CANCER

Hematopoietic stem cell transplantation in its 60s: A platform for cellular therapies

Christian Chabannon,[1]* Jurgen Kuball,[2] Attilio Bondanza,[3] Francesco Dazzi,[4] Paolo Pedrazzoli,[5] Antoine Toubert,[6] Annalisa Ruggeri,[7,8] Katharina Fleischhauer,[9] Chiara Bonini[10]*

Over the last 60 years, more than a million patients received hematopoietic cell transplantation. Having incorporated multiple changes in clinical practices, it remains a complex procedure facing a dual challenge: cure of the underlying disease and prevention of relapse while controlling potentially severe complications. Improved understanding of underlying biological processes resulted in the design of innovative therapies engineered from defined cell populations and testing of these therapies as addition or substitution at virtually every step of the procedure. This review provides an overview of these developments, many of them now applied outside the historical field of hematopoietic cell transplantation.

INTRODUCTION

Over the last decade, biotechnological and scientific breakthroughs have revolutionized the field of cellular therapies and their applications in various medical disciplines, including immunotherapy of cancers. A pillar for these developments comes from the experience and understanding gained from clinical application of hematopoietic stem cell transplantation (HSCT) over more than half a century. Modern cellular therapies not only owe part of their development to HSCT but also hold great promise for improving its applicability, safety, and efficacy and can even substitute for it, as well as find new applications outside of their original field.

HSCT AS A MODEL FOR REGENERATIVE MEDICINE

HSCT was initially developed with the aim of rescuing bone marrow (BM) failure after accidental high-dose radiation. It was the first regenerative approach to enter clinical practice (*1*) and had a profound impact in the medical community (*2*). The regenerative power of HSCT relies on the ability of HSCs to self-renew and differentiate into progenitors and mature cell types and thus to replenish the damaged hematopoietic tissue after a preparative conditioning regimen (high-dose cytotoxic agents or large-field irradiation used to control the underlying malignant disease). The source of HSCs can be either autologous or allogeneic; in the latter (allo-HSCT), this results in the establishment of hematopoietic host-donor chimerism. Reports published by continental registries such as European Society for Blood and Marrow Transplantation (EBMT) (*3*) demonstrate ongoing activities at hundreds of centers worldwide, accounting for thousands of transplants, which makes HSCT the only example of a cell transplant procedure used on a large scale. However, although the concept of HSCT is more than 60 years old, major inequalities persist in the access to these therapies: Most of the reported activity takes place in North America, Europe, East Asia, and, more recently, Middle East and South America; in other parts of the world where low- to middle-income countries are represented in higher proportions and where many candidate patients live, access to HSCT remains limited because of financial constraints (*4*). Furthermore, serial surveys demonstrate persistent unequal access to autologous and allogeneic HSCT across European countries, in relation to gross national products and heterogeneous organizations for health care delivery (*3*).

Self-tolerance facilitates the engraftment of autologous HSCs, thereby largely eliminating clinical risks associated with prolonged immunodeficiency, rejection, and graft-versus-host disease (GVHD) associated with allo-HSCT. In case of malignancy, cancer cells residing in the patient's BM or peripheral blood (PB) can contaminate autologous HSC harvests; our inability to efficiently trace the fate of infused cells in vivo makes it difficult to fully understand the contribution of infused contaminating tumor cells to relapses (*5*). Extensive purification of harvested stem cells did not substantially modify relapse rates or survival so far, suggesting that residual host-resident malignant cells remain the major source of relapse (*6*); this view might be revisited in the future when deeper molecular responses could be induced by induction or salvage treatments or when more efficient purging techniques enter the market.

Control of residual malignant cells through recognition of non-self targets by donor immune cells is a major advantage of allogeneic HSCT, which is associated with lower relapse rates but higher toxicity than autologous HSCT. Moreover, allogeneic but not autologous HSCT can mediate a form of regenerative medicine required for some inherited or acquired disorders affecting the hematopoietic tissue at large, which can be cured by replacing the recipient's dysfunctional BM with a fully functional donor-derived hematopoietic system. Since the first reports on the feasibility and early demonstrations of clinical utility of allogeneic HSCT, the procedure has been greatly refined (*7*); different stem cell sources [BM, PB cells mobilized from donors, and cord blood (CB) units] can now be used. Related and unrelated donors can be solicited. Adding nonmyeloablative or

[1]Institut Paoli-Calmettes, Centre de Lutte Contre le Cancer, Université d'Aix-Marseille, INSERM CBT 1409, Centre d'Investigations Cliniques en Biothérapie, F-13009 Marseille, France. [2]Laboratory of Translational Immunology and Department of Hematology, UMC Utrecht, 3508GA Utrecht, Netherlands. [3]Innovative Immunotherapies Unit, Division of Immunology, Transplantation and Infectious Diseases, University Vita-Salute San Raffaele and Ospedale San Raffaele Scientific Institute, 20132 Milan, Italy. [4]Division of Cancer Studies, King's College London, London SE5 9NU, UK. [5]Fondazione IRCCS Policlinico San Matteo, Medical Oncology Unit, Department of Oncology and Precision Medicine, 27100 Pavia, Italy. [6]Université Paris Diderot, Institut Universitaire d'Hématologie, INSERM U1160; Laboratoire d'Immunologie et Histocompatibilité, Hôpital Saint-Louis, AP-HP, F-75010 Paris, France. [7]Service d'Hématologie et Thérapie Cellulaire, Hôpital Saint-Antoine, AP-HP, Paris, France. [8]Eurocord-Monacord, Hôpital Saint Louis, F-75011 Paris, France. [9]Institute for Experimental Cellular Therapy, University Hospital Essen, Essen, Germany. [10]Experimental Hematology Unit, Division of Immunology, Transplantation and Infectious Diseases, University Vita-Salute San Raffaele and Ospedale San Raffaele Scientific Institute, 20132 Milan, Italy.
*Corresponding author. Email: bonini.chiara@hsr.it (C.B.); chabannonc@ipc.unicancer.fr (C.C.)

