doi:10.1038/mt.2014.148

T-Cell Immunotherapy: Looking Forward

T Cell Immunotherapy: Optimizing Trial Design

Bethesda, Maryland
10–11 September 2013

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The rapidly expanding field of T-cell immunotherapy has experienced clinical successes along with some serious toxicities. "T Cell Immunotherapy: Optimizing Trial Design," a workshop sponsored by the National Institutes of Health's (NIH's) Office of Biotechnology Activities (OBA), brought together researchers to discuss the scientific advances and share new data on key trial design issues, including the selection of new targets, optimizing the T-cell population, preconditioning regimens, strategies to promote persistence of cells, and analysis and management of acute reactions to T-cell infusions with the goal of identifying best practices and a research agenda that will facilitate further development and maximize the safety of this promising approach.

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Introduction

T-cell immunotherapy for cancer is a rapidly growing field for gene therapy. Broadly, this field can be divided into two approaches—the use of gene-modified T-cell receptors (TCRs) in which recognition of the tumor antigen is in the context of human leukocyte antigens (HLAs) or use of chimeric antigen receptors (CARs) that typically link a single-chain variable region domain of an antibody (scFv) to one or more signaling elements of a TCR complex to allow T-cell activation.[1] The decision to use one approach vs. the other may depend on several factors. For example, CARs offer the ability to bind antigens that are not restricted by HLA recognition, and the ability to modify the T-cell signaling effect than transduced" TCRs.[2] TCRs, however, have the ability to recognize intracellular proteins, in addition to cell surface antigens, providing a broader array of target tumor-associated targets.

In 2010, the OBA hosted a meeting to examine the state of the science and key trial design questions for this emerging field.[3] At the time, some clinical benefit and unexpected toxicities highlighted both the therapeutic potential as well as the need to share data and expertise to optimize the safety of trial design. Since 2010, several promising and clinically successful developments have been reported in leading scientific and medical journals[4–7] as well as national media. Given these developments, the OBA and the NIH Recombinant DNA Advisory Committee concluded that it was an opportune time to reconvene the leading experts in the field from the United States to continue to foster sharing of data across protocols and discuss the key issues in trial design, including optimal management of the cytokine release syndrome (CRS) seen in some research participants in response to the expansion of these active T cells.

The following summary of the OBA workshop represents the views of the individual authors and not the NIH. The full presentations and slides are available at the OBA's website.[8]

State of the science

The number of CAR and TCR protocols registered with the OBA has continued to increase rapidly (Figure 1); as of the meeting in September 2013 there were 111 protocols, 104 of which targeted cancer, with more than 500 subjects dosed. More than 40 protocols address hematological malignancies, with CD19 being the most common target in these protocols. Among protocols for solid tumors, the melanoma antigens (gp100, MART-1) and cancer-testis antigens predominate for TCRs; for CARs there are multiple targets, with a slight predominance of Her2/neu, GD2, and mesothelin (**Figures 2 and 3**). Approximately 90% of TCR trials have targeted solid malignancies; approximately 50% of CAR trials have targeted hematological malignancies.

Steven Rosenberg reviewed the extensive portfolio of National Cancer Institute (NCI) research in this area, beginning with a summary of his research using unmodified tumor-infiltrating lymphocytes (TILs)

lymphodepletion before administration of TILs in 2002 and demonstrated increased efficacy.[9] Dr. Rosenberg has continued to apply this approach to melanoma, including ocular melanoma, as well as metastatic gastrointestinal and human papillomavirus–induced cancers. These studies have demonstrated that in a subset of patients (about 20%), administration of T cells can result in prolonged remissions of five years or longer. The results led to a program of research dedicated to gene-modified T cells that accounts for almost 20% of T-cell immunotherapy protocols registered with the OBA to date. The results of the Rosenberg group's first trials with gene-modified TCRs for melanoma were published in 2006 in *Science*.[10] In a recent TCR study targeting the cancer-testis antigen NY-ESO-1, the overall response rate was 50% in the 19 subjects with melanoma, including 4 with complete remissions, and a 67% overall response for those with synovial sarcoma, including one complete remission, in a population that had multiple prior chemotherapy regimens.[11] These results contrasted with the MAGE-A3 trial in which an unexpected off-target neurological toxicity was seen.[12] Rosenberg's group has also developed an extensive portfolio of CAR protocols, focusing primarily on solid tumors, with novel targets such as vascular endothelial growth factor receptor 2 (VEGFR2), epidermal growth factor receptor variant III (EGFRvIII), and mesothelin, as well as new targets in development, such as chondroitin sulfate proteoglycan 4 (CSP4).

