
RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 12, 2012

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health**

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(Note: The latest Human Gene Transfer Protocol List can be found at the Office of Biotechnology Activities' Web site at <http://oba.od.nih.gov/oba/index.html>.)

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
Minutes of Meeting¹**

September 12, 2012

The Recombinant DNA Advisory Committee (RAC) was convened for its 130th meeting at 2:00 p.m. on September 12, 2012, at the Hilton Hotel & Executive Meeting Center, in Rockville, Maryland. Dr. Yuman Fong (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 2:00 p.m. until 4:50 p.m. on September 12. The following individuals were present for all or part of the September 2012 RAC meeting.

Committee Members

Andrew D. Badley, Mayo Clinic and Foundation
Tianxi Cai, Harvard University
Paula M. Cannon, University of Southern California
Saswati Chatterjee, City of Hope National Medical Center
Rebecca Dresser, Washington University School of Law
Yuman Fong, Memorial Sloan-Kettering Cancer Center (RAC Chair)
Norman Fost, University of Wisconsin–Madison (*via teleconference*)
Marie-Louise Hammarskjöld, University of Virginia School of Medicine
Donald B. Kohn, University of California, Los Angeles
Margaret Mallino, Missoula, Montana
David A. Ornelles, Wake Forest University School of Medicine
Joseph Pilewski, University of Pittsburgh
Susan R. Ross, University of Pennsylvania
Marcella Sarzotti-Kelsoe, Duke University School of Medicine
Marshall Strome, St. Luke's–Roosevelt Hospital Center/New York Head & Neck Institute
Dawn P. Wooley, Wright State University
Laurie Zoloth, Northwestern University

Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, Office of the Director (OD), NIH

Ad Hoc Presenters and Speakers

Joseph A. Kanabrocki, Ph.D., The University of Chicago (*via teleconference*)

Non-Voting Agency Representatives

Denise Gavin, U.S. Food and Drug Administration (FDA)

NIH/OD/OBA Staff Members

Linda Gargiulo
Robert Jambou
Marina O'Reilly
Gene Rosenthal

¹ The Recombinant DNA Advisory Committee is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

Attendees

There were 33 attendees at this one-day RAC meeting.

Attachments

Attachment I contains lists of RAC members, ad hoc reviewers and speakers, and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees. Attachment III is a list of abbreviations and acronyms used in this document.

I. Call to Order and Opening Remarks

Dr. Fong, RAC Chair, called the meeting to order at 2:00 p.m. on September 12, 2012. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on August 21, 2012 (77 FR 50516). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of the RAC), public review and discussion of one gene transfer protocol, and presentation and discussion of updates to the *NIH Guidelines*.

RAC members introduced themselves by name, affiliation, and research interests.

Dr. Corrigan-Curay reminded RAC members of the rules of conduct that apply to them as Special Federal Government employees, read into the record the conflict of interest statement, and suggested that related questions be addressed to the committee management officer.

II. Minutes of the June 19, 2012, RAC Meeting

RAC Reviewers: Dr. Chatterjee and Ms. Dresser

Dr. Chatterjee stated that the June 2012 meeting minutes document was well written and accurate; Professor Dresser agreed.

A. Committee Motion 1

A motion was made by Dr. Chatterjee, but not seconded, to approve the June 2012 RAC minutes. The RAC members voted orally and unanimously to approve the June 2012 RAC meeting minutes document.

III. Review and Discussion of Human Gene Transfer Protocol #1206-1169: Phase I/II Study of Adoptive Immunotherapy after Allogeneic HCT with Virus-Specific CD8+ T Cells That Have Been Transduced To Express a WT1-Specific T Cell Receptor for Patients with High-Risk or Relapsed AML, MDS, or CML

Principal Investigator: Merav Bar, M.D., University of Washington (UW)/Fred Hutchinson Cancer Research Center (FHCRC); Aude Chapuis, M.D., UW/FHCRC
Additional Presenters: Philip D. Greenberg, M.D., UW/FHCRC; Thomas Schmitt, Ph.D., UW/FHCRC (*via teleconference*)
RAC Reviewers: Drs. Hammarskjöld, Kohn, and Strome

Dr. Fost was recused from consideration of this protocol due to a conflict of interest.

A. Protocol Summary

Patients with high-risk leukemia or with recurrent leukemia after allogeneic hematopoietic cell transplantation (HCT) have a poor prognosis. Although the transplanted cells from the donor can have an effect against residual leukemia, they are not entirely specific for the leukemia and sometimes attack other tissues from the patient and cause graft-versus-host disease (GVHD). Thus, identifying and targeting proteins that are expressed in leukemia cells but not in other cells of the body could potentially prevent leukemia relapse after HCT and not affect other tissues.