reduced-intensity conditioning regimens to originally designed myeloablative conditioning regimens provides an opportunity to offer allo-HSCT not only to children or young and fit adults but also to older and frailer patients. The introduction of megadoses of $CD34^+$ cells (*8*) and, more recently, modified immunosuppressive regimens, in particular the use of posttransplant cyclophosphamide, has allowed a breach of major clinical importance in the dogma that allogeneic HSCT is feasible only when donor and recipients are fully matched for human leukocyte antigen (HLA) genes and antigens ("HLA identity") (*9*). Our ability to collect cells from haploidentical donors now allows identification of one or more potential donor for virtually all recipients. The clinical experience and in-depth knowledge of HSCT accumulated over the years provide a platform to develop more complex engineering procedures with the aim to genetically correct and permanently cure congenital and acquired disorders (Fig. 1).

CELLULAR GENE THERAPIES COMPLEMENTING DEFICIENT HEMATOPOIETIC FUNCTIONS

To avoid the substantial toxicities associated with allo-HSCT, elegant alternatives were developed for situations where restoring deficient hematopoietic functions is the primary goal. For some monogenic diseases, being able to express a normal copy of the gene in HSCs offers an opportunity for long-term clinical improvement and possibly permanent cure because the pool of genetically modified autologous HSCs will self-renew and eventually differentiate into mature cells expressing sufficient amounts of the protein to produce the desired phenotype. In the early 1990s, gene therapy was pioneered with genetically engineered T lymphocytes and HSCs as a treatment for inherited adenosine deaminase severe combined immunodeficiencies (ADA-SCIDs) (*10*, *11*). Further efforts resulted in successful clinical applications for other lethal or life-threatening immunodeficiencies (*12*–*14*) and congenital disorders, including metabolic neurodegenerative diseases (*15*, *16*) and hemoglobinopathies (Fig. 2A) (*17*–*19*).

Increased safety of newer vectors for gene transfer (*20*) has facilitated clinical translation of gene therapy approaches. Although viral vectors are currently used in about 65% of gene therapy clinical trials (*21*), less expensive nonviral gene transfer vectors are also undergoing clinical evaluation (*22*, *23*). Finally, the recent development of gene editing technologies, which allow gene disruption and more precise gene correction, is likely to further speed up the applicability of gene therapy. In 2016, more than 20 years after the first clinical application, the first HSC-based gene therapy product has received marketing authorization from the European Medicines Agency (EMA), thus representing a major milestone and prototype for a new class of cell therapy drugs (table S1).