Antoni Ribas, who uses a vector developed by Rosenberg's lab, described his work on melanoma using a TCR-targeting MART-1 given with lymphodepletion. He has observed a high frequency of tumor responses (9 of 14 subjects with tumor-size reductions), but few responses were durable. He has also recently started enrolling research participants into a trial using a TCR-targeting NY-ESO-1. He noted that one of the aspects being tested is whether fresh cells are potentially more active than cryopreserved cells.

Other highlights included clinical results from several investigators targeting CD19 in leukemia and lymphoma. In addition to Dr. Rosenberg's summary of his work in this area,[13] Carl June, Re-

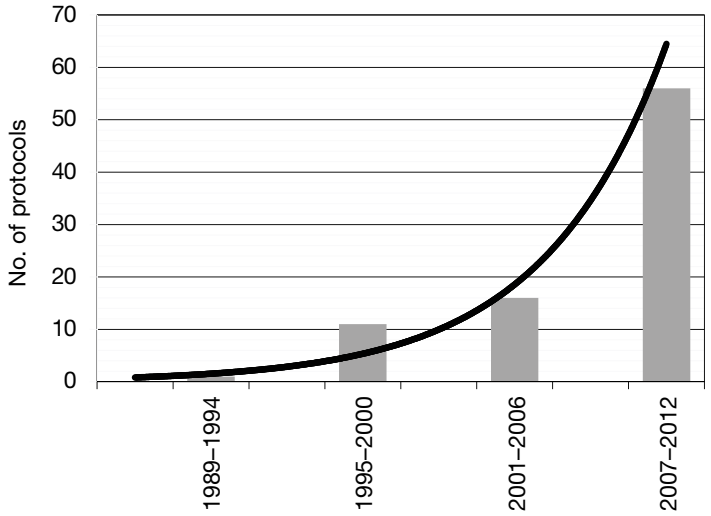

Figure 1 Number of chimeric antigen receptor protocols registered with the National Institutes of Health's Office of Biotechnology Activities by year.

Forman, Michael Jensen, Helen Heslop, and Crystal Mackall summarized their results in ongoing trials using CD19-specific CARs in leukemia and lymphoma.[4,6,14] Dr. Heslop noted that in a trial comparing first- and second-generation CARs, her group found that the second-generation CAR demonstrated both improved expansion and persistence.[15] In addition, several protocols have established that administration of CAR T cells after stem cell transplant does not interfere with engraftment of the transplant. The investigators presented examples of clinical remissions, but, because the goal is often to establish remission so as to proceed with a curative transplant, the durability of remissions from CAR T cells without subsequent transplant has not yet been determined. However, even in the setting of multiple previous therapies, CD19-specific CARs have shown efficacy. Dr. Brentjens reported that in his protocol with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL), 14 of 16 subjects achieved molecular chronic remissions as assessed by deep-sequencing PCR analysis to search for the malignant clone.[16] Another emerging theme was the responsiveness of ALL to this approach, which was also highlighted in Dr. June's and Dr. Mackall's presentations. Dr. Cooper presented data from ongoing trials infusing CD19-specific CAR$^+$ T cells after autologous and allogeneic hematopoietic stem cell transplantation. The intent was ognizing that the current clinical practice for many patients with B-cell malignancies is to infuse tumor-specific T cells as a bridge to transplantation. These trials have advanced a new approach to human gene therapy based on the electrotransfer of DNA plasmids encoding a second-generation CAR stably expressed following transposition from the *Sleeping Beauty* (SB) system.

In parallel to work on CD19-specific CARs, Brian Till highlighted the results of his trials targeting CD20, including a trial that used a third-generation CAR with CD28 and 4–1BB costimulatory domains. Unlike the other trials, which use retroviral vectors or SB transposons, he used an electroporated DNA plasmid. In general, the T cells were well tolerated, with some immediate febrile reactions, and two of the three subjects had prolonged remissions with persistence of the T cells for up to a year.[17] However, the DNA plasmid vector was not an efficient vector, and the IL-2 used to promote persistence also led to an increase in T regulatory cells (Tregs).

