

REVIEW

Children’s Oncology Group’s 2013 Blueprint for Research:  
Stem Cell Transplantation

Stephan A. Grupp, MD, PhD,<sup>1\*</sup> Christopher C. Dvorak, MD,<sup>2</sup> Michael L. Nieder, MD,<sup>3</sup> John E. Levine, MD, MS,<sup>4</sup>  
Donna A. Wall, MD,<sup>5</sup> Bryan Langholz, PhD,<sup>6</sup> and Michael A. Pulsipher, MD<sup>7</sup>  
on behalf of the COG Stem Cell Transplant Scientific Committee

The role of SCT in pediatric oncology has continued to evolve with the introduction of new therapeutic agents and immunological insights into cancer. COG has focused its efforts on the study of hematopoietic stem cell transplantation in the treatment of pediatric malignancies in several major multi-institutional Phase II and Phase III studies. These studies include addressing the impact of allogeneicity in ALL (ASCT0431), and establishing autologous stem cell

transplant as the standard of care in neuroblastoma. Reducing transplant-associated toxicity was addressed in the ASCT0521 study, where the TNF $\alpha$  inhibitor etanercept was tested for the treatment of idiopathic pneumonia syndrome. Impact of cell dose was explored in the single versus tandem umbilical cord blood study CTN-0501, in close collaboration with the BMT-CTN. *Pediatr Blood Cancer* 2013;60:1044–1047. © 2012 Wiley Periodicals, Inc.

**Key words:** SCT; transplantation; stem cell transplantation

INTRODUCTION

State of the Discipline

Pediatric SCT programs have smaller patient volumes compared to adult programs. This makes innovative, well-organized, and inclusive study designs directed at compelling questions paramount. COG has pursued this agenda by addressing three goals: (1) To improve efficacy of SCT in the treatment of childhood cancers through a better understanding and application of allogeneicity (graft vs. tumor or graft vs. leukemia [GVL]) as a therapeutic tool; (2) to improve the safety of SCT by addressing major causes of transplant-related morbidity and mortality; and (3) to optimize design, collaborate in development and assure timely completion of SCT-related therapy and research protocols developed through the COG disease and Cancer Control committees.

COG-focused studies, including ASCT0521, ASCT0431, and CTN 0501 are described below. These SCT studies showcase design approaches that are the foundation of SCT research within COG. The first design strategy is the utilization of novel bench and research observations to design trials targeted at improving outcomes and changing SCT practice. Specifically, ASCT0521 tested a novel treatment of idiopathic pneumonia syndrome (IPS) using a TNF antagonist, based on specific data generated by COG investigators showing the presence of TNF in bronchoalveolar lavage samples of patients with IPS. ASCT0431 was built on built on lab data from COG investigators indicating that mTOR pathway inhibitors (e.g., sirolimus) have an anti-ALL effect; this trial was the first test of an agent used to control both relapse and GVHD after SCT and is defining the current baseline for the role of GVHD and minimal residual disease (MRD) in modern pediatric transplant studies. The ASCT0631 study was built on a phase 2 study conducted by the Pediatric Blood and Marrow Transplant Consortium (PBMT) that showed promising outcome using G-CSF-stimulated bone marrow (G-BM) [1] products from related donors, resulting in a phase 3 study. CTN 0501 was a collaboration between the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) and COG, testing the efficacy of single versus double umbilical cord blood unit transplant.

The second study development area has included disease-specific studies with a significant transplant emphasis, or for

which SCT is a major question. These studies for which a major question is directed toward a transplant intervention include several approaches involving AML and neuroblastoma (AAML0531, AAML1031, and ANBL0532 studies). In the case of transplant for neuroblastoma, the SCT and Neuroblastoma Committees developed the ANBL00P1 tandem transplant pilot trial that developed the SCT regimen which was then used as the experimental arm of the ANBL0532 single versus tandem SCT study. Currently, the implementation of using busulfan/melphalan condition regimen in two studies, ANBL09P1 and ANBL12P1 is being pursued.