White blood CD8+ cells obtained and purified from donors targeting Wilms' tumor antigen 1 (WT1), a transcription factor that contributes to the malignant phenotype and is over-expressed in acute myeloid leukemia (AML), myelodysplastic syndrome (MOS), and chronic myeloid leukemia (CML), have been given to patients after HCT. Although this experimental treatment was safe, and infused cells reached the bone marrow (where most leukemia cells are located), the leukemia killing activity was modest and the cells remained in patients only for a short period of time. To improve this approach, Epstein-Barr virus (EBV)- or cytomegalovirus (CMV)-specific memory T cells that have the potential for longer *in vivo* persistence following transfer as they retain the traits of memory T cells, will be obtained from each subject's HLA-matched donor and transduced with a lentiviral vector to express a characterized high affinity WT1-specific T cell receptor.

The strong receptor for WT1 should greatly increase the strength of the leukemia killing activity, and since the infused cells will originate from common virus immunity, they should survive and therefore continue potentially to seek out leukemia and exercise their killing activity for a long time. For safety, increasing doses of these cells will be given to subjects who are likely to relapse because of their high-risk disease or to subjects who have persistent disease after HCT.

Infusing cells into subjects with measurable disease will allow the investigators to study closely how the cells function and if improvements to this approach are needed. Overall, this research may help patients fight recurrent leukemia with a treatment that potentially may have few side effects. If this experimental treatment is successful after HCT, it could be used before HCT or in patients who are not transplant candidates.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novel target for immunotherapy. Although the investigators' initial study demonstrated the safety of administering CD8+ T-cell clones expressing a WT1-specific T-cell receptor (TCR), the lack of persistence and potentially low avidity may have contributed to the safety of this approach. The potential for on-target, off-tissue toxicity could increase with the use of a gene-modified TCR with greater avidity.

Three RAC members provided written reviews of this proposed Phase I/II trial.

Dr. Hammarskjöld asked whether the investigators have performed, or plan to perform, *in vitro* tests to analyze potential killing of normal WT1-expressing cells, given this protocol's objective to generate high-affinity cytotoxic T cells (CTLs) that would be capable of more efficient killing of leukemia cells expressing increased levels of WT1. She suggested that the investigators consider testing for *gag-pol* recombinants as well as testing for the presence of Vesicular stomatitis virus (VSV) glycoprotein sequences by polymerase chain reaction (PCR), as a surrogate marker for replication-competent lentivirus. Patients who are seropositive for Human immunodeficiency virus (HIV) or Human T-cell leukemia virus (HTLV) will be excluded from this study; since it may take months for antiviral antibodies to appear, Dr. Hammarskjöld suggested that the investigators consider testing for the presence of virus using PCR rather than relying on antibodies. She noted that WT1 is described as a transcription factor; however, an isoform also functions at the post-transcriptional level. Regarding the informed consent document, Dr. Hammarskjöld pointed to several locations at which discrepancies occurred between information provided in the text and the same information in corresponding tables. In addition, she suggested several wording changes to enhance accuracy and clarity and reduce misunderstanding.

Dr. Kohn noted that this is a well-developed protocol by a team of investigators who are highly experienced in performing this type of complex trial of cell and gene transfer in the setting of allogeneic hematopoietic stem cell transplant and the cell processing plan is well developed and will be conducted at an experienced facility. Regarding the informed consent process, he stated that the informed consent documents are well-written, clearly indicate the experimental nature of this research study, and clearly explain the procedure and potential benefits. The primary issue he noted was whether the T cells will be more cytotoxic and/or more persistently cytotoxic for off-target toxicities, in addition to the intended increased on-target anti-leukemic activity. He stated that the provided information from a murine model using higher affinity TCR to WT1 was reassuring, showing distribution of murine WT1 similar to distribution in humans as well as the absence of toxicity. Dr. Kohn asked whether short-term safety information was available from the similar ongoing trial in the United Kingdom using T cells modified to express a high affinity TCR to WT1. He asked whether preclinical toxicology was conducted in an *in vitro* or an *in vivo* model, given that the lentiviral vector contains, as internal promoter, a retroviral long-terminal repeat (LTR) with a relatively strong enhancer. With regard to the informed consent process, Dr. Kohn suggested adding a caveat statement about the T cells proposed for this study possibly being more active and, therefore, that side effects not seen before might occur, to convey potential risk more realistically. He also pointed out two areas of inconsistency in the consent documents.