Philip Greenberg highlighted his group's work using a TCR targeting another hematological malignancy antigen, Wilms tumor antigen 1 (WT1), which is highly expressed in leukemia and some solid tumors but is also expressed on some normal tissues. Their trial built on a previous trial using naturally isolated, cloned T cells targeting WT1, which did not show

virus-specific T cells, they have recently initiated a trial to test a TCR based on a high-avidity, natural clone.

In the solid-tumor area, Dr. Heslop presented a summary of her group's trials for neuroblastoma, targeting GD2 using both virus-specific and non-virus-specific T cells.[18,19] Their data have demonstrated an association between persistence of T cells and reduced tumor progression. In addition, in research participants with prolonged detection of activated T cells, the presence of central memory T cells was important, raising the question of what the optimal T-cell product is.

Other solid-tumor trials discussed included CARs targeting HER2/neu for sarcoma and glioblastoma, including a trial using tri-virus-specific T cells and another trial that combines the CAR with a dominant-negative TGF-β receptor. Data were also presented on first- and second-generation CARs targeting carcinoembryonic antigen (CEA) and prostate-specific membrane antigen. Again, some early indications of clinical efficacy were promising, but an ongoing challenge will be to refine strategies to improve T-cell persistence and efficacy. In some cases, on-target, off-tissue toxicities may ultimately limit the use of certain targets; for example, colitis developed in protocols using CEA-specific TCR and CAR T cells.[20]

Finally, Dr. Jensen reported his work in glioblastoma using a novel CAR called a zetakine. Instead of an antibody, single-chain target domain, he used a human cytokine, IL-13, with a mutation in the sequence that gave high affinity for IL-13 receptor α2. These cells were infused intracranially, establishing the safety of intracranial administration with some antitumor responses.

These talks provided an overview of a field that continues to expand rapidly, in terms of both targets and diseases. Most protocols involve administration of the cells in the setting of lymphodepletion, and some groups, predominantly in protocols for solid tumors, use IL-2 to promote cell persistence. In addition to identifying effective targets that have minimal off-tumor effects, finding the ideal balance between persistence and expansion of T cells without triggering systemic cytokine reactions is a key issue for the field. This may be achieved of the cells, the type of T cells infused, the dose, the immune status of the recipient, and the use of cytokine support. Finally, as with many cancer therapies, some toxicity is likely. Establishing protocols to limit toxicity so that the risk-to-benefit ratio remains favorable is a high priority.

Promoting T-cell persistence

Persistence of the gene-modified T cells is associated with prolonged remission in subjects,[18] and the field has developed strategies to promote persistence. One approach is to create a host environment that is conducive to expansion of the T cells. Expansion should not only promote a rigorous antitumor effect but also lead to the development of a stable population of tumor-specific T cells that can be reactivated in case of recurrence of tumor antigen. Use of selected central memory T cells may be another strategy to promote an enduring T-cell population.

The majority of T-cell protocols registered with the OBA to date involve administration of the cells to subjects when they are lymphopenic. For solid-tumor protocols, this involves administration of the T cells after administration of lymphodepleting chemotherapy, such as cyclophosphamide, whereas the protocols for hematological malignancies have most commonly called for administering cells in the posttransplant setting or the use of disease-specific chemotherapy regimens. However, it is important to note that lymphodepletion has not been universally applied, notable exceptions being studies administering virus-specific T cells, or the successful neuroblastoma protocols targeting GD2, which used both virus-specific and non-virus-specific T cells.[18]

Dr. Rosenberg reviewed his group's clinical data, as well as the animal data that support lymphodepletion for promoting antitumor efficacy. As stated earlier, in the TIL melanoma studies, despite administration of 10^9 to 10^{10} T cells, the cells did not persist and there were minimal objective responses.[21] However, when nonmyeloablative (NMA) chemotherapy using cyclophosphamide and fludarabine was added, and the TIL product was generated with a shorter culture time, providing a more diverse TIL population that contained both $CD4^+$ and $CD8^+$ T cells, 13 subjects showed objective cancer responses.[22] Dr. Rosenberg's group went on to investigate whether the addition of 2 or 12 Gy of total-body irradiation (TBI) to the NMA chemotherapy would further increase efficacy of TIL transfer in melanoma patients. The response rate for those who received chemotherapy alone was about 49%; the addition of 2 Gy resulted in objective response in 52% of subjects, and 12 Gy of TBI resulted in a 72% objective response rate, with a complete response rate of 40%.[23] The addition of TBI to NMA chemotherapy was generally well tolerated, with the exception of one death in a subject with an undetected diverticular abscess in the 12-Gy group. A drawback of escalation to 12 Gy of radiation is the need for autologous peripheral blood stem cell support. An ongoing randomized trial is comparing NMA chemotherapy against NMA and TBI, although preliminary results indicate that the challenges of adding TBI may not be balanced by the improved response.

