OncoImmunology 2:5, e24238; May 2013; © 2013 Landes Bioscience

Trial Watch

Adoptive cell transfer for anticancer immunotherapy

Erika Vacchelli,[1,2,3] Alexander Eggermont,[2] Wolf Hervé Fridman,[4,5,6] Jérôme Galon,[6,7,8,9] Eric Tartour,[6,9,10] Laurence Zitvogel,[2,11] Guido Kroemer[3,4,6,12,13,†] and Lorenzo Galluzzi[1,4,12,†,*]

[1]Institut Gustave Roussy; Villejuif, France; [2]Université Paris-Sud/Paris XI; Le Kremlin-Bicêtre; Paris France; [3]INSERM, U848; Villejuif, France; [4]Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; [5]Equipe 13; Centre de Recherche des Cordeliers; Paris, France; [6]Pôle de Biologie; Hôpital Européen Georges Pompidou; Assistance Publique-Hôpitaux de Paris; Paris, France; [7]Equipe 15; Centre de Recherche des Cordeliers; Paris, France; [8]INSERM; U872; Paris, France; [9]Université Pierre et Marie Curie/Paris VI; Paris, France; [10]INSERM; U970; Paris, France; [11]INSERM; U1015; CICBT507; Villejuif, France; [12]Equipe 11; Labelisée par la Ligue Nationale contre le Cancer; Centre de Recherche des Cordeliers; Paris, France; [13]Metabolomics Platform; Institut Gustave Roussy; Villejuif, France

[†]These authors share senior co-authorship.

Keywords: chimeric antigen receptor, cyclophosphamide, FOXP3$^+$ regulatory T cells, lymphodepletion, T-cell receptor, tumor-infiltrating lymphocytes

Abbreviations: ACT, adoptive cell transfer; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APC, antigen-presenting cell; CAR, chimeric antigen receptor; CBLB, Casitas B-lineage lymphoma B; CCR, chimeric co-stimulatory receptor; CEA, carcinoembryonic antigen; CIK, cytokine-induced killer; CLL, chronic lymphocytic leukemia; CXCR2, chemokine (C-X-C motif) receptor 2; DC, dendritic cell; EBV, Epstein-Barr virus; FAP, fibroblast activation protein; FRα, folate receptor α; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; IFN, interferon; IL, interleukin; LAT, linker for activation of T cells; iPSC, induced pluripotent stem cell; MAGE, melanoma-associated antigen; MDS, myelodysplastic syndrome; MDSC, myeloid-derived suppressor cell; NGFR, nerve growth factor receptor; NK, natural killer; PBMC, peripheral blood mononuclear cell; PTPN6, protein tyrosine phosphatase, non-receptor type 6; STAT5, signal transducer and activator of transcription 5; TAA, tumor-associated antigen; TCR, T-cell receptor; TGFβ, transforming growth factor β; TIL, tumor-infiltrating lymphocyte; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; Treg, FOXP3$^+$ regulatory T cell; T_{SCM}, stem-cell memory T; VEGFR2, vascular endothelial growth factor receptor 2; WT1, Wilms tumor 1

Adoptive cell transfer (ACT) represents a prominent form of immunotherapy against malignant diseases. ACT is conceptually distinct from dendritic cell-based approaches (which de facto constitute cellular vaccines) and allogeneic transplantation (which can be employed for the therapy of hematopoietic tumors) as it involves the isolation of autologous lymphocytes exhibiting antitumor activity, their expansion/activation ex vivo and their reintroduction into the patient. Re-infusion is most often performed in the context of lymphodepleting regimens (to minimize immunosuppression by host cells) and combined with immunostimulatory interventions, such as the administration of Toll-like receptor agonists. Autologous cells that are suitable for ACT protocols can be isolated from tumor-infiltrating lymphocytes or generated by engineering their circulating counterparts for the expression of transgenic tumor-specific T-cell receptors. Importantly, lymphocytes can be genetically modified prior to re-infusion for increasing their persistence in vivo, boosting antitumor responses and minimizing side effects. Moreover, recent data indicate that exhausted antitumor T lymphocytes may be rejuvenated in vitro by exposing them to specific cytokine cocktails, a strategy that might considerably improve the clinical success of ACT. Following up the Trial Watch that we published on this topic in the third issue of *OncoImmunology* (May 2012), here we summarize the latest developments in ACT-related research, covering both high-impact studies that have been published during the last 13 months and clinical trials that have been initiated in the same period to assess the antineoplastic profile of this form of cellular immunotherapy.

*Correspondence to: Lorenzo Galluzzi; Email: galluzzi.lorenzo@aliceadsl.fr
Submitted: 03/08/13; Accepted: 03/08/13
Citation: Vacchelli E, Eggermont A, Fridman WH, Galon J, Tartour E, Zitvogel L. Trial Watch: Adoptive cell transfer for anticancer immunotherapy. OncoImmunology 2013; 2:e24238; http://dx.doi.org/10.4161/onci.24238

Introduction

During the past three decades, it has become clear that the immune system does not constitute a mere bystander of oncogenesis, tumor progression and response to treatment, a conceptual shift that has driven the development and clinical evaluation of several forms of anticancer immunotherapy.[1–5] These include relatively unspecific approaches, such as the administration of immunostimulatory cytokines like interleukin-2 (IL-2) or immunological checkpoint blockers like anti-CTLA4 antibodies (i.e., ipilimumab),[6–11] as well as precisely targeted interventions, encompassing anticancer vaccines[12–14] and adoptive cell transfer (ACT).[1–3,15]

ACT involves the re-infusion into a lymphodepleted patient of large numbers (often up to 10^{11}) of lymphocytes with antitumor

activity,[1–5] hence constituting one—but not the only—form of cell-based anticancer therapy. ACT should indeed be conceptually discriminated from dendritic cell (DC)-based approaches, which de facto constitute anticancer vaccines (and are never performed in the context of lymphodepletion),[12,16–18] as well as from allogeneic hematopoietic stem cell transplantation (HSCT), a therapeutic option for patients affected by hematological malignancies that relies on the elimination of most tumor cells by lymphoablating regimens followed by the re-establishment of an allogenic (and hence potentially tumor-reactive) immune system.[19,20]

In a few settings, i.e., melanoma and renal cell carcinoma patients, the starting material for ACT is a surgical specimen or tumor biopsy, from which tumor-infiltrating lymphocytes (TILs) are isolated and sometimes selected for T-cell receptor (TCR) specificity.[21] Prior to re-infusion, these lymphocytes are expanded ex vivo in the presence of appropriate growth factors (e.g., IL-2) and optionally activated with agonistic anti-CD3 antibodies, alone or combined with tumor-associated antigen (TAAs).[22] In the majority of cases, however, this approach cannot be undertaken, as (1) surgical/biopsic material is not available or (2) tumor lesions contain reduced number of TILs. In these cases, ACT protocols can be implemented starting from circulating lymphocytes that are genetically engineered for the expression of tumor-reactive TCRs.[1] Importantly, genetic engineering can also be used to endow lymphocytes with several other features,[23] including (but not limited to) an increased proliferative potential,[24,25] a prolonged in vivo persistence,[26] the capacity to self-provide immunostimulatory cytokines and/or growth factors,[24] an improved capacity to migrate to tumor tissues[27,28] and robust cytotoxic functions.[29] Finally, so-called chimeric antigen receptors (CARs) can be employed as valid alternatives to TCRs. CARs recognize TAAs through antibody-derived complementarity-determining regions, yet rely on TCR-associated signal transducers, de facto triggering the activation of T cells even when TAA are not presented in complex with MHC molecules.[30,31] Obviously, the efficacy (and safety) of ACT is dramatically influenced (if not entirely dictated) by the specificity of re-infused cells. We have extensively discussed all these aspects one year ago, in the first Trial Watch of the series dealing with ACT,[15] and more recently, in three distinct Trial Watches dealing with anticancer vaccines.[12–14]

Initially, autologous TILs expanded and activated ex vivo were administered to virtually untreated patients, an approach that was episodically associated with measurable, though not durable, clinical responses.[32] This was likely due to the facts that (1) upon re-infusion, TILs normally fail to persist for long periods in vivo;[33,34] (2) the antineoplastic activity of re-infused TILs is rapidly annihilated by local and systemic immunosuppressive networks, such as those established by myeloid-derived suppressor cells (MDSCs)[35–37] and FOXP3$^+$ regulatory T cells (Tregs);[38–42] and (3) endogenous immune effector cells, including T, B and natural killer (NK) lymphocytes, might enter in competition with re-infused TILs for key cytokines such as IL-7 and IL-15, a phenomenon that is known as "cytokine sink."[43,44] To circumvent these issues, various lymphodepleting regimens have been developed, mostly relying on combinations of high-dose cyclophosphamide (an alkylating agent currently approved for the treatment of several cancers), fludarabine (a nucleoside analog often employed against hematological neoplasms) and total body irradiation.[45] Since the intensity of lymphodepletion has been clearly correlated with the clinical efficacy of ACT, preconditioning lymphodepletion is now part of standard ACT protocols.[45]

Along similar lines, it is relatively common to reintroduce TILs into lymphodepleted patients together with high doses of IL-2,[46,47] even though this approach is being increasingly questioned owing to its potential immunosuppressive side effects.[48–50] Several alternative agents have been investigated for their capacity to potentiate the clinical efficacy of ACT, including (1) immunostimulatory cytokines other than IL-2, such as IL-7, IL-12, IL-15 and interferon (IFN)γ;[51–54] (2) inhibitors of angiogenesis, which facilitate the homing to TILs to neoplastic lesions;[55,56] (3) Toll-like receptor (TLR) agonists, as they exert potent adjuvant effects and limit endogenous immunosuppression;[57–60] and (4) a wide panel of immunostimulatory chemotherapeutics, encompassing (but not limited to) metronomic cyclophosphamide, gemcitabine (a nucleoside analog that is used for the treatment of various carcinomas and some forms of lymphoma) and several anthracyclines.[61–63]