Dr. Strome suggested that consideration be given to waiting to enroll research participants who have durable responses with HCT until a Phase II trial to reduce significant risk to those patients and to make this study cleaner with a single arm using dose escalation. He expressed concern that use of the WT1-specific TCR, with its increased avidity for targets expressing lower levels of WT1, puts at-risk organs expressing low levels of WT1; therefore, he suggested that the investigators undertake an animal study using the identical product to be used in the human trial. Dr. Strome noted that stopping endpoints for adverse events of 20 percent and 30 percent seem high. He asked the investigators to discuss whether a seven percent overall improvement in survival (from three percent) should be considered a success, given the initial cost, the potential morbidity of adverse events, and that the associated costs of treating adverse events would, in part, be shouldered by the research participants and their families. Given the potential for significant adverse events, Dr. Strome suggested that the investigators consider having research participants in the initial cohorts live in the surrounding hospital area so that follow up could be consistent after the initial one-month period. Regarding the informed consent document, Dr. Strome suggested two wording changes to enhance accuracy and reduce misunderstanding.

C. RAC Discussion

During the meeting, the following additional questions, concerns, or issues were raised by RAC members:

- Dr. Fong asked whether the informed consent document expresses the various issues well enough for potential participants to understand the pros and cons of participating in this study.
- Professor Dresser asked the ethical question of whether the risk is unreasonable for research participants who have a 50 percent or 60 percent chance of not relapsing quickly (or at all). She emphasized the importance of ensuring that all potential participants understand their “gamble.” Dr. Zoloth added that the percent of patients who might not need additional intervention should be disclosed to potential participants.
- Drs. Cannon and Strome noted that the investigators are willing to accept an adverse event rate of 20 percent, some of which could be Grade 3 or above—a significant number for individuals who otherwise might not be sick.
- Dr. Badley noted concerns expressed by RAC members about the possibility of toxicity from modified T cells, especially in a population that might not develop disease. He asked about the possible use of suicide vectors in the transduced T cells, to shut off toxicity.

- Dr. Cai asked how the investigators will be able to distinguish whether the toxicities that occur are in addition to toxicities associated with drugs, including chemotherapy, taken by these research participants to prevent relapse.
- Because WT1 is known to be expressed in kidney tissues, Dr. Sarzotti-Kelsoe asked whether the investigators planned to include specific tests to look at potential toxicity in the kidney.

D. Investigator Response

1. Written Responses to RAC Reviews

This study proposes to use the routine testing performed on all candidate bone marrow donors and recipients required by the investigators' center and for donors recruited through the national marrow donor program. For research participants, the testing includes assessment of anti-HIV1&2 antibodies and an HIV p24 ELISA (enzyme-linked immunosorbent assay), as well as anti-HTLV1&2 antibodies. The p24 antigen test can detect the p24 protein on average 10 to 14 days after infection with HIV. As research participants will not be dosed until after HCT, the investigators anticipate that preexisting infection with HIV will become evident before dosing is initiated. For donors from whom the transduced cells will be derived, the testing includes assessment of anti-HIV1&2 antibodies as well as a nucleic acid test or HIV PCR.

Data from the investigators' previous trial showed that a WT1-specific clone with avidity equivalent to that achieved with cells transduced with the C4 TCR was associated with the decrease of circulating peripheral leukemic blasts and was not associated with on-target, off-tissue toxicities. The transferred cells did not persist for longer than 14 days *in vivo*; the absence of toxicity is based on data from this period. However, the investigators do have several patients in whom clones persisted at detectable/high levels for longer than 230 days with no on-target, off-tissue toxicities observed.

As described in the updated version of the murine model, the investigators' studies have demonstrated that expression of TCRs with significantly higher affinities than those normally detected in the periphery are safe and well tolerated in adoptive transfer studies. However, when the same TCRs were expressed in stem cells and subjected to thymic selection, these cells were mostly deleted (or modulated to reduce avidity) due to expression of WT1 in the thymus at levels similar to those found in tumors or embryogenesis but much higher than levels found in adult tissues.

Regarding the ongoing trial in the United Kingdom, this group is currently in the process of screening patients for trial participation. They have not yet infused research participants, and thus have no available toxicity data.

Preclinical toxicology with either an *in vitro* or *in vivo* model was not performed with the designed lentiviral vector. These studies were not requested by the FDA.

In a recent report of the long-term results of the combined data of three clinical trials to evaluate gamma-retroviral, vector-engineered T cells for patients with HIV, insertional oncogenesis was not observed. The transduced cells persisted long term, in some cases longer than 10 years, and clinical monitoring of those patients at yearly intervals has not detected suspected or documented occurrences of hematologic disorders suggestive of retroviral genotoxicity, in observation spanning more than 540 patient-years.

In this trial the investigators plan to use a third-generation, self-inactivating lentivirus that has been modified for safety, including truncation of the promoter regions of the LTRs. The expression of the C4 TCR insert is under an internal murine stem cell virus-based promoter, which was selected because it is essential to sustain strong expression of the TCR genes in quiescent as well as activated T cells.