A significant amount of animal work has been done to elucidate the mechanisms that underlie the improved antitumor responses observed with lymphodepletion. These data indicate that lymphodepletion augments the antitumor response by eliminating Tregs, cellular "sinks" for cytokines such as IL-7 and IL-15, and by enhancing antigen-presenting cell activation and availability.[24–26] This activation of the immune system may be due in part to translocation of bacteria from the gut. It was shown in a mouse model that administration of ciprofloxacin, which is effective against Gram-negative bacteria commonly found in the gut, to an irradiated animal reduced the activated dendritic cells in the spleen and reduced the effectiveness of adoptive cell transfer. Of note, it has been demonstrated that the effect of lymphodepletion is on the host rather than on the tumor. Thus, if one shields the host—in this case, the mouse—and treats the tumor, no effect is seen in these melanoma models.

One dilemma is that Tregs are the first T cells to recover after lymphodepletion, and therefore lymphodepletion may foster an environment that works against the antitumor effect. Dr. Rosenberg noted that the NCI group has some data demonstrating an inverse relationship between the

response, supporting the importance of eliminating Tregs. However, others questioned whether we clearly understand the role of Tregs, because suppression of a tumor response may depend on whether the Tregs are actually activated and tumor-specific. Therefore, the presence of Tregs may not be absolutely undesirable, as they may also organize the immune response.

Gene delivery and design of T cells

In addition to host preparation, the design of the T-cell vectors is a critical area of research. Dr. Cooper noted that the ability to stably express transgenes, such as CARs, in T cells has revolutionized adoptive immunotherapy for certain malignancies. Recombinant fusion genes constructed to recognize tumor-associated antigens (e.g., TCR and CAR) have been constitutively expressed in T cells using Moloney murine leukemia virus (MMLV)-based retroviruses, HIV-based lentiviruses, and DNA plasmids, including the SB transposon/transposase system.

Until recently, retroviral transduction by recombinant MMLV-derived vectors has been the most common method for delivery of transgenes intended to be integrated into the T-cell genome. Lentiviral vectors have also been successfully used in the clinic. Both approaches are appealing, and at this time there appears to be equipoise regarding the therapeutic potential of these two viral systems for genetic modification of T cells to express CARs. Transduction using retroviral and lentiviral vectors can be highly efficient, and it is possible to integrate multiple copies of a transgene in a given T cell, which provides for a high level of expression of the transduced gene product. The manufacture of clinical-grade retroviral and lentiviral vector virions is quite similar, although retroviral vectors may be produced from stable packaging cell lines, whereas to date most lentiviral vectors have been produced by transient transfection.

Overall, transduction of T cells with recombinant retrovirus and lentivirus involve similar packaging protocols, utilize similar integration mechanisms, and lead to similar transduction efficiencies. Thus, both viral-based approaches to gene transfer are appealing for the human application of CAR$^+$ T cells, although some individual

DNA transposons now offer an alternative to viral-based gene transfer. Supercoiled plasmids can be directly electroporated into T cells using commercial devices, thus eliminating much of the labor and safety concerns associated with generating recombinant viral particles. DNA transposons, such as those derived from the SB system, insert into the genome via a copy-and-paste mechanism when a transposase is (transiently) available to catalyze the reaction. Dr. Cooper's group has successfully used SB to integrate a CD19-specific CAR into human T cells in four human trials under investigational new drug applications. Unlike retroviral/lentiviral integration into transcriptionally active sites, the SB transposon appears to randomly integrate at TA dinucleotide repeats and is typically present at one or two copies per T-cell genome. As with viral-based gene transfer, there is the possibility that a transposon may cause genotoxicity resulting in oncogenesis. However, because the SB system does not readily target transcriptional or promoter elements, it appears suitable for human application. Furthermore, the relatively low cost of generating DNA plasmids for use in compliance with current good manufacturing practice (GMP), in contrast to the cost and complexity of producing clinical-grade virus, renders the SB system an attractive and nimble approach to generate and modify vectors for delivery of therapeutic genes.