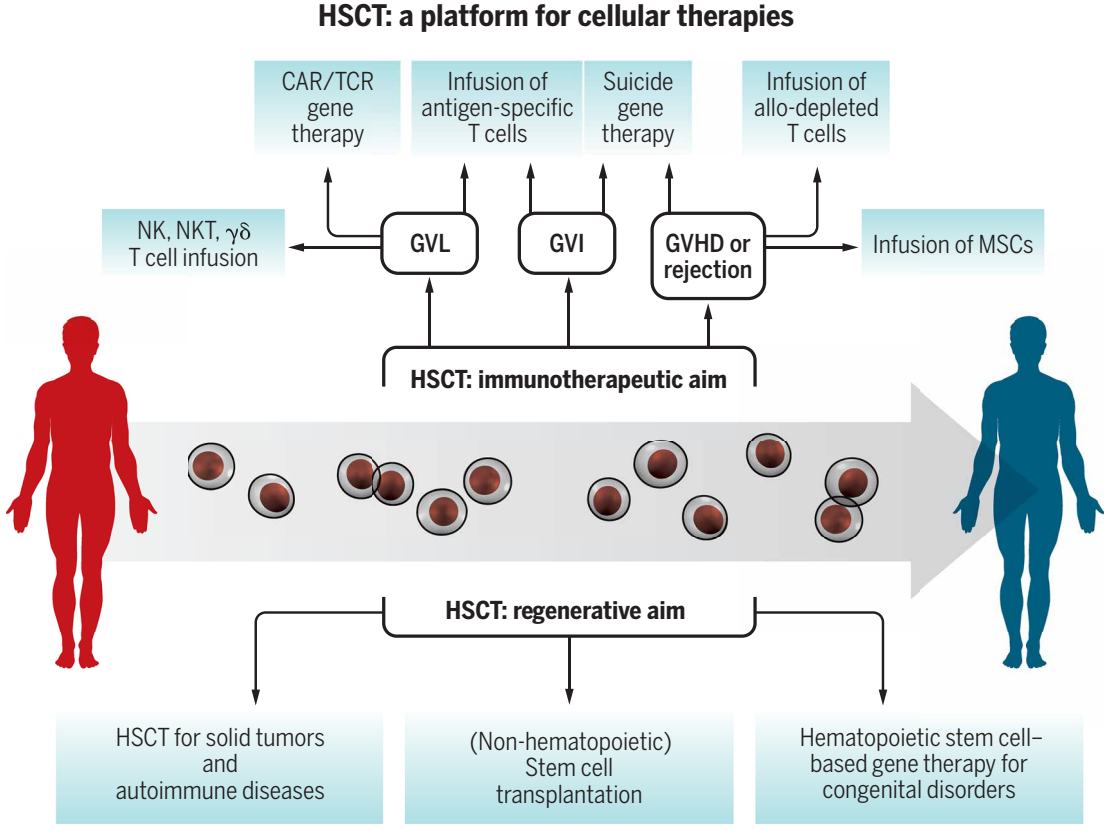

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Fig. 1. HSCT: A platform for cellular therapies. The major biological determinants of clinical outcome after HSCT are the ability of HSCs to regenerate the host hematopoietic system and the immunological events associated with the procedure in the case of allogeneic donors: the beneficial effects of graft-versus-leukemia (GVL) and graft-versus-infection (GVI) and the detrimental effects of GVHD and rejection. Cellular therapy approaches relying on the regenerative capacity of stem cells have also stemmed from HSCT in recent years and have been tested in clinical trials to treat congenital and acquired diseases. In addition, specific cell-based immunotherapy approaches have been designed to boost graft-versus-tumor (GVT) and GVI and to promote immunological tolerance, thus controlling both GVHD and graft rejection. NK, natural killer cells; NKT, natural killer T cells.