Reducing transplant-associated toxicity remains a major challenge. Two open studies are being pursued, including the ACCL1031, a randomized trial of topical Caphosol for mucositis and ACCL0934, a randomized trial of prophylactic levofloxacin. Two additional studies are expected to open within the next 3 months: a randomized trial of caspofungin versus fluconazole in SCT and a trial of testing the ability of chlorhexidine gluconate

<sup>1</sup>Children’s Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; <sup>2</sup>Benioff Children’s Hospital, University of California San Francisco, San Francisco, California; <sup>3</sup>Moffitt Cancer Center, Tampa, Florida; <sup>4</sup>University of Michigan School of Medicine, Ann Arbor, Michigan; <sup>5</sup>University of Manitoba/CancerCare Manitoba, Winnipeg, MB, Canada; <sup>6</sup>Children’s Oncology Group Statistics & Data Center, University of Southern California, Arcadia, California; <sup>7</sup>Primary Children’s Medical Center/Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah

Grant sponsor: Chair’s Grant; Grant number: U10 CA98543; Grant sponsor: Statistics and Data Center Grant; Grant numbers: U10 CA98413, CCOP U10 CA95861; Grant sponsor: Human Specimen Banking; Grant number: U24 CA114766; Grant sponsor: National Cancer Institute, National Institutes of Health, Bethesda, MD, US; Grant sponsor: NCI Grants; Grant numbers: R01 CA1116660, R01 CA102646.

\*Correspondence to: Stephan A. Grupp, MD, PhD, Children’s Hospital of Philadelphia, CTRB 3006, 3501 Civic Center Blvd., Philadelphia, PA 19104-4318. E-mail: grupp@email.chop.edu

Received 15 October 2012; Accepted 13 November 2012

(CHG) to reduce central venous line infections.

### Major Recent Findings

Soluble Tumor Necrosis Factor Receptor: Etanercept for the Treatment of Acute Non-Infectious Pulmonary Dysfunction (Idiopathic Pneumonia Syndrome) Following Allogeneic Stem Cell Transplantation. Pulmonary complications significantly contribute to the mortality associated with allogeneic SCT and are being addressed in a new study (ASCT0521). In approximately 50% of cases, no infectious organisms are identified in the lungs of affected patients. Idiopathic pneumonia syndrome (IPS) refers to a diffuse, non-infectious lung injury that occurs acutely post transplant. Diagnostic criteria for IPS include clinical signs and symptoms of pneumonia, non-lobar radiographic infiltrates, abnormal pulmonary function, and the absence of infectious organisms in the lower respiratory tract. Clinically, IPS is associated with a rapid progression to respiratory failure, and mortality rates of 50–75%. Historically, corticosteroids plus supportive care measures, including supplemental oxygen, have provided the primary treatment for patients with IPS.

Given the mortality rates associated with this disorder, newer treatment modalities are required to improve survival. Recent evidence indicates that immunologic mechanisms resulting in activation of proinflammatory cytokines may contribute to the development of IPS. Both murine models of lung injury and recent human clinical trials have shown that pro-inflammatory cytokines, including TNF $\alpha$  are elevated in the BAL fluid of subjects with IPS post allogeneic transplant. Etanercept is a dimeric protein consisting of two soluble TNF receptors fused to the Fc portion of a human IgG1 molecule. Clinical trials using etanercept have now been conducted in patients with rheumatoid arthritis, Crohn's disease, sepsis syndrome and congestive heart failure. Pharmacokinetic data and toxicity profiles have been generated from these clinical trials. A pilot study for patients with IPS post allogeneic transplant was recently completed and showed response rates were favorable with minimal toxicity reported [2].

ASCT0521 was an open label, non-randomized trial investigating the use of etanercept for the treatment of IPS occurring after allogeneic HCT. It was designed to evaluate the response of IPS to 8 doses of etanercept given over 24 days. The primary objective was to determine the response rate to etanercept plus corticosteroids in patients with IPS. Response was defined strictly as both (a) survival to Day 28, plus (b) the complete discontinuation of supplemental oxygen support by Day 28 of study. Historically, 30% of subjects with IPS have responded successfully to treatment with steroids alone using this definition of response, so a response rate of 55% was targeted in this phase 2 setting. This target was met and the study was closed prior to completing enrollment, which proceeded according to projections, having successfully met the response endpoint prior to accruing 40 patients. Analysis is ongoing.