Patients who enter HCT with high-risk myeloid leukemias have a greater than 50 percent rate of relapse after HCT. Once the leukemia has relapsed after HCT, even if detected at the minimum residual disease (MRD) stage, the treatment options are limited (donor lymphocyte infusions, additional chemotherapy)

and the prognosis remains poor, with a greater than 90 percent mortality rate within 2 years after relapse. In the investigators' prior clinical trial, research participants who received WT1-specific T-cell clones within at least 60 days of achieving remission (three participants) or with MRD (one participant) demonstrated prolonged *in vivo* persistence of the transferred cells, and these individuals have remained in prolonged remission. However, it is not possible to determine definitively if the infused T cells in this initial small study were responsible for maintaining the remission, and thus it is essential to do a larger trial with a defined T-cell population as proposed in this study.

Regarding toxicity assessment, research participants with high tumor burdens (in Arm 2) will likely have confounding toxicities related to tumor progression, as well as additional salvage therapies, which can make it difficult to determine if any observed toxicities reflect consequences of the T-cell infusions. In the context of high tumor burdens, achieving long-term persistence of transferred T cells is unlikely, making it also unlikely that sufficient insights into the safety of transferring T cells for relapse prevention could be obtained from this arm. On the other hand, research participants in complete remission at the time of T-cell infusions will have less disease- or treatment-related toxicities, thus facilitating the clear identification of C4 CTL-related toxicities. The investigators believe that maintaining two cohorts for this trial (research participants with high-risk disease but no evidence of disease post-HCT [Arm 1] and research participants with relapsed disease post-HCT [Arm 2]) is required to provide a comprehensive assessment of the toxicity (Arm 1) and potential efficacy/anti-leukemic activity (Arm 2) of WT1-specific T-cell therapy with a TCR of characterized avidity.

Regarding study design, the protocol is structured as a dose escalation trial, with the effect of the dose escalation being evaluated intra- research participants. As safety measures, the initial doses are a log lower than the investigators administered without toxicity in their previous trial, and each arm has two stages so the safety of cell doses can be evaluated in Stage 1 before progressing to Stage 2.

An animal study using the identical experimental product cannot be conducted feasibly in an informative model. The major problems are that human TCRs are expressed poorly in mouse cells and that the relative expression of human leukocyte antigen (HLA) A2 in transgenic mice is not quantitatively similar to HLA-A2 expression in human cells. Matching relative avidities of T cells with human TCRs for mouse tissues is not feasible, and the investigators believe the studies with mouse TCRs with mouse major histocompatibility-restricting elements are more informative, particularly with the demonstration that mutated high-affinity TCRs are safe.

Patients who relapse after leaving FHCRC typically have aggressive disease and generally require and receive immediate salvage therapies, despite such therapies usually having limited benefit and being associated with significant toxicity. Therefore, the investigators anticipate that the majority of relapsed research participants dosed for this study will be the small number of patients with evidence of relapse in the first 100 days after transplant, resulting in slow accrual to this trial. The infusion of C4-transduced CTL in research participants with high-risk disease but no evidence of disease post-HCT will provide distinct but complementary information to patients with relapsed disease post-HCT, for a comprehensive evaluation of the toxicity and potential efficacy associated with targeting WT1 with a TCR of characterized affinity.

Patients after allogeneic HCT have a high rate of transplant-related adverse events involving major organs (e.g., lung, liver, kidney) of 15 percent to 20 percent. After discussion with FHCRC transplant faculty, biostatisticians, and the local institutional review board (IRB), plus two internal reviews of the protocol, the investigators determined that a similar dose-limiting toxicity rate of 20 percent related to the study's experimental treatment would be acceptable for testing this new therapy for research participants with no evidence of disease after HCT (Arm 1). If sufficient evidence suggests that the true dose-limiting toxicity rate exceeds 20 percent, Arm 1 will be suspended pending review by the data and safety monitoring board.

In addition to experiencing a high rate of adverse events, patients who relapse after transplant (Arm 2) have an exceptionally poor prognosis, with an expected mortality rate of 90 percent within two years after relapse. This group of patients may experience major organ toxicity due to the relapsed disease and/or

cytoreductive therapy. Therefore, the goal is to initiate the experimental T-cell therapy as early as possible after relapse, which will likely make it difficult in many instances to differentiate T-cell therapy-related toxicities from toxicities related to transplant. Due to these factors and the dire prognosis, the acceptable dose-limiting toxicity rate for this cohort was defined at the higher level of 30 percent.

Patients with disease that relapses within six months after transplant have less than a 3 percent 2-year overall survival rate. Therefore, for statistical analysis, 3 percent was used as the benchmark, and an observed rate of 10 percent 2-year overall survival would represent a greater-than-threefold increase in survival—a statistically significant improvement. Potential adverse events will be discussed with the patients and families prior to enrollment.