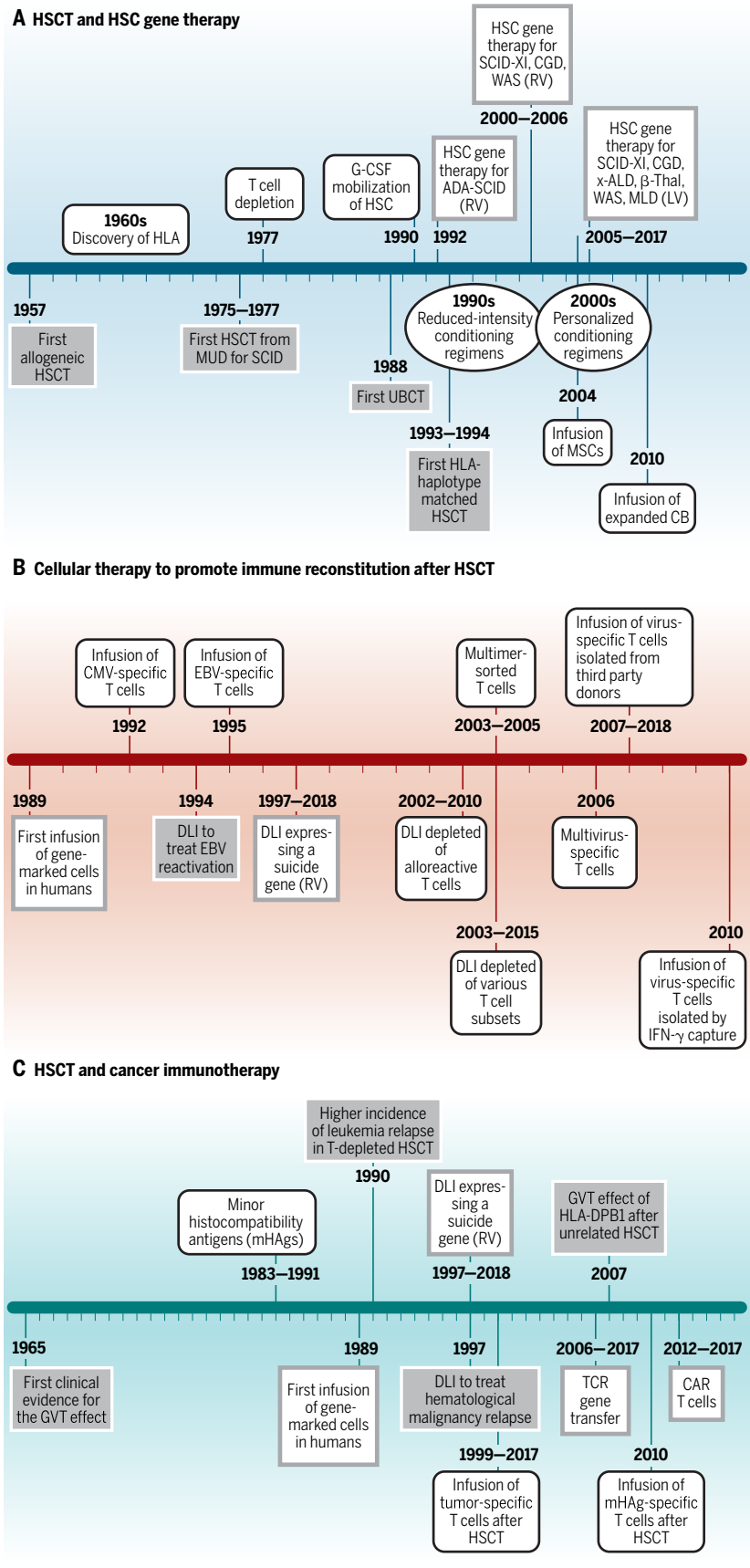


Fig. 2. From HSCT to cellular therapy. Timelines summarizing the milestones in the history of HSCT that led to the development of cellular therapy and in particular to HSC gene therapy (**A**), to cellular therapy approaches able to promote IR after HSCT (**B**), and to cancer immunotherapy (**C**). Clinical HSCT milestones have a gray background if they are related to the donor source, and a white background and an oval shape if they are related to conditioning regimens. Milestones relating to advances in biotechnology and cellular therapy are highlighted with a black border, whereas milestones in gene therapy are highlighted with a gray border. RV, retroviral vectors; LV, lentiviral vectors; SCID-XI, X-linked severe combined immune deficiency; CGD, chronic granulomatous disease; WAS, Wiskott-Aldrich syndrome; β-thal, β-thalassemia; MLD, metachromatic leukodystrophy; x-ALD, x-linked adrenoleukodystrophy; G-CSF, granulocyte colony-stimulating factor; UCBT, umbilical cord blood transplantation; MUD, matched unrelated donor.

INDUCTION OF IMMUNOLOGICAL TOLERANCE AND IMMUNE MODULATION

Understanding of biological mechanisms underlying the clinical efficacy of autologous and allogeneic HSCT inspired other applications for these medical procedures beyond oncology and inherited disorders. One example is induction of tolerance to solid organ transplantation by concomitant HSCT (*24*). Early studies in liver transplantation suggested that the presence of hematopoietic microchimerism was associated with immunological tolerance to the graft, supporting the hypothesis that HSCT from the same donor could promote donor-specific tolerance. This approach was successfully tested in the context of kidney transplant from living donors (*25*). Several recent international multicenter studies demonstrated the ability of a high-dose cytotoxic regimen associated with autologous HSCT to modulate the reactivity of immune cells against autologous tissues and to improve the clinical condition of subsets of patients affected by severe multiple sclerosis (*26*, *27*) and, possibly, other autoimmune or chronic inflammatory disorders [reviewed in (*28*)].

ALLOGENEIC HSCT AS A MODEL OF ANTITUMOR IMMUNOTHERAPY

The mechanisms by which allo-HSCT contributes to the control of malignant diseases—the vast majority of indications—were progressively unraveled by the management and understanding of the many immune complications that specifically occur after infusion of donor cells. Allo-HSCT is associated with delayed immune recovery—explaining why recipients are prone to infections (Fig. 2B)—and GVHD, whereby donor-derived immune cells attack recipient tissues and organs (*29*). Moderate GVHD is associated with improved disease control (*30*). Infusion of the same donor blood mononuclear cells mediating GVHD—the so-called donor-lymphocyte infusions (DLIs)—can control relapse in recipients of allogeneic HSCT (*31*).

Although introduction of tyrosine kinase inhibitors (TKIs) has largely suppressed the need for allogeneic HSCT in chronic myeloid leukemia (CML), the DLI

experience gained in this indication provided important information on efficacy and toxicity. DLIs induce durable remissions that are even longer than those achieved after the primary transplant procedure (*32*). The effective cell dose depends on disease stage and the type of stem cell donor used (*33*). Serial infusions of escalating cell doses maximize DLI efficacy and decrease the risk of GVHD (*34*). DLI is less practicable in other hematological or nonhematological malignancies that are less sensitive and where the pace and the bulk of neoplastic growth require high $CD3^+$ cell doses that, given early after the transplant, frequently produce severe GVHD. These hurdles have been confirmed in acute myeloid leukemia (AML) (20% responses) (*35*) and myelodysplastic syndromes (30 to 40% responses) (*36*), whereas DLIs appear more effective in chronic lymphoid malignancies (up to 80%) (*37*).

These observations demonstrate that antitumor efficacy of allo-HSCT—the so-called GVL effect—is mostly mediated by donor-derived immune effectors, thus qualifying allogeneic HSCT as a form of immunotherapy. DLI also paved the way for modern developments in allo-HSCT, no longer seen as a "one-shot body part replacement," but rather as a complex procedure. To maintain and enhance the immunotherapeutic effects of allo-HSCT for malignant disorders, maintenance therapies are required. These can include the sequential administration of cell-based therapeutics including but not limited to DLI (Fig. 2C) (*38*) or additional application of defined drugs (*39*). Except for the already mentioned introduction of TKI for CML, none of the new drugs that entered the market in the past two decades have eliminated the need for HSCT and its immunotherapeutic effects (*40*). In contrast, some of the recently developed cellular therapies such as chimeric antigen receptor (CAR) T cells can not only complement traditional HSCT but also be administered on their own in transplant-ineligible patients.

CELLULAR THERAPY TO IMPROVE IMMUNE RECONSTITUTION AND PREVENT GVHD AFTER ALLO-HSCT

Delayed immune reconstitution (IR) is a major concern after allogeneic HSCT (*41*), especially in recipients of CB, haploidentical HSCT, and T cell–depleted transplants. In addition to the graft source and conditioning regimen, many recipient parameters are associated with a delayed IR, including advanced age, the nature of the underlying disease and the types of previous treatment, and cytomegalovirus (CMV) status of the donor and recipient. GVHD has a major detrimental and long-lasting effect on IR. The need to boost IR while limiting the risk of GVHD has produced a variety of cellular therapy approaches currently under clinical testing.