Importantly, although the efficacy of ACT is generally attributed to CD8$^+$ T cells, the administration of CD4$^+$ T cells alone has also been shown to induce durable clinical responses in melanoma patients.[64] Moreover, at least theoretically, immune effector cell types other than T lymphocytes, including B and NK cells, can be used in ACT protocols. So far, the adoptive transfer of autologous B cells has only been investigated at the preclinical level.[65] This is presumably linked to the fact that B cells are known to mediate immunosuppressive effects and sustain tumor growth, at least in some models of carcinogenesis.[66,67] Conversely, NK cell-based ACT strategies have already been evaluated in clinical trials, with relatively deceiving results.[68,69] This is at odds with encouraging preclinical observations as well as with the established efficacy of allogeneic NK cells against acute myeloid leukemia (AML).[70–72] Promising results have been obtained with "young TILs," i.e., minimally cultured, bulk TILs that can be generated in a relatively inexpensive and rapid manner that does not entail individualized tumor-reactivity screening steps.[73–75] By abating the costs that are associated with the generation of ACT-compatible TILs, this technology may significantly increase the number of centers that will offer ACT immunotherapy to eligible patients in the near future. As it stands, however, there are no ACT protocols approved by the US FDA or other international regulatory agencies for use in cancer patients (source www.fda.gov).

Along the lines of our monthly Trial Watch series,[9–15,57,59,76–79] here we will summarize the latest advances in the use of ACT as an active immunotherapeutic strategy against cancer, focusing on high-impact studies that have been published and clinical trials that have been launched during the last 13 mo.

Literature Update

Since the submission of our previous Trial Watch on this topic (January 2012),[15] the results of no more than 10 clinical trials investigating the therapeutic potential of ACT in cancer patients have

been published (source www.ncbi.nlm.nih.gov/sites/entrez/). Six of these studies involved individuals bearing hematological (most often B-cell) malignancies,[80–85] especially in settings of post-HSCT relapse.[80,81,83,85] The remaining 4 trials investigated the clinical potential of ACT in patients with neuroblastoma, nasopharyngeal carcinoma, melanoma or recurrent ovarian carcinoma.[86–89] The clinical protocols employed in some of these studies were relatively conventional, such as (1) the infusion of autologous T cells expanded and activated ex vivo to pediatric neuroblastoma patients early after HSCT;[86] (2) the administration of autologous TILs in combination with low-dose IL-2 to lymphodepleted metastatic melanoma patients,[87] (3) the infusion of autologous T cells genetically modified for the expression of a HA-1-specific TCR to leukemia patients relapsing upon HSCT;[83] (4) the administration of originally allogeneic T lymphocytes isolated from B-cell malignancies that failed to respond to HSCT (upon expansion and activation ex vivo with anti-CD3/anti-CD28-coated beads);[80] (5) the infusion of autologous peripheral blood mononuclear cells (PBMCs) expanded ex vivo in the presence of Epstein-Barr virus (EBV)-infected cells to individuals affected by EBV-associated nasopharyngeal carcinoma;[89] and (6) the administration of cytokine-induced killer (CIK) cells, i.e., an heterogeneous population of T lymphocytes and $CD3^+CD56^+$, non-MHC-restricted cells exhibiting a mixed T-cell/NK-cell phenotype,[90] to patients with hematological malignancies relapsing upon HSCT.[85]

Alongside, four studies evaluated the clinical profile of CAR-based ACT immunotherapy.[81,82,84,88] Thus, the groups of Steven Rosenberg (National Cancer Institute, Bethesda, MD) and George Coukos (University of Pennsylvania, Philadelphia, PA) independently investigated (in Phase I clinical trials) the safety and efficacy of autologous T cells genetically modified to express an anti-CD19 CAR in patients bearing advanced B-cell malignancies, either upon a course of conventional chemotherapy[82] or during HSCT.[81] Along similar lines, Oliver Press and collaborators (Fred Hutchinson Cancer Research Center, Seattle, WA) conducted a Phase I clinical trial to preliminarily assess the clinical potential of autologous T cells stably expressing a CD20-specific CAR in indolent B-cell or mantle cell lymphoma patients previously subjected to lymphodepletion with cyclophosphamide.[84] Finally, Coukos and colleagues tested the safety and activity of autologous T cells engineered to express a folate receptor α (FRα)-targeting CAR in (lymphodepleted) patients affected by recurrent ovarian cancer.[88] Taken together, the results of these studies corroborate the notion that the re-administration of autologous T cells genetically engineered for the expression of TAA-specific TCRs or CARs to cancer patients is generally safe[15] and drives robust tumor-specific immune responses that—at least in a fraction of patients—translate into measurable clinical benefits.[1,5,91] Of note, Carl June and collaborators (University of Pennsylvania, Philadelphia, PA) have recently reported the results of a decade-long safety assessment of an ACT protocol involving the administration of T lymphocytes expressing a gp120-specific CAR to HIV-1 patients.[92] This study demonstrates that the use of retroviral transduction to generate CAR-expressing T cells is associated with stable engraftment and durable safety, implying that previously reported side effects linked to insertional mutagenesis[93,94] are either stem cell- or transgene-intrinsic and hence do not constitute a relevant issue for ACT immunotherapy.[92]

During the last 13 months, an intense wave of (preclinical) investigation has focused on the characterization of novel factors that may influence the clinical efficacy of ACT as well as on the refinement of protocols for the isolation, expansion and activation of clinical-grade material for this immunotherapeutic regimen. Moreover, considerable efforts have been dedicated at the identification of maneuvers that may improve the persistence of re-infused lymphocytes and boost their antineoplastic activity while keeping potential side effects at bay.

The refinements of expansion/activation protocols that have recently been suggested to quantitatively and/or qualitatively improve cellular preparations for ACT include, but are not limited to: (1) the addition of an in vitro re-stimulation step with relevant peptides prior to expansion, resulting in an increased proportion of tumor-specific T cells among cultured PBMCs;[95] (2) the use of IL-12 or IFNγ for the priming of TILs with TAA-derived peptides, resulting in increased antitumor activity in vivo;[96,97] (3) the use of low-dose IFNγ as a pre-treatment for autologous cancer (melanoma) cells employed to activate TILs in co-culture settings, de facto boosting their cytotoxic activity;[98] (4) the use of an antigen-presenting cell (APC) platform engineered for the expression of the co-stimulatory molecule 4–1BBL and the secretion of IL-21, resulting in the superior expansion of T cells that exhibit a "young" $CD27^+CD28^+$ phenotype and increased cytotoxic functions, but not of Tregs;[99] (5) the treatment of T cells with the selective A3 adenosine receptor agonist Cl-IB-MECA prior to infusion, resulting in increased tumor necrosis factor α (TNFα) secretion and hence superior cytotoxic potential in vivo;[100] (6) the use of $CD8^+$ T cell-specific lentiviral vectors (as opposed to vector that unselectively target T cells) for the transduction of TAA-targeting TCR-coding genes, resulting in increased granzyme B levels and CD8 expression by a subpopulation of transfected cells and hence in improved antineoplastic effects in vivo;[101] (7) the downregulation of the E3 ubiquitin ligase Casitas B-lineage lymphoma B (CBLB) in T cells prior to infusion, de facto limiting their sensitivity to immunosuppressive signals such as those delivered by transforming growth factor β (TGFβ);[102] (8) the downregulation of protein tyrosine phosphatase, non-receptor type 6 (PTPN6, also known as SHP1), resulting in a superior short-term accumulation of T cells upon re-infusion and increased therapeutic activity;[103] (9) the transgene-driven expression of an ubiquitination-resistant linker for activation of T cells (LAT), resulting in increased TCR signaling and cytotoxic potential;[104] (10) the expression of a constitutively active form of signal transducer and activator of transcription 5 (STAT5), significantly boosting the proliferative potential of TAA-experienced T cells;[105] (11) the expression of a co-receptor-independent TCR, resulting in a increased fraction of cytotoxic $CD3^+$ cells (including $CD4^-CD8^-$ cells);[106] (12) the expression of single-chain IL-12, resulting in the local self-provision of immunostimulatory signals that appear to be required for the clinical efficacy of CAR-expressing T cells in several mouse tumor models;[107] and (13) the depletion of $CD137^+CD44^{high}CD4^+$ cells prior to infusion, as

these cells de facto constitute a subpopulation of highly activated $CD25^+FOXP3^+$ Tregs.[108] Moreover, Somanchi et al. have shown that trogocytosis, the process whereby T, B and NK lymphocytes can acquire transmembrane proteins from APCs,[109,110] can be efficiently used to engineer cells for ACT prior to re-infusion. Thus, NK cells exposed to CCR7-expressing K562 leukemia cells ex vivo have been shown to efficiently take up CCR7 and express it at their own membrane, resulting in increased homing to lymph nodes upon re-infusion.[111]