Samples were collected for biology studies as well. Preliminary studies have shown that a number of pro-inflammatory cytokines and chemokines may be innately involved in the development of IPS [3,4]. Significant roles for LPS, TNF $\alpha$ , and CCR2/MCP-1 in the development of IPS have now been reported in both preclinical and clinical models. We collected BAL fluid and plasma for analysis of a panel of inflammatory cytokines (IL-1, IL-2, IL-6, TNF $\alpha$ , sTNFR, TGF- $\beta$ ), components of the lipopolysaccharide (LPS) activation system (LPS, LPB, and

CD14), and pro-inflammatory chemokines including CCR2/MCP-1, and RANTES. Analysis of these samples is ongoing. The biologic data provided from this study should ultimately help elucidate the underlying mechanism of IPS and lead to predictive models for future trials.

A Randomized Trial of Sirolimus-Based Graft versus Host Disease Prophylaxis after Hematopoietic Stem Cell Transplantation in Relapsed ALL. Based upon preclinical data showing significant single-agent activity of the mTOR inhibitor sirolimus (rapamycin) against human ALL blasts in ALL xenograft models [5–10], combined with a promising pilot study conducted at four COG centers [11], a phase 3 randomized trial ASCT0431 was initiated. This trial tested the hypothesis that the addition of sirolimus to a GVHD prophylaxis regimen of tacrolimus/methotrexate would decrease relapse of high risk ALL after allogeneic SCT. Trial eligibility included selected very high-risk CR1 patients (Ph+ patients with persistent MRD, hypodiploid (<44 chromosomes) and primary induction failure patients), and children with high risk relapsed ALL in CR2. The trial accrual was accruing at target for most of the open period of the trial and ran without major issues.

In May of 2011 the trial was closed when an interim analysis showed that survival reached a planned futility threshold. The analysis showed that further accrual from 145 to the planned 259 patients was unlikely to result in an improvement in survival by 16%, the primary aim of the study. Although the primary hypothesis did not prove to be correct, many key findings were noted and presented at the 2011 American Society of Hematology Meeting [12]. The key observations were as follows: (1) Overall and Event-Free survival was similar between the two arms, with no difference in relapse rates, the finding which triggered the futility stopping rule; (2) patients enrolled on the sirolimus arm had a statistically significant decrease in rates of grade II–IV acute GVHD (49.1% vs. 31.5%,  $P = 0.03$ ); (3) no change was noted between the two arms in rates of chronic GVHD; and (4) transplant related mortality was quite low (14% overall with no difference between the arms). Subanalyses showed several important observations that clarify these findings. First, the most important association with decreased relapse was the presence of any level of acute GVHD. Rates of relapse in patients with grade II–IV acute were 20%, while those without GVHD exceeded 50%. This observation was significant in both study arms. The tight correlation between GVHD and a graft-versus-leukemia effect leads to the supposition that any direct anti-leukemia benefit from sirolimus was offset by suppression of the graft-versus-leukemia effect. Multivariate analysis confirmed that relapse rates in patients with acute GVHD were 20% of those with no acute GVHD. Coupled with the fact that TRM is only slightly affected by significant GVHD (relative risk 1.5), this means that in modern pediatric HCT, mild-moderate GVHD does more good than harm. In addition future studies planned must be mindful of interventions that have could impact on GVL.

Another key observation from this study came from correlation of outcomes with flow cytometry-based minimal residual disease assessment pre- and post-HCT. Detection of any disease pre-HCT by our reference flow laboratory (Michael Borowitz, Johns Hopkins) more than tripled patients' risk of relapse. This suggests that MRD+ patients pre-HCT are at very high risk, and should be a primary target for future interventional studies that are targeted at reducing MRD pre-HCT or preventing relapse after

HCT. Correlative studies currently underway include correlation of chimerism and deep sequencing MRD with outcomes, assessment of the acquisition of ALL blast resistance to sirolimus, assessment of immunogenicity of blasts, and correlation of biomarkers to rates of development of acute and chronic GVHD.