TITRATING AND SECURING DONOR IMMUNE CELLS INFUSED INTO RECIPIENTS

The number of infused donor immune cells, especially T cells, can heavily affect clinical outcome in the recipient, in part through triggering of GVHD (*42*). In clinical practice, allogeneic grafts are nevertheless minimally engineered and mostly T cell–repleted products. Stringent T cell depletion results in the near abrogation of GVHD, albeit at the cost of increased relapse rates and delayed immune recovery, culminating in increased non-engraftment or rejection episodes (*43*, *44*). Although these drawbacks initially had offsetting effects on survival (*43*, *44*), more recent data demonstrate an overall survival benefit of in vitro T cell depletion, with fewer chronic complications such as GVHD (*45*).

Many attempts have been made to further improve donor graft engineering by selective depletion of defined T cell subsets and by engineering DLI to further control their activity in vivo after infusion into the patient. Most of these approaches are based on the experimental demonstration that alloreactivity preferentially clusters in specific T cell subsets, such as naïve T cells (*46*). The explanation is that alloreactivity to minor histocompatibility antigens (mHAgs) follows the classical rules of self-HLA–restricted peptide presentation, and the mHAg peptides have generally never been encountered by the patient (*46*). On the other hand, the mode of recognition in alloreactivity to major HLA mismatches is cross-reactivity (*47*) mediated by both naïve and memory T cells (*48*). Therefore, depending on the nature of the alloantigen, alloreactivity can be found only in the naïve or also in the memory compartment. On the basis of these considerations, the possibilities of negatively and/or positively selecting specific T cell subsets, such as naïve versus memory αβT cells, or sorting and infusing unconventional lymphocytes, such as γδT cells or CD1-restricted T cells, represent innovative cellular therapy approaches (*49*–*51*). These approaches are currently reaching clinical practice due to major improvements in in vitro selection procedures.

Additional opportunities to promote beneficial GVL while taming detrimental GVHD are offered by gene transfer technologies. The infusion of donor T cells expressing a suicide gene [thymidine kinase (TK) or icaspase 9 (iCas9)] to patients undergoing HSCT has been tested in several clinical trials. The activation of the suicide machinery is highly effective in abrogating acute GVHD in all reported trials (*52*–*54*), resulting in conditional approval by the EMA of a gene therapy medicinal product consisting of TK-engineered allogeneic T lymphocytes (table S1). Further attempts to engineer human T cell progenitors in feeder-free culture conditions, taking advantage of Notch signal activation (*55*), or in thymic-like niches (*56*) were recently reported.

Once clinically apparent, GVHD is largely refractory to conventional treatment and is therefore an ideal target to test new cellular therapies. Two approaches produced encouraging results.

A preclinical study (*57*) of regulatory T (T_{reg}) cells that are potent mediators of immunological tolerance in the periphery (*58*) prompted a clinical trial where 23 patients received T_{regs} as prophylaxis for GVHD after CB transplantation (*59*). Compared with identically treated 108 historical controls, there was a reduced incidence of acute GVHD without unwanted effects. The results were largely confirmed in the haploidentical setting (*60*).

An alternative strategy involves harnessing the equally potent immunosuppressive activity of mesenchymal stromal cells (MSCs) (*61*). Usually obtained from the BM, these cells exhibit phenotypic and functional features of tissue fibroblasts (*62*). In contrast to T_{regs}, which may prevent GVHD, MSCs have only been shown to be efficacious when administered at the time of GVHD (*63*), rather than prophylactically (*64*). Several subsequent studies confirmed MSCs' efficacy in GVHD, with about 40 to 50% of the patients responding and achieving long-term survival (*65*). A convincing mechanism was recently proposed, whereby MSC-mediated immunosuppression results from the induction of MSC apoptosis by patients' cytotoxic cells, the presence of which can be used as a biomarker to predict clinical responses (*66*).

ANTIVIRAL T CELL ADOPTIVE THERAPIES

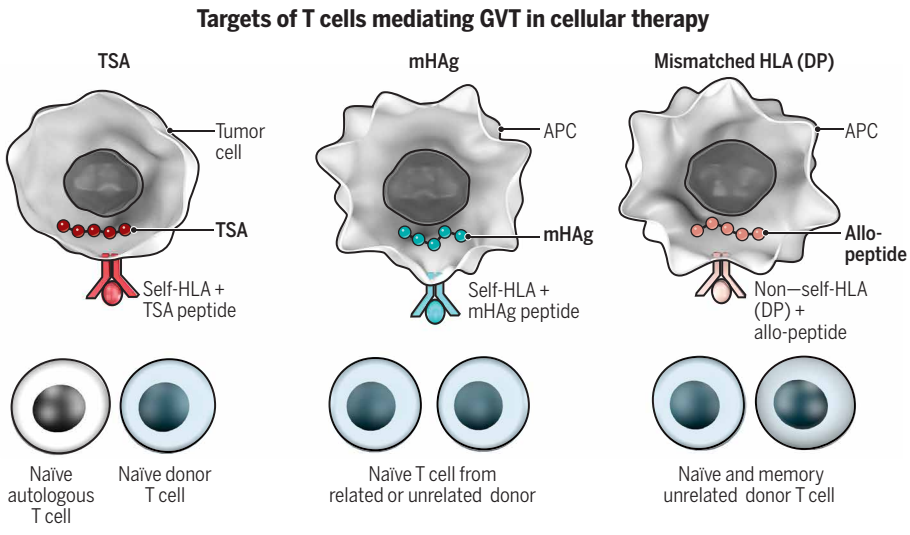
A defective T cell recovery, worsened by reduced thymic function in adults and by GVHD, is associated not only with impaired responses