The study of Chinnasamy and colleagues mentioned above deserves a special mention as the authors not only showed that the local production of IL-12 dictates the efficacy of CAR-transduced T cells, but also demonstrated that T lymphocytes expressing a vascular endothelial growth factor receptor 2 (VEGFR2)-specific CAR mediate antineoplastic effects both as they inhibit angiogenesis and as they target $VEGFR2^+$ MDSCs (in situ and systemically).[107] Along similar lines, we have found of particular interest a recent work from Kloss and colleagues, who proposed a combinatorial strategy whereby CAR-expressing T cells can be rendered truly specific for a given tumor.[112] This is particularly relevant when CARs are designed to target so-called "shared" TAAs—that is, TAAs that are also expressed (generally to low levels) by normal cells—as CAR-engineered T cells are extremely sensitive to cognate antigens and hence may damage non-neoplastic tissues.[113,114] To minimize this possibility, Kloss et al. engineered T cells for the co-expression of a CAR that provides suboptimal activation upon binding to one antigen and a chimeric co-stimulatory receptor (CCR) that recognizes a second antigen, resulting in a significant improvement in T-cell selectivity.[112]

Besides these improvements in the protocols whereby autologous tumor-reactive lymphocytes are isolated, expanded and activated, several strategies have been proposed as possible means to ameliorate the efficacy of ACT immunotherapy at a later stage, that is, at or post re-infusion. These approaches encompass, but are not limited to: (1) the combination of ACT with agonistic anti-CD40 and anti-CD137 monoclonal antibodies (in the latter case at a specific time point upon infusion), both of which are known to mediate potent co-stimulatory signals;[115,116] (2) the co-administration of ACT with 6-gingerol, a capsaicin-like component of ginger that seems to promote the proliferation of TIL in vivo and their ability to infiltrate neoplastic lesions;[117] (3) the administration of ACT together with monoclonal antibodies specific for the immunosuppressive receptor PD-1,[7] resulting in increased IFNγ production at the tumor site and superior antineoplastic activity;[118] (4) the combination of ACT with oncogene-targeting agents, such as compound that specifically inhibit mutant BRAF, which have recently been shown to improve tumor-infiltration by adoptively transferred T cells as well as antitumor responses in murine models of mutant BRAF-expressing melanoma.[119,120]

During the past 13 months, important insights have been gained into the mechanisms that underpin the efficacy of ACT in vivo. For example, it has been demonstrated that (1) the T-cell transcription factor NFAT1 plays a prominent role in the tumor-induced anergy of $CD4^+$ T cells;[121] (2) the absence of functional ligands for L-, P- and E-selectins (adhesion molecules that are involved in leukocyte rolling along high endothelial venules) as well as the dysfunction of the NK-cell activating receptor NKG2D compromises the antineoplastic activity of adoptively transferred $CD8^+$ T cells, in mice;[122,123] (3) the survival of memory $CD8^+$ T cells in the absence of $CD4^+$ T-cell help relies on CD27-transduced signals that result in the expression of the IL-7 receptor;[124] (4) memory T cells that can self-renew upon adoptive transfer to cancer patients respond to antigenic stimuli by producing IL-2- and IFNγ-coding mRNAs in a stoichometrically defined ratio;[125] (5) IL-15, but not IL-2, relieves the immunosuppressive impact of Tregs on adoptively transferred $CD8^+$ T cells, hence favoring their survival, proliferation and effector functions;[126] and (6) one of the mechanisms whereby melanoma cells become refractory to ACT immunotherapy involves a TNFα-dependent inflammatory response that results in the selective loss of melanocytic (but not non-melanocytic) antigens.[127] The results of these studies are highly relevant for the development of novel ACT strategies that exert superior antineoplastic activity. Along similar lines, the discovery that γδ T cells also mediate potent antitumor effects upon re-infusion (following "conventional" expansion/activation only or in combination with the retroviral transduction of CD8 plus a tumor-reactive αβ TCR) paves an interesting avenue for the development of innovative ACT protocols.[128–131]

This said, perhaps the most exciting progress for ACT achieved during the last 13 months relates to the possibility of "rejuvenating" T cells.[132] Indeed, the TAA-specific T cells that are employed in ACT protocols are often highly differentiated, in particular if TILs are used as starting material, as they have been exposed to chronic inflammation and prolonged antigenic stimulation in vivo. Moreover, expansion procedures generally engender (at least some degree of) terminal differentiation, loss of proliferative capacity and exhaustion/senescence.[133,134] To circumvent this issue, protocols that allow for the selective expansion of early-differentiated, stem-cell memory T (T_{SCM}) cells have been developed.[133,135] These cells constitute the most undifferentiated human T-cell compartment exhibiting bona fide memory functions, virtually generating all memory cell subsets, display superior persistence and expansion capabilities in vivo and survive for extended periods even after the loss of cognate antigens.[136,137] In addition, the induced pluripotent stem cell (iPSC) technology has been successfully applied to antigen-experienced T cells, allowing for the generation of mature, rejuvenated T cells that maintain the original rearrangement of TCR-coding genes, produce IFNγ in response to antigenic stimulation, exhibit long telomeres (which are indicative of a high replicative potential), are capable of expanding to considerable extents in vitro, express higher levels of cytotoxic molecules than the T-cell clones they derive from and lack the expression of the exhaustion marker PD-1.[138–140] We firmly believe that the use of rejuvenated T cells will considerably expand the therapeutic potential of ACT.

Update on Clinical Trials

When our latest Trial Watch dealing with ACT anticancer immunotherapy was submitted to *OncoImmunology* for

publication (January 2012), official sources listed no more than 35 recent (started after January 1, 2008), ongoing (not withdrawn, terminated or completed by the day of submission) clinical trials that would assess the safety and efficacy of ACT in cancer patients.[15] The status of 28 of these studies has remained unchanged since, whereas 4 trials (NCT00720031; NCT00730613; NCT00815321; NCT01118091) have been completed, 2 have been terminated (NCT00924001; NCT01212887, the latter of which due to safety concerns and lack of efficacy) and 1 has been suspended (NCT01477021). Of note, only the results of NCT00815321, testing the administration of CIK expanded/activated ex vivo with standard protocols to patients with hematological malignancies relapsing upon HSCT, have already been published (see above).[85]

At present (February 2013), official sources list no less than 27 clinical trials launched after February 1, 2012, that would investigate the safety and efficacy of ACT in oncological indications (source www.clinicaltrials.gov). This rate is strikingly higher than that observed in the previous 4-y period, corroborating the notion that ACT immunotherapy is nowadays considered as one of the most promising strategies against cancer. A majority of ongoing clinical studies involve patients bearing hematological malignancies encompassing (but not limited to) acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS) and several forms of myeloma (10 trials) or skin cancers, such as melanoma and Merkel cell carcinoma (7 trials). Taken together, the remaining 10 studies are performed in a relatively heterogeneous group of patients, including individuals affected by esophageal cancer (2 trials), breast carcinoma (1 trial), mesothelioma (1 trial), cholangiocarcinoma (1 trial) as well as unspecified solid tumors (5 trials) (**Table 1**). Although not always specified at www.clinicaltrials.gov, most (if not all) of these trials involve patient pre-conditioning, which is often achieved with cyclophosphamide and fludarabine optionally combined with one or more cytotoxic chemotherapeutics, as well as the administration of IL-2 upon re-infusion (for the reasons discussed above).

In a majority of cases, the infused material consists of genetically engineered lymphocytes, mostly for the expression of TAA-specific CARs (10 studies) or TCRs (5 studies). Thus, T cells expressing a CD19-specific CAR are being tested (1) in pediatric patients with relapsed B-cell ALL (NCT01683279); (2) children and young adults affected by ALL, B-cell leukemia, large cell lymphoma or non-Hodgkin lymphoma who have failed conventional therapies (NCT01593696); (3) patients with relapsed or refractory chronic lymphocytic leukemia (NCT01747486; NCT01653717); and (4) subjects suffering from not better defined variants of $CD19^+$ leukemia or lymphoma (NCT01626495). Moreover, (1) T cells expressing a CD20-directed CAR are being tested in patients affected by a large variety of hematological neoplasms (NCT01735604); (2) T lymphocytes engineered for the expression of a CAR targeting the Lewis Y carbohydrate antigen are being assessed as a therapeutic intervention in AML, MDS and multiple myeloma patients (NCT01716364); (3) T cells expressing a fibroblast activation protein (FAP)-specific CAR are being evaluated in patients with malignant pleural mesothelioma (NCT01722149); (4) the antineoplastic activity of mesothelin-redirected T cells is being assessed in metastatic mesothelioma and pancreatic carcinoma patients (NCT01583686); and (5) T lymphocytes redirected against the carcinoembryonic antigen (CEA) by means of a specific CAR are investigated as a therapeutic option for subjects affected by metastatic carcinomas (NCT01723306). The safety and preliminary efficacy of T lymphocytes engineered to express TCRs that recognize NY-ESO-1 (a cancer-testis antigen),[141] tyrosinase and various other melanoma-associated antigens (MAGEs) or Wilms tumor 1 (WT1, a TAA overexpressed by various hematological and renal tumors)[142] are being investigated in cohorts of patients affected by AML or chronic myeloid leukemia (NCT01621724), melanoma (NCT01586403), ovarian carcinoma (NCT01567891), as well as advances solid tumors (NCT01694472; NCT01697527). Finally, T cells co-expressing nerve growth factor receptor (NGFR) or chemokine (C-X-C motif) receptor 2 (CXCR2), improving their ability to proliferate in vivo and to migrate to neoplastic lesions, are being tested as a standalone therapeutic intervention in melanoma patients (NCT01740557).

