results from the combination of paid and unpaid donations.

It is debatable whether the worldwide demand for donated plasma could be satisfied in the absence of the large supplies of paid donated plasma of the USA and Germany. For example, 70% of the immunoglobulins distributed in Canada are made from plasma sourced from the USA. Until recently, France achieved self-sufficiency in therapeutic plasma through the legal monopoly of the Establishment Français du Sang (EFS).

However, the capacity of the EFS to maintain self-sufficiency is contested currently, following the decision of the Conseil d'Etat (the French highest administrative jurisdiction) to authorize imports for one type of therapeutic plasma^e.

Ownership of, and Compensation for, Hscs Donated for RBC Manufacturing

As described in Section 1, the manufacturing of RBCs will use HSCs as one of its basic inputs. HSCs will be provided by banks of cord blood in the short-medium term and also, possibly, by induced pluripotent stem cells in the longer run. In view of the discussion above, the basic question addressed in this paper may be rephrased as follows: How would the HSCs used to manufacture RBCs be acquired from individual donors? What would the consequences be for donors and the industry, in terms of property rights, compensations and costs?

Concerning property rights, the stem cell lines developed from HSCs for the purposes of RBC manufacturing belong to the owners of the corresponding patent, according to the standard law of intellectual and industrial property. We saw above, notably through the representative example of the *Moore* case, that law denied to donors any property right on their bodily materials donated for research. More generally, law distinguishes donated HSCs from the lines of stem cells developed from them. The former cannot be a patrimonial asset of the donor; whereas the latter, utilized in the manufacturing of RBCs, would definitely be an industrial asset of the operating firm. In other words, the remuneration of stem cell donation, if any, cannot be a share in the sales (as in the case of author's rights) or financial surpluses

of the user cell therapy industry. It can consist only of a compensation for the expenses, discomfort or time spent in relation to donation.

The question that comes next is whether the development of an RBC industry can plausibly result in the emergence of a (quasi-) market in HSC donation, comparable to the existing markets in plasma donation described above.

The answer is clearly negative, because HSC donation is not susceptible to become a scarce resource as plasma donation is at present. The basic reason for this difference between RBC and plasma industries is technological. Up to a 30-million fold expansion of CD34+ stem cells can be reached currently in the laboratory, implying the theoretical possibility of generating 10 to 50 units of RBCs from a single cord blood unit [15]. Moreover, the possibility of programming human induced pluripotent stem cells for erythroid differentiation and maturation has been established in the laboratory [16]. Industrial applications might remove any quantitative limitation of the resources in HSCs, this source of stem cells being potentially unlimited. Finally, ongoing research aims at developing immortalized cell lines, that is, cells which can self-renew *ex vivo* indefinitely in an appropriate medium while maintaining their ability to undergo erythroid differentiation. These technological data and prospects suggest that HSC donation may not impose any lasting limitation on the quantitative expansion of RBC production. Whereas plasma donation (currently about 25 million liters worldwide) actively constrains the quantitative expansion of plasma industries.

These arguments imply that HSCs should be collected, in the long run, mainly through voluntary unpaid donations. That is, their monetary value for donors should be close to zero, except maybe in the rare cases briefly discussed below, where the development of a cell line might require some time spent on behalf of donors. The patented cell lines developed by the RBC industry, on the contrary, will have a substantial market value, covering at least the costs of the R&D involved and the costs of conservation of stem cells (cryo preserved or cultured in an appropriate medium), including an appropriate remuneration of the capital invested in these activities of development and conservation of cell lines^f.

The development of an RBC industry will involve, therefore, the coexistence of: (i) free HSC donations on the one hand; and (ii) derived lines of HSCs, of high market value, on the other hand. This might raise a number

^eSee for example <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/plasma-eng.php> concerning the Canadian situation, and <http://www.sfvtt.org/category/actualites/reglementaire/> concerning the present regulatory situation of France.

^fA partial indication is provided by the price of a unit of cord blood imported in, or exported from France, which is typically situated in the range of $\text{€}15,000$ to $\text{€}25,000$. For example, the bare fee for the procurement of a unit of cord blood by the French (public) cord blood bank to a foreign patient was $\text{€}18,500$ on the 1st of January 2012 (http://www.sante.gouv.fr/fichiers/bo/2012/12-01/ste-20120001_0100_0047.pdf)

of issues concerning the social acceptability of the new industry, especially if it is run on a for-profit basis. Let us briefly discuss, to finish with, some aspects of this question, in relation to the notions of unjust enrichment, fair compensation and benefit sharing.

The case *Greenberg v. Miami Children's Hospital Research Institute* (2003) complemented the *Moore* jurisprudence by introducing the idea of fair compensation for the time and money spent by donors of bodily materials who participate actively in a research program. The son of Dan and Debbie Greenberg suffered from Canavan disease. They had taken the initiative, together with an association, to actively support Dr. Matalon's research on the gene responsible for the disease, by providing financial support and by collecting tissue samples from a large network of patients. Dr. Matalon discovered the gene, and he and the Miami hospital subsequently filed for a patent and began to charge expensive fees for the utilization of the genetic sequence, including in the diagnosis and treatment of the disease. The court confirmed, as in the *Moore* case, that donors retained no property rights on bodily materials donated for research. But it upheld their claim of "unjust enrichment" against Dr. Matalon and the hospital, because it had been established that the active support of the Greenbergs, the family donors, and the association had benefitted the research. Following the judgment, a compensation was decided by a contractual arrangement between the parties.