All research participants enrolled in the initial cohorts (Stage 1) on this study will be treated and followed in the FHCRC and will not be discharged prior to completion of all study-related treatment as well as confirmation that they are not experiencing any early toxicities. During this time, which will require approximately three or four months, the HCT clinical team at FHCRC will serve as each research participant's primary provider for all medical needs. The clinical trial team will follow all study participants closely to detect any potential study-related toxicities.

The investigators agreed to modify the informed consent documents as suggested by the RAC reviewers.

2. Responses to RAC Discussion Questions

Dr. Bar summarized the informed consent process in terms of the research participants who have active disease or relapse and the research participants who do not have active disease. Drs. Bar and Greenberg agreed to look at the informed consent document and ensure that discussion of the potential for relapse is precise and clear. They agreed to make the document more clear as to the risk of participating in this study and what fraction of potential participants might be getting an experimental therapy they may not need.

Dr. Greenberg explained that relapsed leukemia after transplant is a rapidly fatal disease unless treated; therefore, waiting to recruit patients to this trial until they relapse is risky and not a viable option. The proposed antigen has been targeted in about 1,000 patients for vaccines. The evidence that a normal cell will be recognized by this antigen is not likely to be feasible, and the risk to these research participants is extremely low.

Drs. Bar and Greenberg reiterated that 50 percent to 60 percent of patients will relapse after transplant, and two-thirds of those patients will relapse within the first 2 years. Patients who relapse in the first 2 years after transplant are 90 percent likely to die within those 2 years.

Dr. Greenberg explained that the investigators' biostatistician recommended including a 20 percent toxicity rate as the stopping point for the trial. A lower rate would result in the trial not being able to go forward because of toxicities associated with chemotherapy and the drugs being used in these patients to prevent relapse, most of which have adverse event rates higher than 20 percent.

Dr. Greenberg stated that the investigators do not have access to a viable suicide vector. Such a vector might be available in the future, but it is not available now.

Dr. Chapuis explained that toxicities are probably, possibly, or unlikely related to the experimental therapy. If lymphocyte levels drop the day after the research participant receives the T cells, without concurrent chemotherapy, that event would probably be related to the T cells but it would be an expected adverse event. Dr. Greenberg further stated that the investigators will examine each toxicity and, if it was possibly caused by a T cell, that toxicity will be included in the 20 percent of adverse events needed to stop the trial.

Dr. Greenberg said that the investigators will monitor kidney function closely. The critical potential targets are hematopoietic stem cells, kidney, and lining of the lung and peritoneum. The investigators have never

seen a T cell localized to any of those sites in any of the transplant models, and no toxicities to those tissues have been reported in any of the vaccine trials. Biopsies or other specific tests to look at T-cell infiltration are too invasive to conduct as part of this protocol; only if toxicities occur will the investigators conduct those procedures.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

Clinical and Trial Design Issue

- There have been reports of T-cell infusions leading to systemic inflammatory reactions, and cytokine analysis is useful in evaluating such events. The protocol should include a plan for collection of blood for cytokine analysis that would be performed in the case of an unexpected toxicity and should specify the cytokines that will be evaluated.
- The Appendix M responses submitted with this protocol state that “no HIV-1 derived sequences are transcribed from the provirus and only the therapeutic sequences will be expressed.” This statement should be revised, since the literature shows that transcription of proviral sequences has been detected from self-inactivating vectors presumably integrated near active cellular promoters (Miyoshi, H, *et al.*, Development of a Self-Inactivating Lentivirus Vector, *J. Virol.* 1998. 72:8150–8157).

Ethical, Legal, Social Issues

- This protocol will enroll two different cohorts of patients: 1) research participants who have already relapsed prior to or after HCT (based on molecular detection of the presence of minimal residual disease) and therefore have a very poor prognosis, with lifespan often measured in months, and 2) research participants who have not had a molecular relapse pre- or post-transplant but are at high risk of relapse. Patients who have already had a molecular relapse have very few clinical options and are appropriate candidates for unproven experimental therapies.

The decision to enroll patients who are in remission but are at high risk of relapse was based on several factors. First, it is estimated that 60 percent of these patients will relapse within 2 years, and 90 percent of those patients who relapse will not survive beyond 2 years, and many may not survive 1 year. Therefore, even if remission is achieved after HCT, many of these patients will not survive more than several years, underscoring the need for additional therapies. In addition, data from the investigators' previous trial that used autologous, non-gene-modified T cells expressing WT1 demonstrated prolonged *in vivo* persistence of the T cells in four research participants who were in chronic remission or had minimal residual disease at the time of infusion of these T cells. These individuals remain in remission 22 to 38 months after HCT.