The remaining clinical studies involve genetically unmodified cells. In particular: (1) TILs isolated and amplified with conventional protocols are being assessed, in combination with either the BRAF-specific inhibitor vemurafenib[143,144] or the anti-CTL4 monoclonal antibody ipilimumab,[9,10,145] for the treatment of metastatic melanoma patients (NCT01659151; NCT01701674); (2) young TILs, alone or combined with vemurafenib, are being assessed in cohort of patients affected by human papillomavirus $(HPV)^+$ tumors (mainly oropharyngeal, cervical, vaginal and anal carcinoma) and melanoma, respectively (NCT01585428; NCT01585415); (3) autologous polyclonal $CD8^+$ TILs specific for a Merkel cell polyomavirus-associated antigen are being tested, in combination with local irradiation or intralesional IFNβ, in subjects bearing metastatic Merkel cell carcinomas (NCT01758458);[146] (4) the safety and therapeutic potential of EBV-specific cytotoxic T lymphocytes are being evaluated in patients with various forms of EBV^+ lymphomas and lymphoproliferative disorders (NCT01555892); and (5) activated T cells armed with a bispecific antibody simultaneously targeting CD3 and ERBB2, a TAA that is often overexpressed in breast carcinoma,[147] are being tested in combination with conventional chemotherapeutic regimens for the treatment of resectable Stage II–III breast cancer (NCT01658969). In addition, (1) CIK cells are being investigated as a standalone intervention for the therapy of cholangiocarcinoma patients (NCT01573455) or combined with conventional chemotherapy and/or radiation in subjects bearing esophageal carcinomas (NCT01691625; NCT01691664); and (2) the safety and efficacy of umbilical cord blood-derived NK cells are being assessed in a cohort of myeloma patients concomitantly subjected to chemotherapy and autologous stem cell transplantation (NCT01729091).

Concluding Remarks

As detailed above, no less than 27 new clinical trials that would evaluate the safety and efficacy of ACT immunotherapy in

Table 1. Recent clinical trials assessing the safety and efficacy of ACT immunotherapy in cancer patients*

Type	Indication(s)	Phase	Status	Note(s)	Ref.
Engineered T cells	Advanced solid tumors	I	Active, not recruiting	MAGE-A4-specific TCR-expressing T cells	NCT01694472
		II	Recruiting	T cells expressing an NY-ESO-1-specific TCR plus NY-ESO-1-pulsed DCs	NCT01697527
		II	Recruiting	CEA-specific CAR-expressing T cells, as a standalone intervention	NCT01723306
	AML CML	I/II	Recruiting	T cells expressing a WT1-specific TCR, as a standalone intervention	NCT01621724
	AML MDS MM	I	Active, not recruiting	T cells expressing a CAR specific for the Lewis Y carbohydrate antigen	NCT01716364
	B-cell ALL	I	Recruiting	CD19-specific CAR-expressing T cells, in pediatric patients with relapsing disease	NCT01683279
	CLL	I	Not yet recruiting	CD19-specific CAR-expressing T cells	NCT01653717
		II	Recruiting	CD19-specific CAR-expressing T cells, in patients with relapsed/refractory disease	NCT01747486
		I	Recruiting	CD20-specific CAR-expressing T cells, in patients with chemorefractory disease	NCT01626495
	Leukemia Lymphoma	n.a.	Not yet recruiting	CD20-redirected T cells, in patients with chemorefractory disease	NCT01735604
		I	Recruiting	CD19-redirected T cells, in children and young adults failing conventional therapies	NCT01593696
	Mesothelioma	I	Not yet recruiting	FAP-specific CAR-expressing T cells, in patients with FAP^+ pleural disease	NCT01722149
	Mesothelioma Pancreatic carcinoma	I/II	Recruiting	T cells expressing a CAR specific for mesothelin, as a standalone intervention	NCT01583686
	Melanoma	I	Recruiting	T cells expressing a tyrosinase-specific, co-receptor-independent TCR	NCT01586403
		I/II	Not yet recruiting	CXCR2- or NGFR-expressing T cells, in patients with metastatic disease	NCT01740557
	Ovarian carcinoma	I/II	Active, not recruiting	T cells expressing a TCR specific for NY-ESO-1 or MAGE-A3/A6/B18	NCT01567891
Unmodified T cells	Breast carcinoma	II	Recruiting	Activated T cells armed with a bispecific antibody targeting CD3 and ERBB2	NCT01658969
	HPV^+ carcinoma	II	Recruiting	Young TILs as a standalone intervention	NCT01585428
	Lymphoproliferative disorders	I	Not yet recruiting	EBV-specific cytotoxic T lymphocytes	NCT01555892
	Melanoma	n.a.	Recruiting	Conventional TILs plus ipilimumab	NCT01701674
		I	Recruiting	Young TILs combined with vemurafenib	NCT01585415
		II	Recruiting	Conventional TILs plus vemurafenib	NCT01659151
	Merkel cell carcinoma	I/II	Not yet recruiting	Autologous polyclonal $CD8^+$ TILs plus local irradiation or intralesional IFNβ	NCT01758458

ACT, adoptive cell transfer; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CXCR2, chemokine (C-X-C motif) receptor 2; DC, dendritic cell; EBV, Epstein-Barr virus; FAP, fibroblast activation protein; HPV, human papillomavirus; IFN, interferon; MAGE, melanoma-associated antigen; MDS, myelodysplastic syndrome; MM, multiple myeloma; n.a., not available; NGFR, nerve growth factor receptor; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; WT1, Wilms tumor 1. *Started after January 31, 2012.

Table 1 (Continued). Recent clinical trials assessing the safety and efficacy of ACT immunotherapy in cancer patients*

Type	Indication(s)	Phase	Status	Note(s)	Ref.
Other cell types	Cholangiocarcinoma	I	Recruiting	CIK cells as a standalone intervention	NCT01573455
	Esophageal carcinoma	n.a.	Recruiting	CIK cells plus radiotherapy and conventional chemotherapy	NCT01691625
		n.a.	Recruiting	CIK cells plus radiotherapy	NCT01691664
	Myeloma	I/II	Not yet recruiting	Umbilical cord blood-derived NK cells plus chemotherapy and ASCT	NCT01729091

ASCT, autologous stem cell transplantation; CIK, cytokine-inducer killer; n.a., not available; NK, natural killer. *Started after January 31, 2012.

cancer patients have been launched during the past 14 months. By comparison, only 35 of such studies were launched from January 1, 2008, and January 31, 2012, reflecting the interest that this immunotherapeutic modality has generated among clinicians. Along similar lines, the molecular and cellular circuitries that may influence the clinical efficacy of ACT are being intensively investigated, as demonstrated by the constantly increasing amount of high quality scientific publications dealing with topics (source www.ncbi.nlm.nih.gov/pubmed/).

As it stands, CAR-based approaches are on the limelight, at least in part due to the development of "third-generation" molecules that contain multiple intracellular signaling domains, including CD3ζ-, CD28- and OX40- or 4–1BB-derived modules, and hence exert robust antineoplastic effects.[148–150] In addition, Carl June and collaborators have recently reported that the administration of CAR-expressing T cells to HIV-1 patients is associated with a stable engraftment (CAR^+ cells could be detected as long as 11 y after infusion), even in the absence of lymphodepleting regimens, but (1) no severe side effects and (2) no evidence of insertional mutagenesis.[92] It will be interesting to see whether these observations hold true in cancer patients, in particular in view of the fact that both HIV-1 infection and cancer are expected to induce (at least some extent of) immunosuppression, though by distinct mechanisms. In this setting, approaches in which T cells are engineered for the expression of suicide proteins, such as an inducible variant of caspase-9,[151] should provide an additional level of security for the development of novel and safe immunotherapeutic protocols based on ACT. Future will tell whether the great expectations that are being generated by ACT immunotherapy will ever translate into a clinical reality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Authors are supported by the European Commission (ArtForce); Agence National de la Recherche (ANR); Ligue contre le Cancer (Equipe labelisée); Fondation pour la Recherche Médicale (FRM); Institut National du Cancer (INCa); LabEx Immuno-Oncologie; Fondation de France; Fondation Bettencourt-Schueller; AXA Chair for Longevity Research; Cancéropôle Ile-de-France and Paris Alliance of Cancer Research Institutes (PACRI).

References

1. Rosenberg SA. Cell transfer immunotherapy for metastatic solid cancer--what clinicians need to know. Nat Rev Clin Oncol 2011; 8:577-85; PMID:21808266; http://dx.doi.org/10.1038/nrclinonc.2011.116
2. Rosenberg SA. Raising the bar: the curative potential of human cancer immunotherapy. Sci Transl Med 2012; 4:ps8; PMID:22461638; http://dx.doi.org/10.1126/scitranslmed.3003634
3. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. J Clin Oncol 2011; 29:4828-36; PMID:22042955; http://dx.doi.org/10.1200/JCO.2011.38.0899
4. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer 2008; 8:299-308; PMID:18354418; http://dx.doi.org/10.1038/nrc2355
5. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol 2012; 12:269-81; PMID:22437939; http://dx.doi.org/10.1038/nri3191
6. Margolin K. Ipilimumab in a Phase II trial of melanoma patients with brain metastases. Oncoimmunology 2012; 1:1197-9; PMID:23170278; http://dx.doi.org/10.4161/onci.20687
7. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1223-5; PMID:23243584; http://dx.doi.org/10.4161/onci.21335
8. Beyer M. Interleukin-2 treatment of tumor patients can expand regulatory T cells. Oncoimmunology 2012; 1:1181-2; PMID:23170272; http://dx.doi.org/10.4161/onci.20639
9. Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Zitvogel L, Kroemer G, et al. Trial Watch: Monoclonal antibodies in cancer therapy. OncoImmunology 2013; 2:e22789; http://dx.doi.org/10.4161/onci.22789
10. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, et al. Trial Watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938
11. Vacchelli E, Galluzzi L, Eggermont A, Galon J, Tartour E, Zitvogel L, et al. Trial Watch: Immunostimulatory cytokines. Oncoimmunology 2012; 1:493-506; PMID:22754768; http://dx.doi.org/10.4161/onci.20459
12. Galluzzi L, Senovilla L, Vacchelli E, Eggermont A, Fridman WH, Galon J, et al. Trial watch: Dendritic cell-based interventions for cancer therapy. Oncoimmunology 2012; 1:1111-34; PMID:23170259; http://dx.doi.org/10.4161/onci.21494
13. Senovilla L, Vacchelli E, Garcia P, Eggermont A, Fridman WH, Galon J, et al. Trial Watch: DNA vaccines for cancer therapy. OncoImmunology 2013; 2:e23803
14. Vacchelli E, Martins I, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: Peptide vaccines in cancer therapy. Oncoimmunology 2012; 1:1557-76; PMID:23264902; http://dx.doi.org/10.4161/onci.22428
15. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial Watch: Adoptive cell transfer immunotherapy. Oncoimmunology 2012; 1:306-15; PMID:22737606; http://dx.doi.org/10.4161/onci.19549
16. Ueno H, Klechevsky E, Schmitt N, Ni L, Flamar AL, Zurawski S, et al. Targeting human dendritic cell subsets for improved vaccines. Semin Immunol 2011; 23:21-7; PMID:21277223; http://dx.doi.org/10.1016/j.smim.2011.01.004
17. Ueno H, Palucka AK, Banchereau J. The expanding family of dendritic cell subsets. Nat Biotechnol 2010; 28:813-5; PMID:20697407; http://dx.doi.org/10.1038/nbt0810-813
18. Palucka K, Banchereau J, Mellman I. Designing vaccines based on biology of human dendritic cell subsets. Immunity 2010; 33:464-78; PMID:21029958; http://dx.doi.org/10.1016/j.immuni.2010.10.007
19. Jenq RR, van den Brink MR. Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer. Nat Rev Cancer 2010; 10:213-21; PMID:20168320; http://dx.doi.org/10.1038/nrc2804