to reactivation of herpes viruses such as CMV and Epstein-Barr virus (EBV) but also with opportunistic infections by adenoviruses (AdVs) and fungal pathogens (*Candida* and *Aspergillus*). These complications led to develop donor-derived antiviral cellular therapies (Fig. 2B). The first demonstration was offered in 1992 (*67*) with the successful transfer of CMV-specific T cell clones, soon followed by the transfer of EBV-specific T cells (*68*). Thereafter, in vitro generation of virus-specific T cells was achieved using HLA class I/peptide multimer cell sorting (*69*) or interferon-γ (IFN-γ) secretion capture assays (*70*). The advantage of this last option is the enrichment of $CD4^+$ and $CD8^+$ T cells, both required for long-lasting immunity, without the need for HLA restriction. It may also be applied to multipathogen-derived antigenic viral peptides. Good manufacturing practice (GMP)–compliant procedures are available for CMV-, EBV-, and AdV-specific T cells, but manufacturing conditions remain a limitation for many centers. A major hurdle for this approach is raised by pathogen-naïve donors, as exemplified by CB HSCT, for which the in vitro isolation of pathogen-specific T cells is a daunting task. This resulted in the usage of partially matched, third party–derived, virus-specific T cells, the first "off-the-shelf" immunotherapy products used in clinical trials (*71*, *72*). Being obtained from healthy subjects other than the transplant donors, these T cell products have the advantage of being immediately available. The products are well characterized and can be selected on the basis of the viral epitope specificity and on the HLA restriction element. Being only partially matched with the recipient, third party, viral-specific T cells usually do not persist long term but often long enough to bridge to IR.

HARNESSING THE ANTITUMOR ACTIVITY OF ALLO-HSCT

Elimination of residual tumor cells relies on the recognition of TSAs, mHAg, and/or mismatched HLA molecules by immune effectors (Fig. 3). Immunological differences between donor and host offer an opportunity to elicit alloreactive donor T cell responses against polymorphic non–self-antigens expressed by patient cells. When the donor is an HLA-identical sibling, these antigens are exclusively mHAg, peptides derived from polymorphic intracellular proteins processed and presented in the context of self-HLA restriction elements (*73*). The first mHAgs to be identified were HA-1 and HA-2, which are specifically expressed on hematopoietic tissues and thus represent relevant targets for a specific graft-versus-tumor (GVT) effect [reviewed in (*74*)]. This is confirmed by leukemia clearance after HLA-matched, but mHag-mismatched, allo-HSCT, concomitant with in vivo expansion of high-avidity cytotoxic T lymphocytes specific for HA-1 and HA-2 (*75*). mHags elicit high-avidity T cell responses. Depending on their narrow or broad tissue expression profile, targeting mHags might limit the risk of GVHD (*76*). Technological advances in big data genomics and proteomics have enabled the development of high-throughput technologies for mHAg screening: More than 50 mHAgs are identified to date [reviewed in (*77*)]. Of these, at least 13 are hematopoietic-specific and thus represent promising new targets for cellular therapy.

In the case of HSCT from unrelated donors, in addition to mHAgs, mismatched HLA molecules can also serve as polymorphic targets for alloreactive T cells (Fig. 3). In general, unrelated donors are selected to be matched for 9 to 10 of 10 HLA-A, HLA-B, HLA-C, DRB1, and DQB1 alleles; however, HLA-DPB1 is mismatched in more than 85% of the cases (*78*). In contrast to mHAgs, which are recognized by self-HLA–restricted alloreactive T cells mainly from the naïve pool with a generally low precursor frequency, HLA-DPB1 mismatches elicit direct T cell alloreactivity or cross-recognition by T cells that can reside in both the naïve and memory pools and generally have an at least 1-log higher precursor frequency compared with T cells reactive to mHAg. Alloreactive T cells specific for mismatched HLA-DPB1 can elicit both GVT and GVHD, resulting in no overall survival benefit for HLA-DPB1–mismatched compared with HLA-DPB1 allele–matched HSCT (*78*). However, increasing evidence suggests the existence of certain mismatch combinations that elicit limited T cell alloreactivity, thereby maintaining GVT without increasing GVHD. These so-called permissive mismatches can be identified on the basis of polymorphisms regulating HLA-DP peptide binding (*79*), surface expression (*80*), or both and have entered current recommendations for unrelated donor



	TSA	mHAg	Mismatched HLA
Donor	Autologous, related, unrelated	Related, unrelated	Unrelated
Recognition	Self-HLA—restricted peptide	Self-HLA—restricted peptide	Cross reactivity to non—self-HLA (DP)
Main compartment	Naïve	Naïve	Naïve and memory