The investigators also postulate that it may be difficult to achieve long-term persistence of the transferred T cells in patients who have relapsed and develop large tumor burdens. In addition, these patients are more likely to have medical complications due to their advanced disease, making it more difficult to assess the safety of the gene-modified T-cell infusions. Therefore, to gather sufficient data on safety as well as the potential anti-leukemic activity of these gene-modified cells, the investigators propose to enroll both populations.

However, enrollment of patients who are in remission after HCT raises an ethical question. At least 40 percent of these patients will not relapse. Such patients will not need additional therapies and therefore it is important to weigh carefully the risks and benefits for these patients. Unfortunately, there is no way after transplant to predict into which group a patient will fall.

Because an individual patient cannot know at the time of enrollment whether they will achieve long-term remission, and subjects who have not relapsed may be most informative regarding safety and anti-leukemic activity, it is reasonable to enroll these patients but only if they have a clear understanding of the risks and benefits.

First, it is important that the informed consent document and process stress that no clinical benefit is expected in this Phase I trial, which is primarily a safety and feasibility study. For patients who may be cured by conventional therapy, the only potential benefit is the knowledge gained for other patients. This should be articulated together with detailed information regarding relapse rates and survival. Patients should understand that there is a 40 percent chance that they will not need any additional therapy for their cancer. For such patients, there is no potential for direct benefit to enrollment, but there is the possibility of unexpected and serious adverse events. In addition, for those patients who have molecular evidence of relapse, as the chance of any direct benefit is extremely remote and there are questions regarding the ability to evaluate anti-leukemic activity and safety in this population, the consent process must be rigorous in articulating the competing risks and benefits for this population as well.

G. Committee Motion 2

Dr. Fong summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. A motion was made but not seconded to approve these recommendations, and the RAC approved these summarized recommendations by a vote of 16 in favor, 0 opposed, 0 abstentions, and one recusal.

IV. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Badley, Chiocca, Fong, Kiem, Kohn, and Strome

A. GTSAB Report

Dr. Badley reported on the GTSAB meeting that occurred earlier in September 2012. The OBA had received 13 protocol submissions in the past three months, 12 of which were not selected for public review at this RAC meeting. Of the 12 protocols not selected for public review, 11 were oncology protocols and one was for heart failure. In these 12 protocols, three used retrovirus vectors, two each used adenovirus and lentivirus vectors, and one each used plasmid, modified bacteria, VSV, adeno-associated virus (AAV), and RNA transfer vectors. Dr. Badley noted that information about these trials would be available on the OBA Web site after this RAC meeting.

Twenty-eight serious adverse events (SAEs) from 19 protocols were reviewed by the GTSAB, including initial and follow-up reports. After analyzing these events, the GTSAB concluded that none warranted public discussion at this RAC meeting.

The OBA received notification from investigators that ten protocols were newly open to enrollment. Two of those ten had been reviewed previously at a RAC public meeting, and one of those two provided responses to the issues raised following public review: OBA protocol #1089, reviewed in June 2011—Phase I Trial of Attenuated Vaccinia Virus (GL-ONC1) Delivered Intravenously with Concurrent Cisplatin and Radiotherapy in Patients with Locoregionally Advanced Head and Neck Carcinoma.

Dr. Badley reported on two noteworthy events that were discussed at the GTSAB meeting:

- The European Medicines Agency's Committee for Medicinal Products for Human Use recommended that the alipogene tiparovec be approved as a therapy. This product uses an AAV vector encoding for the lipoprotein lipase (LPL) gene and is intended for patients with LPL deficiency who have severe or multiple attacks of pancreatitis despite dietary fat restrictions. Dr. Badley stated that discussion about the development of this product and the related regulatory

process would take place at the workshop on Gene Therapy and Rare Diseases on September 13, 2012. The entire conference will be webcast by NIH.

- The University of Pennsylvania and Novartis have formed an alliance to expand the use of T-cell immunotherapy for cancer. A Center for Advanced Cellular Therapies will be built on the University of Pennsylvania campus; it will be devoted to discovery, development, and manufacturing of adoptive T-cell immunotherapy. Novartis will have an exclusive global license to the technologies used in an ongoing trial of patients with chronic lymphocytic leukemia, as well as future chimeric antigen receptor-based therapies developed through the collaboration.

B. RAC Discussion

No discussion occurred.

C. Public Comment

No public comments were offered.

V. Updates to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nuclei Acid Molecules*

Presenters: Dr. Corrigan-Curay and Joseph Kanabrocki, Ph.D., University of Chicago (via teleconference)

A. Presentation by Dr. Corrigan-Curay

Dr. Corrigan-Curay presented a brief update on recent amendments to the *NIH Guidelines* in two areas—research with synthetic nucleic acids and transfer of drug resistance traits to microorganisms. Two factors suggested the need for these changes:

- 1) Recognition that appropriate biosafety containment of an agent is critical regardless of whether that technology was generated by recombinant or synthetic means, and
- 2) A report from the National Science Advisory Board for Biosecurity (NSABB), which cited a “need to examine the language and implementation of current biosafety guidance to ensure that such guidelines and regulations provide adequate guidance for working with synthetically derived DNA and are understood by all those working in areas addressed by the *Guidelines*.”