20. Barriga F, Ramírez P, Wietstruck A, Rojas N. Hematopoietic stem cell transplantation: clinical use and perspectives. Biol Res 2012; 45:307-16; PMID:23283440; http://dx.doi.org/10.4067/S0716-97602012000300012
21. Bouquié R, Bonnin A, Bernardeau K, Khammari A, Dréno B, Jotereau F, et al. A fast and efficient HLA multimer-based sorting procedure that induces little apoptosis to isolate clinical grade human tumor specific T lymphocytes. Cancer Immunol Immunother 2009; 58:553-66; PMID:18751701; http://dx.doi.org/10.1007/s00262-008-0578-2
22. Yun YS, Hargrove ME, Ting CC. In vivo antitumor activity of anti-CD3-induced activated killer cells. Cancer Res 1989; 49:4770-4; PMID:2527087
23. Merhavi-Shoham E, Haga-Friedman A, Cohen CJ. Genetically modulating T-cell function to target cancer. Semin Cancer Biol 2012; 22:14-22; PMID:22210183; http://dx.doi.org/10.1016/j.semcancer.2011.12.006
24. Liu K, Rosenberg SA. Transduction of an IL-2 gene into human melanoma-reactive lymphocytes results in their continued growth in the absence of exogenous IL-2 and maintenance of specific antitumor activity. J Immunol 2001; 167:6356-65; PMID:11714800
25. Zhou J, Shen X, Huang J, Hodes RJ, Rosenberg SA, Robbins PF. Telomere length of transferred lymphocytes correlates with in vivo persistence and tumor regression in melanoma patients receiving cell transfer therapy. J Immunol 2005; 175:7046-52; PMID:16272366
26. Kalbasi A, Shrimali RK, Chinnasamy D, Rosenberg SA. Prevention of interleukin-2 withdrawal-induced apoptosis in lymphocytes retrovirally cotransduced with genes encoding an antitumor T-cell receptor and an antiapoptotic protein. J Immunother 2010; 33:672-83; PMID:20664359; http://dx.doi.org/10.1097/CJI.0b013e3181e475cd
27. Hinrichs CS, Borman ZA, Gattinoni L, Yu Z, Burns WR, Huang J, et al. Human effector CD8+ T cells derived from naive rather than memory subsets possess superior traits for adoptive immunotherapy. Blood 2011; 117:808-14; PMID:20971955; http://dx.doi.org/10.1182/blood-2010-05-286286
28. Bellone M, Calcinotto A, Corti A. Won't you come on in? How to favor lymphocyte infiltration in tumors. Oncoimmunology 2012; 1:986-8; PMID:23162781; http://dx.doi.org/10.4161/onci.20213
29. Kershaw MH, Teng MW, Smyth MJ, Darcy PK. Supernatural T cells: genetic modification of T cells for cancer therapy. Nat Rev Immunol 2005; 5:928-40; PMID:16322746; http://dx.doi.org/10.1038/nri1729
30. Davila ML, Brentjens R, Wang X, Rivière I, Sadelain M. How do CARs work?: Early insights from recent clinical studies targeting CD19. Oncoimmunology 2012; 1:1577-83; PMID:23264903; http://dx.doi.org/10.4161/onci.22524
31. Park TS, Rosenberg SA, Morgan RA. Treating cancer with genetically engineered T cells. Trends Biotechnol 2011; 29:550-7; PMID:21663987; http://dx.doi.org/10.1016/j.tibtech.2011.04.009
32. Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med 1988; 319:1676-80; PMID:3264384; http://dx.doi.org/10.1056/NEJM198812223192527
33. Olurinde MO, Shen CH, Drake A, Bai A, Chen J. Persistence of tumor-infiltrating CD8 T cells is tumor-dependent but antigen-independent. Cell Mol Immunol 2011; 8:415-23; PMID:21666707; http://dx.doi.org/10.1038/cmi.2011.18
34. Song A, Tang X, Harms KM, Croft M. OX40 and Bcl-xL promote the persistence of CD8 T cells to recall tumor-associated antigen. J Immunol 2005; 175:3534-41; PMID:16148096
35. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009; 9:162-74; PMID:19197294; http://dx.doi.org/10.1038/nri2506
36. Montero AJ, Diaz-Montero CM, Kyriakopoulos CE, Bronte V, Mandruzzato S. Myeloid-derived suppressor cells in cancer patients: a clinical perspective. J Immunother 2012; 35:107-15; PMID:22306898; http://dx.doi.org/10.1097/CJI.0b013e318242169f
37. Nagaraj S, Gabrilovich DI. Myeloid-derived suppressor cells in human cancer. Cancer J 2010; 16:348-53; PMID:20693846; http://dx.doi.org/10.1097/PPO.0b013e3181eb3358
38. Cheng G, Yu A, Malek TR. T-cell tolerance and the multi-functional role of IL-2R signaling in T-regulatory cells. Immunol Rev 2011; 241:63-76; PMID:21488890; http://dx.doi.org/10.1111/j.1600-065X.2011.01004.x
39. Rudensky AY. Regulatory T cells and Foxp3. Immunol Rev 2011; 241:260-8; PMID:21488902; http://dx.doi.org/10.1111/j.1600-065X.2011.01018.x
40. Yao X, Ahmadzadeh M, Lu YC, Liewehr DJ, Dudley ME, Liu F, et al. Levels of peripheral CD4(+)FoxP3(+) regulatory T cells are negatively associated with clinical response to adoptive immunotherapy of human cancer. Blood 2012; 119:5688-96; PMID:22555974; http://dx.doi.org/10.1182/blood-2011-10-386482
41. Kodumudi KN, Weber A, Sarnaik AA, Pilon-Thomas S. Blockade of myeloid-derived suppressor cells after induction of lymphopenia improves adoptive T cell therapy in a murine model of melanoma. J Immunol 2012; 189:5147-54; PMID:23100512; http://dx.doi.org/10.4049/jimmunol.1200274
42. Pere H, Tanchot C, Bayry J, Terme M, Taieb J, Badoual C, et al. Comprehensive analysis of current approaches to inhibit regulatory T cells in cancer. Oncoimmunology 2012; 1:326-33; PMID:22737608; http://dx.doi.org/10.4161/onci.18852
43. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. J Exp Med 2005; 202:907-12; PMID:16203864; http://dx.doi.org/10.1084/jem.20050732
44. Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol 2005; 26:111-7; PMID:15668127; http://dx.doi.org/10.1016/j.it.2004.12.003
45. Wrzesinski C, Paulos CM, Kaiser A, Muranski P, Palmer DC, Gattinoni L, et al. Increased intensity lymphodepletion enhances tumor treatment efficacy of adoptively transferred tumor-specific T cells. J Immunother 2010; 33:1-7; PMID:19952961; http://dx.doi.org/10.1097/CJI.0b013e3181b88ffc
46. Tartour E, Latour S, Mathiot C, Thiounn N, Mosseri V, Joyeux I, et al. Variable expression of CD3-zeta chain in tumor-infiltrating lymphocytes (TIL) derived from renal-cell carcinoma: relationship with TIL phenotype and function. Int J Cancer 1995; 63:205-12; PMID:7591205; http://dx.doi.org/10.1002/ijc.2910630210
47. Tartour E, Mathiot C, Fridman WH. Current status of interleukin-2 therapy in cancer. Biomed Pharmacother 1992; 46:473-84; PMID:1306361; http://dx.doi.org/10.1016/0753-3322(92)90005-R
48. Ahmadzadeh M, Rosenberg SA. IL-2 administration increases CD4+ CD25(hi) Foxp3+ regulatory T cells in cancer patients. Blood 2006; 107:2409-14; PMID:16304057; http://dx.doi.org/10.1182/blood-2005-06-2399
49. Saadoun D, Rosenzwajg M, Joly F, Six A, Carrat F, Thibault V, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl J Med 2011; 365:2067-77; PMID:22129253; http://dx.doi.org/10.1056/NEJMoa1105143
50. Koreth J, Matsuoka K, Kim HT, McDonough SM, Bindra B, Alyea EP 3rd, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med 2011; 365:2055-66; PMID:22129252; http://dx.doi.org/10.1056/NEJMoa1108188
51. Mignot G, Ullrich E, Bonmort M, Ménard C, Apetoh L, Taieb J, et al. The critical role of IL-15 in the antitumor effects mediated by the combination therapy imatinib and IL-2. J Immunol 2008; 180:6477-83; PMID:18453565
52. Ullrich E, Bonmort M, Mignot G, Jacobs B, Bosisio D, Sozzani S, et al. Trans-presentation of IL-15 dictates IFN-producing killer dendritic cells effector functions. J Immunol 2008; 180:7887-97; PMID:18523252
53. Liu DL, Håkansson CH, Seifert J. Immunotherapy in liver tumors: II. Intratumoral injection with activated tumor-infiltrating lymphocytes, intrasplenic administration of recombinant interleukin-2 and interferon alpha causes tumor regression and lysis. Cancer Lett 1994; 85:39-46; PMID:7923100; http://dx.doi.org/10.1016/0304-3835(94)90236-4
54. Helms MW, Prescher JA, Cao YA, Schaffert S, Contag CH. IL-12 enhances efficacy and shortens enrichment time in cytokine-induced killer cell immunotherapy. Cancer Immunol Immunother 2010; 59:1325-34; PMID:20532883; http://dx.doi.org/10.1007/s00262-010-0860-y
55. Dings RP, Vang KB, Castermans K, Popescu F, Zhang Y, Oude Egbrink MG, et al. Enhancement of T-cell-mediated antitumor response: angiostatic adjuvant to immunotherapy against cancer. Clin Cancer Res 2011; 17:3134-45; PMID:21252159; http://dx.doi.org/10.1158/1078-0432.CCR-10-2443
56. Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010; 70:6171-80; PMID:20631075; http://dx.doi.org/10.1158/0008-5472.CAN-10-0153
57. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial Watch: Experimental Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:699-716; PMID:22934262; http://dx.doi.org/10.4161/onci.20696
58. Paulos CM, Kaiser A, Wrzesinski C, Hinrichs CS, Cassard L, Boni A, et al. Toll-like receptors in tumor immunotherapy. Clin Cancer Res 2007; 13:5280-9; PMID:17875756; http://dx.doi.org/10.1158/1078-0432.CCR-07-1378
59. Vacchelli E, Galluzzi L, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:894-907; PMID:23162757; http://dx.doi.org/10.4161/onci.20931
60. Yang Y, Huang CT, Huang X, Pardoll DM. Persistent Toll-like receptor signals are required for reversal of regulatory T cell-mediated CD8 tolerance. Nat Immunol 2004; 5:508-15; PMID:15064759; http://dx.doi.org/10.1038/ni1059
61. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:215-33; PMID:22301798; http://dx.doi.org/10.1038/nrd3626
62. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 2011; 334:1573-7; PMID:22174255; http://dx.doi.org/10.1126/science.1208347
63. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science 2012; 337:1678-84; PMID:23019653; http://dx.doi.org/10.1126/science.1224922
64. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008; 358:2698-703; PMID:18565862; http://dx.doi.org/10.1056/NEJMoa0800251

