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**RECOMBINANT DNA ADVISORY COMMITTEE**

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**Minutes of Meeting**

**March 12, 2014**

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

## Contents

I.	Call to Order and Opening Remarks .....	2
II.	Minutes of RAC Meeting, December 4–5, 2013.....	2
	A. Committee Motion 1 .....	2
III.	Review and Discussion of Human Gene Transfer Protocol #1401-1287: Phase I Study of Cellular Immunotherapy Using T Cells Lentivirally Transduced to Express a CD123-Specific, Hinge-Optimized, CD28-Costimulatory Chimeric Antigen Receptor and a Truncated EGFR for Patients with Relapsed or Refractory CD123+ Acute Myeloid Leukemia .....	2
	A. Protocol Summary .....	3
	B. Written Reviews by RAC Members .....	3
	C. RAC Discussion .....	4
	D. Investigator Response .....	4
	1. Written Responses to RAC Reviews .....	4
	2. Responses to RAC Discussion Questions.....	6
	E. Public Comment.....	7
	F. Synopsis of RAC Discussion and RAC Observations and Recommendations .....	7
	G. Committee Motion 2.....	7
IV.	Review and Discussion of Human Gene Transfer Protocol #1401-1288: Phase I Study to Determine the Effects of Mesenchymal Stem Cells Secreting Interferon Beta in Patients with Advanced Ovarian Cancer.....	7
	A. Protocol Summary .....	8
	B. Written Reviews by RAC Members .....	8
	C. RAC Discussion .....	9
	D. Investigator Response .....	9
	1. Written Responses to RAC Reviews .....	9
	2. Responses to RAC Discussion Questions .....	12
	E. Public Comment.....	12
	F. Synopsis of RAC Discussion and RAC Observations and Recommendations .....	13
	G. Committee Motion 3.....	14
V.	Review and Discussion of Human Gene Transfer Protocol #1401-1289: Phase I/II Gene Transfer Clinical Trial of rAAV9.MCV.hNAGLU for Mucopolysaccharidosis (MPS) IIIB.....	14
	A. Protocol Summary .....	14
	B. Written Reviews by RAC Members .....	14
	C. RAC Discussion .....	15
	D. Investigator Response .....	16
	1. Written Responses to RAC Reviews .....	16
	2. Responses to RAC Discussion Questions .....	18
	E. Public Comment.....	19
	F. Synopsis of RAC Discussion and RAC Observations and Recommendations .....	19
	G. Committee Motion 4.....	20
VI.	Gene Transfer Safety Assessment Board Report .....	20
	A. GTSAB Report .....	20
	B. RAC Discussion .....	21
	C. Public Comment.....	21
VII.	Closing Remarks and Adjournment.....	21
	Appendix: Verbatim Public Comments from Protocol #1401-1289 .....	App-1

Attachment I. Recombinant DNA Advisory Committee Roster ..... Att-I-1  
Attachment II. Public Attendees ..... Att-II-1  
Attachment III. Abbreviations and Acronyms ..... Att-III-1

*[Note: The latest Human Gene Transfer Protocol List can be found on the Office of Biotechnology Activities website 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 Meeting<sup>1</sup>**

March 12, 2014

The Recombinant DNA Advisory Committee (RAC) convened for its 137th meeting at 9:30 a.m. on March 12, 2014, at the Rockledge II Conference Center, 6701 Rockledge Drive, Bethesda, Maryland. Dr. Donald B. Kohn (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:30 a.m. until 3:20 p.m. on March 12, 2014. The following individuals were present, either in person or by teleconference, for all or part of the March 2014 RAC meeting.

**Committee Members**

Michael Atkins, Georgetown University School of Medicine  
Tianxi Cai, Harvard University (*via teleconference*)  
Paula M. Cannon, University of Southern California  
Saswati Chatterjee, City of Hope National Medical Center  
William Curry, Harvard Medical School (pending)  
Rebecca Dresser, Washington University School of Law  
Norman Fost, University of Wisconsin, Madison (*via teleconference*)  
Marie-Louise Hammarskjöld, University of Virginia School of Medicine  
Hans-Peter Kiem, University of Washington School of Medicine/Fred Hutchinson Cancer Research Center  
Walter J. Koch, Temple University School of Medicine  
Donald B. Kohn (RAC Chair), University of California, Los Angeles  
David A. Ornelles, Wake Forest University School of Medicine  
Joseph Pilewski, University of Pittsburgh (*via teleconference*)  
Michael Sadelain, Memorial Sloan-Kettering Cancer Center (pending)  
Marcella Sarzotti-Kelsoe, Duke University School of Medicine  
Marshall Strome, St. Luke's–Roosevelt Hospital Center/New York Head and Neck Institute (*via teleconference*)  
Richard Whitley, University of Alabama, Birmingham (*via teleconference*)  
Laurie Zoloth, Northwestern University