In summary, the investigator has available multiple approaches to genetically modify T cells. The use of a particular approach will depend on resident expertise and the desired T-cell product.

Design of CARs. CARs are recombinant receptors for antigens that retarget and eventually reprogram T-cell function. Unlike the physiological TCR for antigens, which signals T-cell activation through the associated CD3 complex, CARs possess in a single molecule the ability to trigger multiple antigen-specific T-cell functions. The CARs that have recently shown impressive clinical outcomes in research participants with B-cell malignancies are "second-generation CARs," to distinguish them from earlier forms of activating fusion receptors, which only initiate T-cell activation and are now referred to as "first-

Michel Sadelain described how the incorporation of co-stimulatory receptor signaling domains into the cytoplasmic tails of CAR ("embedded costimulation") greatly increased the potency of CAR-modified T cells in preclinical models.[4,28,29] Several costimulatory domains have been incorporated in CARs over the past decade, including CD28 (ref. 28), 4–1BB (ref. 30), OX40 (ref. 31), and others (ref. 2). Different costimulatory molecules play roles in T-cell activation, proliferation, survival, cytokine secretion, antitumor cytolytic activity, and reactivation upon secondary stimulation. The second- and third-generation CARs have varying activities by recruiting multiple T-cell signaling pathways.[2] Dr. Sadelain emphasized that small nuances in structural design of different CAR molecules can eventually exert a significant effect on the relative activity of CARs encoding the same signaling domains, depending on epitope position, CAR affinity, physical parameters of the extracellular domains, and transmembrane elements. Levels of CAR expression also affect overall function, making it an important parameter to consider when comparing different CARs. Forced expression of co-stimulatory ligands in the CAR T cells themselves can produce auto- or trans-costimulation and increase T-cell potency.[32]

Clinical efficacy has been reported in trials from several institutions for B-lineage malignancies using CAR-modified T cells.[4–6,14,16,33,34] Many features of the trials differ, including CARs (origin of scFv, epitope of CD19 targeted, antigen affinity, signaling domains), enhancer/promoters (varied expression levels, propensity to silencing), T-cell manufacturing techniques (activation of T cells with antibodies to CD3 with or without anti-CD28, different culture media, duration of culture), cell products (cell dose, CD4/CD8 ratio, central memory T cells), lymphodepletion conditioning regimens (cyclophosphamide vs. cyclophosphamide/fludarabine vs. bendamustine), and patient selection (chemosensitive vs. chemoresistant disease). Future trials will need to define the relative importance of these differences to improve response rates. It is noteworthy that the outcomes of CD19 CAR therapy may vary depending on the disorder. Thus, results reported to date show greater efficacy in ALL than in chronic lymphocytic leukemia (CLL), for reasons that

Design of T-cell receptors. TCRs are the physiological recognition system of T cells and react to a major histocompatibility complex–antigen complex. Their two chains, α and β, are necessary and sufficient for T cells to recognize their targets, including cancer cells. Engineering of T cells with genetically modified TCR α- and β-chains redirects their antigen specificity and has been used in the clinic in adoptive cell transfer strategies. Clinical trials expressing TCRs for MART-1, gp100, and NY ESO-1 have demonstrated antitumor activity in subjects with metastatic melanoma and sarcoma. However, these early clinical trials suggest that durable tumor responses seem to occur at lower frequency than with TILs or with CAR-engineered T cells.

The clinical trials thus far have used TCRs with physiological peptide affinities, and most have used intact TCRs. However, studies with NY ESO-1 and MAGE-A3 as targets used TCRs with altered affinities due to targeted mutations in their complementarity-determining region 2 or 3 (CDR2 or CDR3), the variable regions of the TCR that interact with the major histocompatibility complex–antigen complex. However, care must be taken because a CDR2-modified MAGE-A3 TCR led to cardiac toxicities, due to loss of specificity with cross-reaction to an off-target peptide.[35]

Other means to increase antitumor activity of TCR-modified T cells are being developed preclinically, such as additional genetic engineering of the T cells to express other immune-activating genes, engineering the signaling pathways downstream of the TCR, or blocking negative regulatory receptors. These approaches would provide simultaneous genetic redirection of T cells with increased T-cell functionality that may no longer be blocked by physiological immune regulatory processes.