In addition to these studies conducted by the SCT Committee, several other cooperative studies were successfully completed by our committee together with other COG Committees or with another cooperative group, the BMT-CTN. One of these was ANBL0532, the single versus tandem SCT study for patients with high-risk neuroblastoma, which recently completed accrual. Similarly, we partnered with the Neuroblastoma Disease Committee on A3973, a successfully completed trial testing the impact of peripheral blood stem cell purging on outcome after single SCT for neuroblastoma [13].

Multi-center, Open Label, Randomized trial Comparing Single versus Double Umbilical Cord Blood (UCB) Transplantation in Pediatric Patients with High Risk Leukemia and Myelodysplasia. Cell dose is a major determinant of leukemia-free survival in a number of BMT studies. In nearly every large single center or registry analysis of outcomes after umbilical cord blood (UCB) transplantation, cell dose is identified as an important factor influencing the incidence and rate of hematopoietic recovery, risk of transplant-related mortality and probability of survival. Pilot data suggest that infusion of two partially HLA-matched UCB units, which always augments the graft cell dose, is safe and may improve neutrophil recovery and survival. To determine whether the infusion of two UCB units enhances survival, a multi-center, open-label, randomized trial was designed (CTN-0501) by the BMT-CTN; COG SCT participated in an intergroup fashion to maximize accrual to this important trial. As adequate single UCB units can be identified for >80% of pediatric recipients (in contrast to <30% for adults), the study was open only to pediatric patients, which made access to COG SCT centers key to this study's success. The study population was restricted to patients with high-risk hematologic malignancy, the most common indication of UCB transplantation in children.

The objective was to determine the efficacy of using two UCB units versus one UCB unit, with the primary endpoint being 1-year survival. There were several secondary endpoints, including evaluating the incidence and time to engraftment subjects receiving a single UCB unit as compared to two UCB units and evaluating the impact of two UCB units on immune reconstitution on chimerism, infections, and immune reconstitution. CTN-0501 was designed as a Phase 3, randomized, open-label, multi-center, prospective study of single UCB transplantation versus double UCB transplantation in pediatric patients with hematologic malignancies. The target sample size was 110 patients per study arm (total of 220 patients). Because of the study's pediatric HCT focus, it proceeded as a major collaborative interaction between two major stakeholders in transplant research, COG and the BMT-CTN. The study has met accrual, and half of the subjects were enrolled through the COG, demonstrating the ability of two cooperative groups to collaborate on these kinds of multicenter studies.

## Futute Trials and Challenges

A Randomized Phase II Study Comparing Two Different Conditioning Regimens Prior to Allogeneic Hematopoietic Cell Transplantation (HCT) for Children with Juvenile

Myelomonocytic Leukemia (JMML). ASCT1221 is a randomized phase II study comparing two different conditioning regimens prior to allogeneic HCT for children with JMML. JMML is an uncommon disease occurring exclusively in young children and, with rare exceptions, cures have only been achieved following SCT. We have hypothesized that the primary mechanism by which SCT results in long-term disease-free survival in some patients with JMML is due to the provision of a source of alloreactive graft-versus leukemia (GVL) activity. As such, we further hypothesized that the myeloablative preparative regimen prior to SCT plays little role *per se* in the long-term disease-control of patients with JMML, provided that it is sufficient to achieve donor cell engraftment and adequate transfer of alloreactive cells.

The trial's primary objective is to determine the preferred regimen for future trials in patients with JMML based on the observed Day 100 treatment-related mortality (TRM) and event-free survival (EFS) rates. Eligible patients will have JMML, and most patients will have genotypically confirmed disease, the testing of which will be performed at a CLIA/CAP-certified central laboratory funded by an approved National Cancer Institute Biomarker, Imaging, Quality of Life, and Cost Effectiveness Analyses Funding Program (BISQFP) grant. Patients with Noonan Syndrome are excluded. Patients will be randomized to one of two myeloablative conditioning regimens within strata defined by donor type and PTPN11 mutation status. Our hypothesis is that patients randomized to receive a busulfan-fludarabine (BU-FLU) conditioning regimen will have less TRM and equivalent EFS when compared to a busulfan-cyclophosphamide-melphalan (BU-CY-MEL) conditioning regimen, a regimen that has emerged as the standard of care in Europe [14]. Pre-transplant therapy is left to the discretion of the treating institution. Patients will be followed for a minimum of 18 months, and the frequency of research samples will coincide with the schedule utilized by the European EWOG-MDS JMML protocol to enhance possible collaborations in this rare disease.