Fig. 3. Targets of T cells mediating GVT in cellular therapy. Control of malignant disease by self-HLA–restricted T cells can be targeted to tumor-specific antigens (TSAs; red), mHAgs (blue), or mismatched HLA molecules (pink). TSA-specific T cells are the only ones that are potentially present not only in the allogeneic but also in the autologous context. mHAgs are the only alloantigens in related sibling donors, whereas both mHAgs and mismatched HLA (mainly HLA-DP) can be recognized by unrelated or mismatched related donor T cells. TSA- and mHAg-specific T cells are found mainly in the naïve compartment and have a low precursor frequency, whereas alloreactive T cells against mismatched HLA occur both in the naïve and in the memory compartment and have a higher precursor frequency. APC, antigen-presenting cell. Autologous patient cells are depicted in gray, and donor T cells are depicted in blue.

selection [reviewed in (*78*)]. They also represent potentially promising targets for cellular therapy approaches (*81*).

Tumors with pronounced genomic instability, such as AML, can evade alloreactive immunological pressure. Relapse remains the leading cause of death after allo-HSCT. In a large proportion of patients relapsing after a mismatched HSCT, mechanisms for tumor escape such as de novo genomic mutations have been identified, resulting in the permanent loss of only those HLA molecules targeted by alloreactive donor T cells (*82*).

The possibility of isolating and expanding antigen-specific T cells has also resulted in the production of leukemia-specific cellular products (Fig. 2C) that might overcome some of the limitations associated with alloreactive cells. Infusion of leukemia-specific T cells from an HLA-identical related donor induced remission in a patient with CML in accelerated phase (*83*). Prophylactic infusions of $CD8^+$ T cells reactive against PR1, WT1, and BCR-ABL peptides, isolated from related and unrelated HSCT donors and expanded in vitro, induced persistent remissions in 13 of 14 patients with CML (*84*). Infusion of WT1-reactive $CD8^+$ T cells showed antileukemic activity in patients affected by relapse or high-risk AML (*85*). Finally, p190 BCR-ABL–directed T cells induced leukemia control in patients with Philadelphia-positive acute lymphoblastic leukemia (*86*). $CD4^+$ donor T cells adoptively transferred after HLA-DPB1–mismatched unrelated donor HSCT induced long-lasting remission of B cell leukemia and other hematologic malignancies (*87*). Clinical responses observed in these studies appeared tightly associated with in vivo persistence of transferred cells. Modulation of alloreactivity by means other than cell-based therapeutics was recently reported: Administration of immune checkpoint inhibitors to treat relapses appears feasible, although at the expense of GVHD and immune-mediated side effects in a large proportion of recipients (*88*).

BEYOND ALLOREACTIVITY: CELLULAR THERAPIES WITH ANTITUMOR ACTIVITY

Progress in fundamental immunology has resulted in the development of immune cell therapies outside of the allogeneic HSCT context, with possible applications for diseases that are not susceptible to alloreactivity. Adoptive T cell therapy using ex vivo expanded or engineered autologous patient T cells has emerged as an active field of investigation (*89*). However, the relatively low frequency of immune cells with antitumor activity in cancer patients, such as tumor-infiltrating lymphocytes, has limited the clinical success of these endeavors (*89*).

One of the most attractive opportunities offered by modern gene transfer technologies is the possibility to genetically and permanently redirect high numbers of T cells against tumor antigens by expressing either tumor-specific αβ T cell receptors (TCRs) or CARs in autologous or allogeneic T cells. In addition, a new set of tumor antigens was recently explored by in-depth analyses of alternative receptors like γδ TCR (*90*). In recent years, impressive clinical successes were reported with CAR T cells targeting CD19 in children and adults affected by a variety of B cell malignancies [for a review, see (*91*)]. This prompted pharmaceutical and biotech companies to race to obtain marketing authorizations for this category of medicinal products, the first two of which were recently granted (table S1). Current CAR T cells are generated in an autologous setting. Using an allogeneic source of T cells could allow for immediate availability (off-the-shelf product) but raises safety issues in terms of GVHD and efficacy, depending on their in vivo persistence.

Genome editing tools offer additional opportunities for cellular therapy. These are artificial "genetic scissors," able to bind preselected genomic regions and induce a DNA double-strand break [reviewed in (*92*)]. Depending on the additional genetic tools that are combined with these scissors, the DNA break will result in gene disruption or in gene correction (*92*), beyond single gene addition permitted by viral vectors. Genome editing of HSCs (*93*) and T cells produced convincing preclinical results (*94*, *95*) and has been successfully tested in patients (*96*, *97*).

TRANSITIONING FROM CELL TRANSPLANTATION TO ADMINISTRATION OF SOMATIC CELLULAR THERAPY AND GENE THERAPY MEDICINAL PRODUCTS

Cell transplantation was historically developed as a service provided to patients by hospitals and blood centers, with an organization that shares many aspects with organ and tissue transplantation. In particular, the association of clinical, collection, and processing facilities usually serves one or a few transplant programs that are geographically contiguous. Although notable harmonization has resulted from initiatives such as accreditation using the Foundation for the Accreditation of Cellular Therapy (FACT)–Joint Accreditation Committee ISCT-EBMT (JACIE) international standards for hematopoietic cellular therapies (*98*), this type of organization leaves room for procedural and organizational variation between programs. The regulatory