A problem with some transgenic TCRs is that, when expressed in T cells that have their own endogenous TCR α- and β-chains, there can be heterologous pairing between the transgenic and endogenous TCR chains. This may decrease the expression of the transgenic TCR and even lead to altered specificities that may potentially result in autoimmune toxicities. Several means to improve self-pairing of the transgenic TCR chains include the use of picornavirus-derived highly efficient self-cleaving 2A-like sequences to allow stoichiometric protein expression, including additional cysteine motifs allowing formation of an increased number of disulfide bonds between the α- and β-chains, partially murinizing the constant region of both TCR chains for preferential pairing, and the use of leucine zippers at the 3′ ends of both α- and β-chains for forced transgenic TCR pairing. As these approaches move into the clinic, it will be important to test them in carefully designed clinical trials to minimize risks but also foster continued improvements in treatment options.

Longer-term antitumor activity may be achievable by targeting hematopoietic stem cells (HSCs), which would continually produce transduced T cells. David Baltimore listed potential advantages of targeting HSCs. Because of the requirement for coexpression of CD3, transgenic TCRs can be expressed only on the surface of T cells derived from the transduced HSCs. The TCRs introduced by the vector should allelically exclude the rearrangement of endogenous TCR genes to yield monoclonal cells. However, one potential limitation of this approach may be that highly active T cells from HSCs that contain highly avid TCRs for self-antigens may be selected out by the thymus. In the trials using a MART-specific TCR, clinical effect was observed when the avidity of the natural TCR was increased several-fold, but such highly active T cells may be negatively selected by the thymus.

HSCs transduced with CAR vectors produce CAR-expressing myeloid and natural killer cells in addition to T cells, and thus may provide more rapid and broader antitumor activity.[36] In a mouse model with an EL4 tumor expressing the ovalbumin gene, an antitumor effect was observed using HSCs transduced with lentiviral vectors expressing TCR reactive to ovalbumin. A clinical trial involving autologous $CD34^+$ cells transduced with a lentiviral vector expressing a $CD19^+$ CAR in subjects with non-Hodgkin's lymphoma is being developed at UCLA and the City of Hope Medical Center.

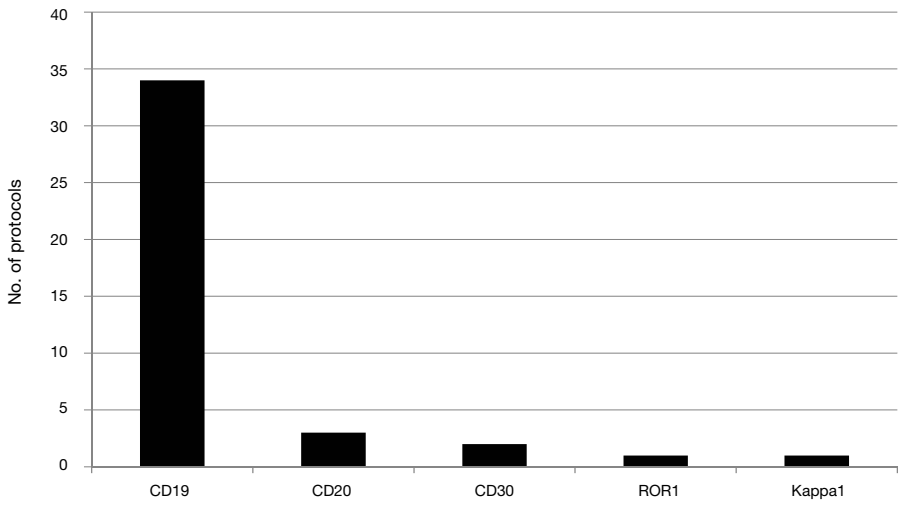

Figure 2 Chimeric antigen receptor targets for hematological-malignancy protocols

Target selection

Dr. Rosenberg reviewed the status of target selection, which he viewed as the critical challenge confronting immunotherapy. He considered the targets identified thus far to fall into five categories. The category that has been most extensively studied with TCRs is differentiation antigens that are overexpressed on cancers compared with normal tissues (e.g., MART-1, gp100, CEA, HER-2). As with conventional chemotherapy, this approach requires identifying a window of toxicity against the tumor cells without unacceptable damage to normal tissue. In the studies using the melanocyte differentiation antigens, an approximately 25% objective response rate was obtained; however, normal melanocytes were also attacked, causing skin rashes, uveitis, and auditory and vestibular problems, all of which

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