A total of 108 patients are estimated to be needed to answer the primary question of the study, and the enrollment period is expected to last 5 years. Secondary objectives include determining the 18-month relapse incidence (RI) and the graft failure rates following the two different myeloablative conditioning regimens. Clinical exploratory objectives include determining the rates of severe toxicities and GVHD post-SCT between the two conditioning regimens, as well as creating a JMML-specific pre-SCT index to allow better risk-stratification of future patients. Correlative biologic studies will determine the feasibility of assessing post-transplant disease burden by donor chimerism measurements and mutant allele burden. We will also attempt to validate gene expression classifiers using RNA-based or methylation-based arrays in patients with JMML that may predict relapse, and will comprehensively assess genetic and biochemical alterations amongst patients with JMML who are treated on this transplant protocol.

The COG SCT committee works in partnership with two other clinical trials groups, the BMT CTN and the PBMTTC. The PBMTTC is 1 of 19 Core Centers of the BMT CTN, working to develop pediatric-focused trials and facilitate pediatric enrollment onto BMT CTN trials. This collaboration of the NCI/NHLBI sponsored BMT CTN and COG has resulted in rapid patient accrual (220+ patients) on clinical trials; this type of collaboration is a

good example of bringing together different consortia to accrue sufficient numbers of subjects to answer key questions.

In terms of future efforts that exploit this collaboration with the PBMTTC, the COG SCT Committee plans to develop and complete innovative early phase/pilot HCT trials in oncology, which can then move to larger phase III trials in the BMT CTN or COG. These efforts to improving survival in pediatric patients with high-risk leukemia undergoing allogeneic HCT, include four key hypotheses as follows.

Increasing BM CD34+ cell dose (by G-CSF primed BM) or cord blood cell dose (1 unit vs. 2 units) improves survival. Studies to test this hypothesis are now complete. MRD detection pre- and post-transplant will (a) guide the choice of intensity of preparative regimens that optimize survival and decrease late effects, (b) identify very high risk patients pre-transplant who can/should receive novel approaches pre-, during-, and post-transplant, and (c) identify patients at high risk post-transplant, prompting early interventions to prevent relapse. Here, the detailed analysis of the MRD and chimerism data from ASCT0431 will be key in developing approaches to prevent relapse in ALL. Use of pre- and post-transplant MRD will be key measures of risk and the foundation of future transplant approaches to these diseases.

Reduced toxicity regimens can increase cure of selected patients with leukemia by reducing TRM. This is being approached the development of a new preparative regimen approach into the AAML1031 trial. Busulfan/fludarabine has been shown to have less risk of TRM compared to busulfan/cyclophosphamide in adult studies. This approach is not being piloted in AML patients through COG. A similar agent, treosulfan, shows promise of even less TRM. In addition, therapeutic monitoring, essential to the use of busulfan, is not needed for children receiving treosulfan. The PBMTTC is piloting this agent in the study PBMTTC ONC1101. If treosulfan looks promising, it can be compared with either busulfan/fludarabine or busulfan/cyclophosphamide in a future COG study.

Post-transplant relapse can be decreased by use of targeted agents and novel immunological interventions. The first COG SCT Committee attempt to use a targeted agent was sirolimus post-transplant, as outlined previously. Future approaches need to be more specific and not interfere with graft versus leukemia effects. Several potential approaches are being used. First, we are working with the relapsed ALL group to develop a bridging trial that uses blinatumomab to decrease MRD pre-transplant in high risk relapsed ALL patients. Other approaches may use this agent post-transplant to prevent relapse as well. Testing a CD19 antibody conjugated to pseudomonas endotoxin is planned in the pre-transplant setting. Approaches using chimeric antigen receptor-T-cells (CAR-T-cells) against CD19 developed at the University of Pennsylvania [15–19] will moved to limited center studies in the next few years, with the ultimate goal of moving to multi-center studies in COG as soon as possible.