65. Li Q, Lao X, Pan Q, Ning N, Yet J, Xu Y, et al. Adoptive transfer of tumor reactive B cells confers host T-cell immunity and tumor regression. Clin Cancer Res 2011; 17:4987-95; PMID:21690573; http://dx.doi.org/10.1158/1078-0432.CCR-11-0207
66. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 2005; 7:411-23; PMID:15894262; http://dx.doi.org/10.1016/j.ccr.2005.04.014
67. Schioppa T, Moore R, Thompson RG, Rosser EC, Kulbe H, Nedospasov S, et al. B regulatory cells and the tumor-promoting actions of TNF-α during squamous carcinogenesis. Proc Natl Acad Sci U S A 2011; 108:10662-7; PMID:21670304; http://dx.doi.org/10.1073/pnas.1100994108
68. Lister J, Rybka WB, Donnenberg AD, deMagalhaes-Silverman M, Pincus SM, Bloom EJ, et al. Autologous peripheral blood stem cell transplantation and adoptive immunotherapy with activated natural killer cells in the immediate posttransplant period. Clin Cancer Res 1995; 1:607-14; PMID:9816022
69. Parkhurst MR, Riley JP, Dudley ME, Rosenberg SA. Adoptive transfer of autologous natural killer cells leads to high levels of circulating natural killer cells but does not mediate tumor regression. Clin Cancer Res 2011; 17:6287-97; PMID:21844012; http://dx.doi.org/10.1158/1078-0432.CCR-11-1347
70. Pegram HJ, Jackson JT, Smyth MJ, Kershaw MH, Darcy PK. Adoptive transfer of gene-modified primary NK cells can specifically inhibit tumor progression in vivo. J Immunol 2008; 181:3449-55; PMID:18714017
71. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 2002; 295:2097-100; PMID:11896281; http://dx.doi.org/10.1126/science.1068440
72. Velardi A, Ruggeri L, Mancusi A, Aversa F, Christiansen FT. Natural killer cell allorecognition of missing self in allogeneic hematopoietic transplantation: a tool for immunotherapy of leukemia. Curr Opin Immunol 2009; 21:525-30; PMID:19717293; http://dx.doi.org/10.1016/j.coi.2009.07.015
73. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O, Hershkovitz L, et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. Clin Cancer Res 2010; 16:2646-55; PMID:20406835; http://dx.doi.org/10.1158/1078-0432.CCR-10-0041
74. Donia M, Junker N, Ellebaek E, Andersen MH, Straten PT, Svane IM. Characterization and comparison of "Standard" and "Young" tumor infiltrating lymphocytes for adoptive cell therapy at a Danish Translational Research Institution. Scand J Immunol 2011; In press; PMID:21955245
75. Dudley ME, Gross CA, Langhan MM, Garcia MR, Sherry RM, Yang JC, et al. CD8+ enriched "young" tumor infiltrating lymphocytes can mediate regression of metastatic melanoma. Clin Cancer Res 2010; 16:6122-31; PMID:20668005; http://dx.doi.org/10.1158/1078-0432.CCR-10-1297
76. Menger L, Vacchelli E, Kepp O, Eggermont A, Tartour E, Zitvogel L, et al. Trial Watch: Cardiac glycosides and cancer therapy. OncoImmunology 2013; 2:e23082; http://dx.doi.org/10.4161/onci.23082
77. Vacchelli E, Galluzzi L, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, et al. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2012; 1:179-88; PMID:22720239; http://dx.doi.org/10.4161/onci.1.2.19026
78. Vacchelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, et al. Trial watch: Chemotherapy with immunogenic cell death inducers. OncoImmunology 2013; 2:e23510; http://dx.doi.org/10.4161/onci.23510
79. Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, et al. Trial watch: Prognostic and predictive value of the immune infiltrate in cancer. Oncoimmunology 2012; 1:1323-43; PMID:23243596; http://dx.doi.org/10.4161/onci.22009
80. Hardy NM, Fellowes V, Rose JJ, Odom J, Pittaluga S, Steinberg SM, et al. Costimulated tumor-infiltrating lymphocytes are a feasible and safe alternative donor cell therapy for relapse after allogeneic stem cell transplantation. Blood 2012; 119:2956-9; PMID:22289893; http://dx.doi.org/10.1182/blood-2011-09-378398
81. Kebriaei P, Huls H, Jena B, Munsell M, Jackson R, Lee DA, et al. Infusing CD19-directed T cells to augment disease control in patients undergoing autologous hematopoietic stem-cell transplantation for advanced B-lymphoid malignancies. Hum Gene Ther 2012; 23:444-50; PMID:22107246; http://dx.doi.org/10.1089/hum.2011.167
82. Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Maric I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood 2012; 119:2709-20; PMID:22160384; http://dx.doi.org/10.1182/blood-2011-10-384388
83. Meij P, Jedema I, van der Hoorn MA, Bongaerts R, Cox L, Wafelman AR, et al. Generation and administration of HA-1-specific T-cell lines for the treatment of patients with relapsed leukemia after allogeneic stem cell transplantation: a pilot study. Haematologica 2012; 97:1205-8; PMID:22511490; http://dx.doi.org/10.3324/haematol.2011.053371
84. Till BG, Jensen MC, Wang J, Qian X, Gopal AK, Maloney DG, et al. CD20-specific adoptive immunotherapy for lymphoma using a chimeric antigen receptor with both CD28 and 4-1BB domains: pilot clinical trial results. Blood 2012; 119:3940-50; PMID:22308288; http://dx.doi.org/10.1182/blood-2011-10-387969
85. Linn YC, Niam M, Chu S, Choong A, Yong HX, Heng KK, et al. The anti-tumour activity of allogeneic cytokine-induced killer cells in patients who relapse after allogeneic transplant for haematological malignancies. Bone Marrow Transplant 2012; 47:957-66; PMID:21986635; http://dx.doi.org/10.1038/bmt.2011.202
86. Grupp SA, Prak EL, Boyer J, McDonald KR, Shusterman S, Thompson E, et al. Adoptive transfer of autologous T cells improves T-cell repertoire diversity and long-term B-cell function in pediatric patients with neuroblastoma. Clin Cancer Res 2012; 18:6732-41; PMID:23092876; http://dx.doi.org/10.1158/1078-0432.CCR-12-1432
87. Ellebaek E, Iversen TZ, Junker N, Donia M, Engell-Noerregaard L, Met O, et al. Adoptive cell therapy with autologous tumor infiltrating lymphocytes and low-dose Interleukin-2 in metastatic melanoma patients. J Transl Med 2012; 10:169; PMID:22909342; http://dx.doi.org/10.1186/1479-5876-10-169
88. Kandalaft LE, Powell DJ Jr., Coukos G. A phase I clinical trial of adoptive transfer of folate receptor-alpha redirected autologous T cells for recurrent ovarian cancer. J Transl Med 2012; 10:157; PMID:22863016; http://dx.doi.org/10.1186/1479-5876-10-157
89. Smith C, Tsang J, Beagley L, Chua D, Lee V, Li V, et al. Effective treatment of metastatic forms of Epstein-Barr virus-associated nasopharyngeal carcinoma with a novel adenovirus-based adoptive immunotherapy. Cancer Res 2012; 72:1116-25; PMID:22282657; http://dx.doi.org/10.1158/0008-5472.CAN-11-3399
90. Sangiolo D. Cytokine induced killer cells as promising immunotherapy for solid tumors. J Cancer 2011; 2:363-8; PMID:21716717; http://dx.doi.org/10.7150/jca.2.363
91. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 2011; 17:4550-7; PMID:21498393; http://dx.doi.org/10.1158/1078-0432.CCR-11-0116
92. Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. Sci Transl Med 2012; 4:32ra53; PMID:22553251; http://dx.doi.org/10.1126/scitranslmed.3003761
93. Cavazzana-Calvo M, Payen E, Negre O, Wang G, Hehir K, Fusil F, et al. Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia. Nature 2010; 467:318-22; PMID:20844535; http://dx.doi.org/10.1038/nature09328
94. Hacein-Bey-Abina S, Garrigue A, Wang GP, Soulier J, Lim A, Morillon E, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 2008; 118:3132-42; PMID:18688285; http://dx.doi.org/10.1172/JCI35700
95. Brimnes MK, Gang AO, Donia M, Thor Straten P, Svane IM, Hadrup SR. Generation of autologous tumor-specific T cells for adoptive transfer based on vaccination, in vitro restimulation and CD3/CD28 dynabead-induced T cell expansion. Cancer Immunol Immunother 2012; 61:1221-31; PMID:22237888; http://dx.doi.org/10.1007/s00262-011-1199-8
96. Rubinstein MP, Cloud CA, Garrett TE, Moore CJ, Schwartz KM, Johnson CB, et al. Ex vivo interleukin-12-priming during CD8(+) T cell activation dramatically improves adoptive T cell transfer antitumor efficacy in a lymphodepleted host. J Am Coll Surg 2012; 214:700-7, discussion 707-8; PMID:22360982; http://dx.doi.org/10.1016/j.jamcollsurg.2011.12.034
97. Hervas-Stubbs S, Mancheño U, Riezu-Boj JI, Larraga A, Ochoa MC, Alignani D, et al. CD8 T cell priming in the presence of IFN-α renders CTLs with improved responsiveness to homeostatic cytokines and recall antigens: important traits for adoptive T cell therapy. J Immunol 2012; 189:3299-310; PMID:22925929; http://dx.doi.org/10.4049/jimmunol.1102495
98. Donia M, Hansen M, Sendrup SL, Iversen TZ, Ellebæk E, Andersen MH, et al. Methods to improve adoptive T-cell therapy for melanoma: IFN-γ enhances anticancer responses of cell products for infusion. J Invest Dermatol 2013; 133:545-52; PMID:23014345; http://dx.doi.org/10.1038/jid.2012.336
99. Santegoets SJ, Turksma AW, Suhoski MM, Stam AG, Albelda SM, Hooijberg E, et al. IL-21 promotes the expansion of CD27+CD28+ tumor infiltrating lymphocytes with high cytotoxic potential and low collateral expansion of regulatory T cells. J Transl Med 2013; 11:37; PMID:23402380; http://dx.doi.org/10.1186/1479-5876-11-37
100. Montinaro A, Forte G, Sorrentino R, Luciano A, Palma G, Arra C, et al. Adoptive immunotherapy with Cl-IB-MECA-treated CD8+ T cells reduces melanoma growth in mice. PLoS One 2012; 7:e45401; PMID:23028986; http://dx.doi.org/10.1371/journal.pone.0045401
101. Zhou Q, Schneider IC, Edes I, Honegger A, Bach P, Schönfeld K, et al. T-cell receptor gene transfer exclusively to human CD8(+) cells enhances tumor cell killing. Blood 2012; 120:4334-42; PMID:22898597; http://dx.doi.org/10.1182/blood-2012-02-412973
102. Lutz-Nicoladoni C, Wallner S, Stoitzner P, Pircher M, Gruber T, Wolf AM, et al. Reinforcement of cancer immunotherapy by adoptive transfer of cblb-deficient CD8+ T cells combined with a DC vaccine. Immunol Cell Biol 2012; 90:130-4; PMID:21383769; http://dx.doi.org/10.1038/icb.2011.11