The current *NIH Guidelines*, dated October 2011, recognize synthetic DNA but only in the context of being joined through a recombinant technique. When the new amendments are implemented in March 2013, the *NIH Guidelines* will explicitly include certain basic and clinical research with nucleic acid molecules created solely by synthetic means, providing exemptions for certain classes of research with synthetic nucleic acids paralleling the existing exemptions for research with recombinant DNA.

The amended *NIH Guidelines* go into effect in six months. This time allows institutions to develop new procedures and reach out to investigators performing research not currently covered under the *NIH Guidelines*, but that will be covered when the new amendments take effect. An institution can choose to implement the new guidelines immediately or it can wait until March 2013 to do so, depending on its procedures. Composition of institutional biosafety committees (IBCs) does not need to change, but an institution may choose to add to IBC membership to bring in department(s) not currently represented. The following specific sections of the *NIH Guidelines* have been amended and will take effect in March 2013:

Section I	Scope of the <i>NIH Guidelines</i>
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Section I-B	Definition of Recombinant DNA
Section I-C	General Applicability
Section II-A-3	Comprehensive Risk Assessment
Section III-A-1	Major Actions under the <i>NIH Guidelines</i>
Section III-B	Experiments that Require NIH-OBA and Institutional Biosafety Committee Approval Before Initiation
Section III-D	Experiments Involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA Derived from Recombinant DNA, into One or More Human Research Participants
Section III-F	Exempt Experiments
Section IV-A	Policy

Dr. Corrigan-Curay reviewed the changes in these and other areas, including the following points:

- The *NIH Guidelines* do not cover the chemical synthesis of nucleic acids—and do not intend to do so. While the scope of the *NIH Guidelines* refers to “constructing” nucleic acids, the *NIH Guidelines* exempt research with nucleic acids that are not contained in cells, organisms, or viruses. Therefore, the chemical synthesis of nucleic acids is exempt. The *NIH Guidelines* only apply once synthetic nucleic acids are placed in a biological system.
- Section III-F includes a number of exemptions, and Section III-F-2 now exempts experiments “...that are not in organisms, cells, or viruses and that have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes.”
- Synthesis of naturally occurring organisms is not covered. Section III-F-3 exempts experiments that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature.
- Section III-F-1 exempts basic research with synthetic nucleic acids that can neither replicate nor generate nucleic acids that can replicate in any living cell, are not designed to integrate into DNA, and do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight.
- Section III-C-1 defines human gene transfer as the deliberate transfer into human research participants of either 1) recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or 2) synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of four criteria: contain more than 100 nucleotides, possess biological properties that enable integration into the genome, have the potential to replicate in cells, or can be translated or transcribed. This definition excludes small-interfering RNA protocols and microRNA protocols that are being delivered directly or into a nanoparticle.
- Throughout the *NIH Guidelines*, the term “recombinant DNA molecules” will be replaced with “recombinant or synthetic nucleic acids.” As a result, the *NIH Guidelines* apply to both recombinant and synthetically derived nucleic acids, including those that are chemically or otherwise modified analogs of nucleotides.

Section III-A-1-a, applying to the deliberate transfer of a drug resistance trait to microorganisms, was also amended to clarify whether a drug is therapeutically useful. Consideration should be given as to whether the drug resistance trait to be used in the experiment would render that microorganism resistant to the primary drug available to and/or indicated for certain populations, for example, children or pregnant women. A new section III-B-2 was added to expedite review of “me too” experiments. If a single investigator is approved, for example, for tetracycline use in chlamydia, the next investigator from another institution would not have to go through the entire review and approval process if the experiment were identical. Experiments approved prior to implementation of these changes will be included retroactively.

Additional information on these changes can be found in the published *Federal Register* Notice 77 FR 54584 (September 5, 2012), which is available at: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. OBA Frequently Asked Questions and Guidelines is available at: http://oba.od.nih.gov/rdna/rdna_faq_list.html.

B. Presentation by Dr. Kanabrocki

Dr. Kanabrocki presented his view of the impact of these changes to the *NIH Guidelines* on institutional biosafety committees (IBC). He explained that the purpose of the changes is to provide a mechanism whereby appropriate biocontainment and biosafety could be applied to this research, with a goal of ensuring that consistency with current risk assessment processes for recombinant DNA research. Dr. Kanabrocki opined that the changes as written do meet that goal and that the net impact of these changes is favorable to the research community.