## ACKNOWLEDGMENT

This work was supported by the Chair's grant U10 CA98543, Statistics and Data Center grant U10 CA98413, CCOP U10 CA95861, Human Specimen Banking U24 CA114766 grants of the Children's Oncology group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, US. A complete listing of grant support for research conducted by the Children's Cancer Group and Pediatric Oncology Group before initiation of the COG grant in 2003 is available online at: [www.childrensoncologygroup.org/admin/grantinfo.htm](http://www.childrensoncologygroup.org/admin/grantinfo.htm). The biology studies related to ASCT0431 were supported by NCI grants R01 CA1116660 and R01 CA102646, an RSG from the American Cancer Society, as well as the Weinberg and Stanford Funds of the Children's Hospital of Philadelphia (SG).

## REFERENCES

1. Frangoul H, Nemecek ER, Billheimer D, et al. A prospective study of G-CSF primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children: A Pediatric Blood and Marrow Transplant Consortium (PBMTTC) study. *Blood* 2007;110:4584–4587.
2. Yanik GA, Ho VT, Levine JE, et al. The impact of soluble tumor necrosis factor receptor etanercept on the treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Blood* 2008;112:3073–3081.
3. Uberti JP, Ayash L, Ratanatharathorn V, et al. Pilot trial on the use of etanercept and methylprednisolone as primary treatment for acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2005;11:680–687.
4. Yanik G, Hellerstedt B, Custer J, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002;8:395–400.
5. Brown VI, Hultitt J, Fish J, et al. Thymic stromal-derived lymphopoietin induces proliferation of pre-B leukemia and antagonizes mTOR inhibitors, suggesting a role for interleukin-7/Ralpha signaling. *Cancer Res* 2007;67:9963–9970.
6. Brown VI, Seif AE, Reid GS, et al. Novel molecular and cellular therapeutic targets in acute lymphoblastic leukemia and lymphoproliferative disease. *Immunol Res* 2008;42:84–105.
7. Cooperman J, Neely R, Teachey DT, et al. Cell division rates of primary human precursor B cells in culture reflect in vivo rates. *Stem Cells* 2004;22:1111–1120.
8. Teachey DT, Grupp SA, Brown VI. Mammalian target of rapamycin inhibitors and their potential role in therapy in leukaemia and other haematological malignancies. *Br J Haematol* 2009;145:569–580.
9. Teachey DT, Obzut DA, Cooperman J, et al. The mTOR inhibitor CCI-779 induces apoptosis and inhibits growth in preclinical models of primary adult human ALL. *Blood* 2006;107:1149–1155.
10. Teachey DT, Sheen C, Hall J, et al. mTOR inhibitors are synergistic with methotrexate: An effective combination to treat acute lymphoblastic leukemia. *Blood* 2008;112:2020–2023.
11. Pulsipher MA, Wall DA, Grimley M, et al. A phase I/II study of the safety and efficacy of the addition of sirolimus to tacrolimus/methotrexate graft versus host disease prophylaxis after allogeneic hematopoietic cell transplantation in paediatric acute lymphoblastic leukaemia (ALL). *Br J Haematol* 2009;147:691–699.
12. Pulsipher M, Langholz B, Wall D, et al. A randomized trial of sirolimus-based graft versus host disease (GVHD) prophylaxis after hematopoietic stem cell transplantation (HSCT) in selected patients with CR1 and CR2 ALL: Results from Children's Oncology Group study ASCT 0431. *Blood* 2011;118:731.
13. Kreissman SG, Villablanca JG, Seeger RC, et al. A randomized phase III trial of myeloablative autologous peripheral blood stem cell (PBSC) transplant for high-risk neuroblastoma (HR-NB) employing immunomagnetic purged versus unpurged PBSC: A Children's Oncology Group study. *J Clin Oncol* 2008;26:10011.
14. Locatelli F, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): Results of the EWOG-MDS/EBMT trial. *Blood* 2005;105:410–419.
15. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med* 2011;365:725–733.
16. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced Leukemia. *Sci Transl Med* 2011;3:95ra73.
17. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther* 2009;17:1453–1464.
18. Barrett DM, Zhao Y, Liu X, et al. Treatment of advanced leukemia in mice with mRNA engineered T cells. *Hum Gene Ther* 2011;22:1575–1586.
19. Grupp SA, June CH. Adoptive cellular therapy. *Curr Top Microbiol Immunol* 2011;344:149–172.