The notion of fair compensation implied in the *Greenberg* case could find an application, in the context of HSC donation, in very specific cases of universal donors. We recalled above that one of the first indications for the utilization of cultured RBCs in transfusion would concern cases of complex allo-immunization. [15] showed that only three RBC cell lines, properly chosen, would be sufficient to cover the transfusion needs of 99% of a large sample of allo-immunized patients[§]. One can imagine that the participation in research of individuals endowed with such remarkable phenotypes would be actively solicited. This specific type of HSC donation will require an adequate ethical treatment, including importantly the design of suitable forms of compensation, monetary or otherwise, for the donors' time, care and attention.

This type of fair compensation would concern only a small number of donors. The bulk of HSC donations would remain unpaid. The emergence of an RBC industry could perturb, therefore, the organization of blood donation by generating tensions between donors, patients and the industry, as was observed in France in the case of plasma in the late 1970s: In this case, hemophiliacs, who supported actively through their associations, the

provision of costly products of the plasma industry such as concentrates of factor VIII, then sharply opposed the views of many donors, whose associations complained about the industrial exploitation of blood donation [17]. The French experience shows also that the public or non-profit legal status of industrial operators does not solve the problem. Financial considerations, and notably the price of products and the financing of industrial investments do play an essential role in the functioning of the industry, whatever the status of operators (public, non-profit or for-profit). These facts are not easy to reconcile with the ethics -and psychology- of altruistic blood donation.

A potential solution to this type of problem could be provided by the practices or policies of "benefit sharing", resulting in the investment of a suitable share of the financial surpluses generated by the RBC industry into actions of common interest for the stakeholders of the transfusion community (i.e. donors, patients, health care units and industrial operators). The Human Genome Organization, for example, recommends that up to 3% of the net profits generated from human genetic material be devoted to technology transfers or invested in the development of health care facilities [18]. HSCs clearly have some characteristics of public goods. Moreover, patented lines of HSCs, if any, would become part of the public domain when patent term is reached, usually 20 years after filing. Therefore, in the context of RBC manufacturing, a suitable form of benefit sharing could involve the contribution of the industry to the development of non-profit banks of HSCs at the national and international levels.

References

1. Giarratana MC, Rouard H, Dumont A, et al. (2011) Proof of principle for transfusion of in vitro-generated red blood cells. *Blood* 118: 5071-5079.
2. Rousseau GF, Giarratana MC, Douay L (2014) Large-scale production of red blood cells from stem cells: what are the technical challenges ahead? *Biotechnol J* 9: 28-38.
3. Schnitzler AC, Anjali V, Daniel EK, et al. (2016) Bioprocessing of human mesenchymal stem/stromal cells for therapeutic use: Current technologies and challenges. *Biochemical Engineering Journal* 108: 3-13.
4. Mason C, David A Brindley, Emily J Culme-Seymour, et al. (2011) Cell therapy industry: billion dollar global business with unlimited potential. *Regenerative Medicine* 6: 265-272.
5. Lederer SE (2008) *Flesh and Blood: Organ Transplantation and Blood Transfusion in Twentieth-Century America*. New York: Oxford University Press 23: 196-197.
6. World Health Organization (2016) Blood safety and availability. Fact sheet.
7. Titmuss R (1971) *The Gift Relationship: From Human Blood to Social Policy*. New York, USA.

[§]This was established on a cohort of 16,486 patients with RBC antibodies detected consecutively in a regional settlement of the EFS from 2000 to 2009.

8. Arrow KJ (1972) Gift and exchanges. *Philosophy and Public Affairs* 1: 343-362.
9. Steiner P (2010) *La Transplantation d'Organes: Un Commerce Nouveau entre les Etres Humains*. La Découverte, Paris, France.
10. Whitaker BI, Schlumpf K, J Schulman (2011) The 2011 national blood collection and utilization survey report. Report of the US Department of Health and Human Services, USA.
11. Agence Nationale de Securite du Medicament (2011) Rapport d'activité hémovigilance 2011.
12. Alvin E Roth (2007) Repugnance as a constraint on markets. *Journal of Economic Perspectives* 21: 37-58.
13. (2013) Health Canada Fact Sheet.
14. Niessen-Ruenzi A, Weber M, David MB (2016) Do direct cash payments increase whole blood supply? SSRN.
15. Peyrard T, Bardiaux L, Krause C, et al. (2011) Banking of pluripotent adult stem cells as an unlimited source for red blood cell production: potential applications for alloimmunized patients and rare blood challenges. *Transfus Med Rev* 25: 206-216.
16. Lapillonne H, Kobari L, Mazurier C, et al. (2010) Red blood cells generation from human induced pluripotent stem cells. *Haematologica* 95: 1651-1659.
17. Chauveau S (2011) Du don a l'industrie: La transfusion sanguine en France depuis les années 1940. *Terrain* 56: 74-89.
18. Phillips A (2013) *Our Bodies: Whose Property?* Princeton University Press, USA.