The primary challenge to IBCs is that the inclusion of synthetic nucleic acids expands the applicability of the *NIH Guidelines* beyond the life sciences to include the physical sciences, a community that is generally unfamiliar with Federal and local oversight mechanisms and the requirements related to recombinant DNA. As a result, this expansion will require significant outreach and education at the local level. The NSABB recommendations discuss formal mechanisms to establish and promote an institution-wide culture of responsibility for safety and security and to establish a formal code of conduct.

Exemptions to the applicability of the *NIH Guidelines* to synthetic nucleic acids parallel those already existing for recombinant DNA. Chemical synthesis of nucleic acids is excluded, so this expansion is only applicable if synthetic nucleic acids are placed in a biologic system. Risks from chemical synthesis alone are considered low.

The impact in human gene transfer is relatively negligible, as risk assessments for synthetic molecules expressed by a molecular vector are similar to those involving recombinant DNA, with oligonucleotides excluded.

The risk assessment paradigm is largely unchanged relative to standard recombinant DNA risk assessment. However, chimeras will require close scrutiny, as outcomes may not be predictive. The potential exists for the need to add IBC expertise in the physical sciences and in computational biology.

Regarding the transfer of drug resistance traits to microorganisms, the Criteria for Major Actions remain unchanged. Additional language clarifying the therapeutic utility of a particular drug is helpful. Dr. Kanabrocki noted the streamlined review process that will delegate authority to the OBA to approve requests similar to those previously approved (“me too” research), a change that will facilitate registration of these experiments and make the process easier and clearer.

C. RAC Questions and Discussion

Noting that she has worked with synthetic biologists, Dr. Zoloth stated that such researchers oftentimes have little or no understanding of biology—they are engineers who have skills and a sense of the regulatory efforts appropriate only to engineering, or they are chemists. Many of them have never worked with an IRB or a patient. She suggested that an individual with that background be added to the RAC.

Dr. Wooley suggested the need to consider how nucleic acids would be manipulated even if research does not propose to work with cells or does not plan to put nucleic acids into a biological system, because of the possibility of accidental injection.

Dr. Zoloth mentioned that much of the interesting work in this field is being undertaken at the undergraduate and graduate school and postdoc levels. For example, the International Genetically Engineered Machine (iGEM) competition is a large international competition that is unregulated. Dr. Corrigan-Curay responded that iGEM now requires addition of a biosafety section to their submitted protocols, and she reiterated that institutions that receive NIH funding must comply with the *NIH Guidelines*.

Dr. Pilewski queried as to how the 100 nucleotide criterion was derived. Dr. Corrigan-Curay explained that, during the discussion of what to do about oligonucleotides, it was noted that most of the oligonucleotides for which exclusion was desired were at about 20, 30, or 40 nucleotides. Therefore, using the 100 nucleotide criterion provided an acceptable way to obtain that result.

D. Public Comment

No public comments were offered.

VI. Closing Remarks and Adjournment

Dr. Fong thanked the RAC members and the OBA staff and adjourned the September 2012 RAC meeting at 4:50 p.m. on September 12, 2012.

(Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, they are not considered final until approved by the NIH Director.)

Jacqueline Corrigan-Curay, J.D., M.D.
RAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following Attachments are accurate and complete.

This Minutes document will be considered formally by the RAC at a subsequent meeting; any corrections or notations will be incorporated into the Minutes after that meeting.

Date: _____

Yuman Fong, M.D.
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Recombinant DNA Advisory Committee

Attachment I: RAC Roster
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(This list includes only individuals who are not identified elsewhere.)

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Holli Jaffe, NIH Ethics Office

Xiaobin Lu, FDA

Antony Schwartz, National Biosafety and Biocontainment Program/Institute of Health Sciences

Anna Snouffer, Office of Federal Advisory Committee Policy

Attachment III Abbreviations and Acronyms

AAV	adeno-associated virus
AML	acute myeloid leukemia
CML	chronic myeloid leukemia
CTLs	cytotoxic T cells
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
FHCRC	Fred Hutchinson Cancer Research Center
GTSAB	Gene Transfer Safety Assessment Board
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HTLV	human T-cell leukemia virus
IBCs	institutional biosafety committees
iGEM	International Genetically Engineered Machine
IRB	institutional review board
LPL	lipoprotein lipase
LTR	long-terminal repeat
MDS	myelodysplastic syndrome
MRD	minimum residual disease
NIH	National Institutes of Health
<i>NIH Guidelines</i>	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>
NSABB	National Science Advisory Board for Biosecurity
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PCR	polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
SAEs	serious adverse events
TCR	T-cell receptor
UW	University of Washington
VSV	vesicular stomatitis virus
WT1	Wilms' tumor antigen 1