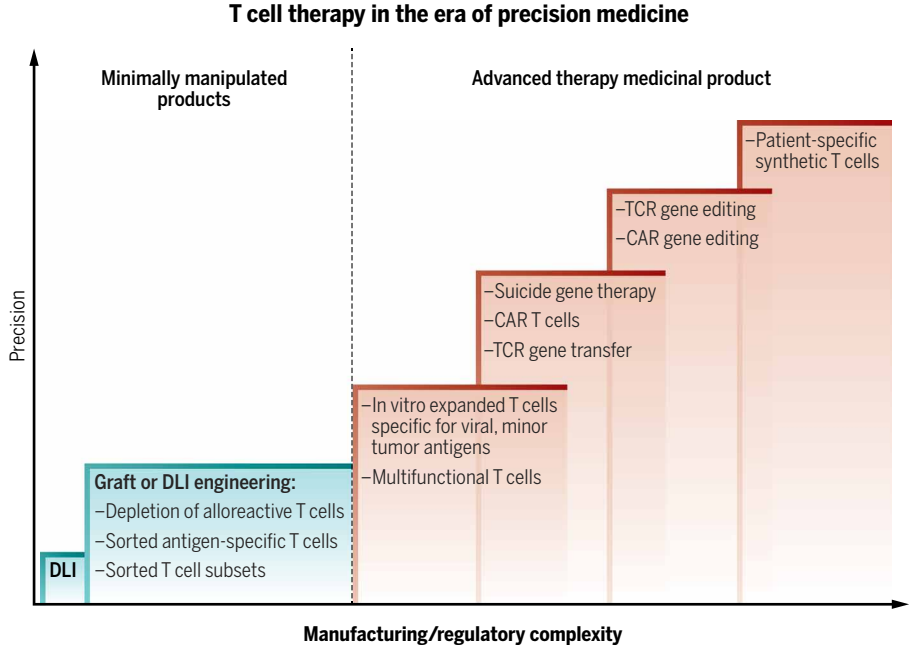


Fig. 4. T cell therapy in the era of precision medicine. Increased complexity in manufacturing costs and regulatory issues arise together with improved potency, specificity, and safety of cellular therapy products in the era of personalized precision medicine. The figure indicates the degree of precision (*y* axis) versus complexity (*x* axis) for different cellular therapy approaches.

framework developed in the United States and in Europe postulates that human cells subjected to substantial engineering are medicinal products; these are intended to be placed on the market and must be manufactured in aseptic conditions as described in GMPs commonly used by the pharmaceutical industry. Adaptation of this organization to the production of such personalized medicines as CAR T cells from starting material procured by blood banks or hospitals (*99*) contributes to but does not fully explain high price tags (up to US$475,000 for tisagenlecleucel and US$377,000 for axicabtagene ciloleucel, not to mention the cost of inpatient administration and supportive care). The commercialization of these innovative therapeutics will raise unprecedented medical, ethical, financial, and liability issues to be settled between all stakeholders. Because medicinal products made from human living cells or tissues are likely to not only exert positive effects but also trigger side effects over prolonged periods of time, if not for the entire remaining life span of treated individuals, long-term follow-up (up to 15 years) will be mandatory. Regulatory authorities such as the EMA and the U.S. Food and Drug Administration (FDA) are simultaneously pushing for rapid access to promising approaches and requesting accurate monitoring of their safety and efficacy in "real-life" conditions (*100*). This is where registries established by professional associations such as the EBMT or the Center for International Blood and Marrow Transplant Research (CIBMTR) will potentially prove of crucial importance. However, this will depend on their ability to capture sufficient details on the nature of cellular therapies in a timely fashion, in addition to the clinical data that they collect, which have already allowed successful postmarketing evaluation surveys of chemical drugs in the past.

CONCLUSIONS

Cellular therapies are among the most exciting innovations in medicine over the last decade and have the potential to offer curative solutions to a number of dismal diseases that affect patients of all ages and thus represent a major social and economical burden. The rapid developments in this field have been made possible by combining advancements in biotechnology and improved knowledge of biological mechanisms underlying the efficacy and safety of cellular therapies. The latter has been fostered by the six decades of experience in HSCT, which has been the platform, the hub, and, in some cases, the springboard for the first cellular therapy protocols (Fig. 4). Our ability to not only continue striving for further improvement in the understanding and feasibility of these approaches but also overcome the logistic, economic, and regulatory challenges of harmonization and recognition by the relevant authorities will determine whether cellular therapies will fulfill their promise as a true breakthrough in modern medicine in years to come. Full cooperation from all stakeholders—pharma industry, scientists, health care providers, health care payers, regulators, and, of course, patients—will be needed to reach this goal. Whether current upheaval in the field of hematopoietic cellular therapies will signal the decline of the more than 60-year practice of BM transplantation remains to be seen; it is likely, however, that both categories of therapeutics will witness simultaneous and complementary developments in the near future.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/10/436/eaap9630/DC1
Table S1. A non-exhaustive list of somatic cell therapy and gene therapy medicinal products authorized by the FDA or EMA.

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Hematopoietic stem cell transplantation in its 60s: A platform for cellular therapies

Christian Chabannon, Jurgen Kuball, Attilio Bondanza, Francesco Dazzi, Paolo Pedrazzoli, Antoine Toubert, Annalisa Ruggeri, Katharina Fleischhauer and Chiara Bonini

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