103. Stromnes IM, Fowler C, Casamina CC, Georgopolos CM, McAfee MS, Schmitt TM, et al. Abrogation of SRC homology region 2 domain-containing phosphatase 1 in tumor-specific T cells improves efficacy of adoptive immunotherapy by enhancing the effector function and accumulation of short-lived effector T cells in vivo. J Immunol 2012; 189:1812-25; PMID:22798667; http://dx.doi.org/10.4049/jimmunol.1200552

104. Kunii N, Zhao Y, Jiang S, Liu X, Scholler J, Balagopalan L, et al. Enhanced function of redirected human T cells expressing linker for activation of T cells that is resistant to ubiquitylation. Hum Gene Ther 2013; 24:27-37; PMID:22998346; http://dx.doi.org/10.1089/hum.2012.130

105. Grange M, Buferne M, Verdeil G, Leserman L, Schmitt-Verhulst AM, Auphan-Anezin N. Activated STAT5 promotes long-lived cytotoxic CD8+ T cells that induce regression of autochthonous melanoma. Cancer Res 2012; 72:76-87; PMID:22065720; http://dx.doi.org/10.1158/0008-5472.CAN-11-2187

106. Mehrotra S, Al-Khami AA, Klarquist J, Husain S, Naga O, Eby JM, et al. A coreceptor-independent transgenic human TCR mediates anti-tumor and anti-self immunity in mice. J Immunol 2012; 189:1627-38; PMID:22798675; http://dx.doi.org/10.4049/jimmunol.1103271

107. Chinnasamy D, Yu Z, Kerkar SP, Zhang L, Morgan RA, Restifo NP, et al. Local delivery of interleukin-12 using T cells targeting VEGF receptor-2 eradicates multiple vascularized tumors in mice. Clin Cancer Res 2012; 18:1672-83; PMID:22291136; http://dx.doi.org/10.1158/1078-0432.CCR-11-3050

108. Goldstein MJ, Kohrt HE, Houot R, Varghese B, Lin JT, Swanson E, et al. Adoptive cell therapy for lymphoma with CD4 T cells depleted of CD137-expressing regulatory T cells. Cancer Res 2012; 72:1239-47; PMID:22232735; http://dx.doi.org/10.1158/0008-5472.CAN-11-3375

109. Joly E, Hudrisier D. What is trogocytosis and what is its purpose? Nat Immunol 2003; 4:815; PMID:12942076; http://dx.doi.org/10.1038/ni0903-815

110. Brown R, Suen H, Favaloro J, Yang S, Ho PJ, Gibson J, et al. Trogocytosis generates acquired regulatory T cells adding further complexity to the dysfunctional immune response in multiple myeloma. Oncoimmunology 2012; 1:1658-60; PMID:23264928; http://dx.doi.org/10.4161/onci.22032

111. Somanchi SS, Somanchi A, Cooper LJ, Lee DA. Engineering lymph node homing of ex vivo-expanded human natural killer cells via trogocytosis of the chemokine receptor CCR7. Blood 2012; 119:5164-72; PMID:22498742; http://dx.doi.org/10.1182/blood-2011-11-389924

112. Kloss CC, Condomines M, Cartellieri M, Bachmann M, Sadelain M. Combinatorial antigen recognition with balanced signaling promotes selective tumor eradication by engineered T cells. Nat Biotechnol 2013; 31:71-5; PMID:23242161; http://dx.doi.org/10.1038/nbt.2459

113. Morgan RA. Faster, cheaper, safer, T-cell engineering. J Immunother 2013; 36:1-2; PMID:23211627; http://dx.doi.org/10.1097/CJI.0b013e3182791257

114. Morgan RA, Dudley ME, Rosenberg SA. Adoptive cell therapy: genetic modification to redirect effector cell specificity. Cancer J 2010; 16:336-41; PMID:20693844; http://dx.doi.org/10.1097/PPO.0b013e3181eb3879

115. Liu C, Lewis CM, Lou Y, Xu C, Peng W, Yang Y, et al. Agonistic antibody to CD40 boosts the antitumor activity of adoptively transferred T cells in vivo. J Immunother 2012; 35:276-82; PMID:22421945; http://dx.doi.org/10.1097/CJI.0b013e31824e7f43

116. Noji S, Hosoi A, Takeda K, Matsushita H, Morishita Y, Seto Y, et al. Targeting spatiotemporal expression of CD137 on tumor-infiltrating cytotoxic T lymphocytes as a novel strategy for agonistic antibody therapy. J Immunother 2012; 35:460-72; PMID:22735804; http://dx.doi.org/10.1097/CJI.0b013e31826092db

117. Ju SA, Park SM, Lee YS, Bae JH, Yu R, An WG, et al. Administration of 6-gingerol greatly enhances the number of tumor-infiltrating lymphocytes in murine tumors. Int J Cancer 2012; 130:2618-28; PMID:21792901; http://dx.doi.org/10.1002/ijc.26316

118. Peng W, Liu C, Xu C, Lou Y, Chen J, Yang Y, et al. PD-1 blockade enhances T-cell migration to tumors by elevating IFN-γ inducible chemokines. Cancer Res 2012; 72:5209-18; PMID:22915761; http://dx.doi.org/10.1158/0008-5472.CAN-12-1187

119. Koya RC, Mok S, Otte N, Blacketor KJ, Comin-Anduix B, Tumeh PC, et al. BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy. Cancer Res 2012; 72:3928-37; PMID:22693252; http://dx.doi.org/10.1158/0008-5472.CAN-11-2837

120. Liu C, Peng W, Xu C, Lou Y, Zhang M, Wargo JA, et al. BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. Clin Cancer Res 2013; 19:393-403; PMID:23204132; http://dx.doi.org/10.1158/1078-0432.CCR-12-1626

121. Abe BT, Shin DS, Mocholi E, Macian F. NFAT1 supports tumor-induced anergy of CD4(+) T cells. Cancer Res 2012; 72:4642-51; PMID:22865456; http://dx.doi.org/10.1158/0008-5472.CAN-11-3775

122. Stark FC, Gurnani K, Sad S, Krishnan L. Lack of functional selectin ligand interactions compromises long term tumor protection by CD8+ T cells. PLoS One 2012; 7:e32211; PMID:22359671; http://dx.doi.org/10.1371/journal.pone.0032211

123. André MC, Sigurdardottir D, Kuttruff S, Pömmerl B, Handgretinger R, Rammensee HG, et al. Impaired tumor rejection by memory CD8 T cells in mice with NKG2D dysfunction. Int J Cancer 2012; 131:1601-10; PMID:21607945; http://dx.doi.org/10.1002/ijc.26191

124. Dong H, Franklin NA, Roberts DJ, Yagita H, Glennie MJ, Bullock TN. CD27 stimulation promotes the frequency of IL-7 receptor-expressing memory precursors and prevents IL-12-mediated loss of CD8(+) T cell memory in the absence of CD4(+) T cell help. J Immunol 2012; 188:3829-38; PMID:22422886; http://dx.doi.org/10.4049/jimmunol.1103329

125. Wang A, Chandran S, Shah SA, Chiu Y, Paria BC, Aghamolla T, et al. The stoichiometric production of IL-2 and IFN-γ mRNA defines memory T cells that can self-renew after adoptive transfer in humans. Sci Transl Med 2012; 4:ra120; PMID:22932225; http://dx.doi.org/10.1126/scitranslmed.3004306

126. Perna SK, De Angelis B, Pagliara D, Hasan ST, Zhang L, Mahendravada A, et al. Interleukin 15 provides relief to CTLs from regulatory T cell-mediated inhibition: implications for adoptive T cell-based therapies for lymphoma. Clin Cancer Res 2013; 19:106-17; PMID:23149818; http://dx.doi.org/10.1158/1078-0432.CCR-12-2143

127. Landsberg J, Kohlmeyer J, Renn M, Bald T, Rogava M, Cron M, et al. Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. Nature 2012; 490:412-6; PMID:23051752; http://dx.doi.org/10.1038/nature11538

128. Hanagiri T, Shigematsu Y, Kuroda K, Baba T, Shiota H, Ichiki Y, et al. Antitumor activity of human γδ T cells transducted with CD8 and with T-cell receptors of tumor-specific cytotoxic T lymphocytes. Cancer Sci 2012; 103:1414-9; PMID:22621620; http://dx.doi.org/10.1111/j.1349-7006.2012.02337.x

129. Zhao H, Xi X, Cui L, He W. CDR3δ-grafted γ9δ2T cells mediate effective antitumor reactivity. Cell Mol Immunol 2012; 9:147-54; PMID:21909128; http://dx.doi.org/10.1038/cmi.2011.28

130. Zhou J, Kang N, Cui L, Ba D, He W. Anti-γδ TCR antibody-expanded γδ T cells: a better choice for the adoptive immunotherapy of lymphoid malignancies. Cell Mol Immunol 2012; 9:34-44; PMID:21666706; http://dx.doi.org/10.1038/cmi.2011.16

131. Siegers GM. Anti-leukemia activity of human gamma delta T cells. Oncoimmunology 2012; 1:237-9; PMID:22720255; http://dx.doi.org/10.4161/onci.1.2.18231

132. Galluzzi L, Lugli E. Rejuvenated T cells attack old tumors. OncoImmunology 2013; 2:e24103; http://dx.doi.org/10.4161/onci.24103

133. Gattinoni L, Klebanoff CA, Restifo NP. Paths to stemness: building the ultimate antitumour T cell. Nat Rev Cancer 2012; 12:671-84; PMID:22996603; http://dx.doi.org/10.1038/nrc3322

134. Somerville RP, Dudley ME. Bioreactors get personal. Oncoimmunology 2012; 1:1435-7; PMID:23243620; http://dx.doi.org/10.4161/onci.21206

135. Cieri N, Camisa B, Cocchiarella F, Forcato M, Oliveira G, Provasi E, et al. IL-7 and IL-15 instruct the generation of human memory stem T cells from naive precursors. Blood 2013; 121:573-84; PMID:23160470; http://dx.doi.org/10.1182/blood-2012-05-431718

136. Lugli E, Dominguez MH, Gattinoni L, Chattopadhyay PK, Bolton DL, Song K, et al. Superior T memory stem cell persistence supports long-lived T cell memory. J Clin Invest 2013; In press; PMID:23281401; http://dx.doi.org/10.1172/JCI66327

137. Gattinoni L, Lugli E, Ji Y, Pos Z, Paulos CM, Quigley MF, et al. A human memory T cell subset with stem cell-like properties. Nat Med 2011; 17:1290-7; PMID:21926977; http://dx.doi.org/10.1038/nm.2446

138. Nishimura T, Kaneko S, Kawana-Tachikawa A, Tajima Y, Goto H, Zhu D, et al. Generation of rejuvenated antigen-specific T cells by reprogramming to pluripotency and redifferentiation. Cell Stem Cell 2013; 12:114-26; PMID:23290140; http://dx.doi.org/10.1016/j.stem.2012.11.002

139. Haymaker C, Wu R, Bernatchez C, Radvanyi L. PD-1 and BTLA and CD8(+) T-cell "exhaustion" in cancer: "Exercising" an alternative viewpoint. Oncoimmunology 2012; 1:735-8; PMID:22934265; http://dx.doi.org/10.4161/onci.20823

140. Vizcardo R, Masuda K, Yamada D, Ikawa T, Shimizu K, Fujii S, et al. Regeneration of human tumor antigen-specific T cells from iPSCs derived from mature CD8(+) T cells. Cell Stem Cell 2013; 12:31-6; PMID:23290135; http://dx.doi.org/10.1016/j.stem.2012.12.006

141. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nat Rev Cancer 2005; 5:615-25; PMID:16034368; http://dx.doi.org/10.1038/nrc1669

142. Huff V. Wilms' tumours: about tumour suppressor genes, an oncogene and a chameleon gene. Nat Rev Cancer 2011; 11:111-21; PMID:21248786; http://dx.doi.org/10.1038/nrc3002

143. Donia M, Fagone P, Nicoletti F, Andersen RS, Høgdall E, Straten PT, et al. BRAF inhibition improves tumor recognition by the immune system: Potential implications for combinatorial therapies against melanoma involving adoptive T-cell transfer. Oncoimmunology 2012; 1:1476-83; PMID:23264894; http://dx.doi.org/10.4161/onci.21940

144. Wilmott JS, Scolyer RA, Long GV, Hersey P. Combined targeted therapy and immunotherapy in the treatment of advanced melanoma. Oncoimmunology 2012; 1:997-9; PMID:23189245; http://dx.doi.org/10.4161/onci.19865

145. Waitz R, Fassò M, Allison JP. CTLA-4 blockade synergizes with cryoablation to mediate tumor rejection. Oncoimmunology 2012; 1:544-6; PMID:22754781; http://dx.doi.org/10.4161/onci.19442
146. Gerdemann U, Katari U, Christin AS, Cruz CR, Tripic T, Rousseau A, et al. Cytotoxic T lymphocytes simultaneously targeting multiple tumor-associated antigens to treat EBV negative lymphoma. Mol Ther 2011; 19:2258-68; PMID:21915103; http://dx.doi.org/10.1038/mt.2011.167
147. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 2009; 9:463-75; PMID:19536107; http://dx.doi.org/10.1038/nrc2656
148. Liu L, Sun M, Wang Z. Adoptive T-cell therapy of B-cell malignancies: conventional and physiological chimeric antigen receptors. Cancer Lett 2012; 316:1-5; PMID:22099879; http://dx.doi.org/10.1016/j.canlet.2011.10.027
149. Wilkie S, Picco G, Foster J, Davies DM, Julien S, Cooper L, et al. Retargeting of human T cells to tumor-associated MUC1: the evolution of a chimeric antigen receptor. J Immunol 2008; 180:4901-9; PMID:18354214
150. Hombach AA, Heiders J, Foppe M, Chmielewski M, Abken H. OX40 costimulation by a chimeric antigen receptor abrogates CD28 and IL-2 induced IL-10 secretion by redirected CD4(+) T cells. Oncoimmunology 2012; 1:458-66; PMID:22754764; http://dx.doi.org/10.4161/onci.19855
151. Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Martinez C, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med 2011; 365:1673-83; PMID:22047558; http://dx.doi.org/10.1056/NEJMoa1106152