**NIH Office of Biotechnology Activities (OBA)**

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

**Nonvoting Agency Representatives**

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

**NIH/OD/OBA Staff Members**

Linda Gargiulo  
Morad Hassani  
Robert Jambou  
Maureen Montgomery  
Carolyn Mosby  
Marina O'Reilly  
Gene Rosenthal

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<sup>1</sup> The Recombinant DNA Advisory Committee is advisory to the 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 67 attendees at this 1-day RAC meeting.

## Attachments

Attachment I contains a list of RAC members and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees. Attachment III contains a list of abbreviations and acronyms used in this document.

### I. Call to Order and Opening Remarks

Dr. Kohn, the RAC Chair, called the meeting to order at 9:30 a.m. on March 12, 2014. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* was published in the *Federal Register* on February 18, 2014 (79 FR 9243). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of the RAC) and public review and discussion of three gene transfer protocols.

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 Government Employees, read into the record the conflict of interest statement, and suggested that related questions be addressed to the OBA committee management officer.

### II. Minutes of RAC Meeting, December 4–5, 2013

RAC Reviewers: Drs. Koch and Ornelles

Dr. Ornelles suggested that the RAC approve the minutes of the December 2013 RAC meeting, with a few minor changes previously provided; Dr. Koch concurred. No changes to the document were suggested by other RAC members.

#### A. Committee Motion 1

Dr. Kohn asked the RAC to approve the minutes of the December 4–5, 2013, RAC meeting. The RAC voted unanimously by voice to do so.

*(Dr. Kiem chaired the following portion of the RAC meeting because Dr. Kohn was recused from discussion of this protocol due to a conflict of interest.)*

### III. Review and Discussion of Human Gene Transfer Protocol #1401-1287: Phase I Study of Cellular Immunotherapy Using T Cells Lentivirally Transduced to Express a CD123-Specific, Hinge-Optimized, CD28-Costimulatory Chimeric Antigen Receptor and a Truncated EGFR for Patients with Relapsed or Refractory CD123+ Acute Myeloid Leukemia

Principal Investigator: L. Elizabeth Budde, M.D., Ph.D., City of Hope National Medical Center  
Project Leader: Stephen J. Forman, M.D., City of Hope  
Additional Presenters: Christine Brown, Ph.D., City of Hope; Craig Jordan, University of Colorado, Denver; Armen Mardiros, M.S., City of Hope; Jamie Wagner, City of Hope (*all via teleconference*)  
RAC Reviewers: Ms. Dresser, Dr. Kiem, and Dr. Sadelain

Drs. Chatterjee, Cannon, and Kohn recused themselves from consideration of this protocol due to conflicts of interest.

### **A. Protocol Summary**

Acute myeloid leukemia (AML) is a biologically heterogeneous group of related diseases of bone marrow and blood that have the highest death rate of all leukemias. After standard therapy, the majority of AML patients who achieve complete remission (CR) will relapse, many within one year, unless they receive allogeneic stem-cell transplantation (alloSCT). Other patients might not even be able to achieve CR after first-line induction therapy. The five-year overall survival rate from first relapse for these patients is only 10 percent. Thus, there is an urgent unmet need for developing safe and effective therapies for these patients.

This clinical trial will be a single center, Phase I, open-label, non-randomized study in which adult research participants with CD123+ relapsed or refractory AML, who have an identifiable donor available for alloSCT, will receive immunotherapy with adoptively transferred autologous T cells. Those cells will be genetically modified to express a CD123-specific, hinge-optimized, CD28-costimulatory chimeric antigen receptor (CAR) as well as a truncated human epidermal growth factor (EGFRt; CD123R(EQ)28ζ/EGFRt+ T cells) following a lymphodepleting preparative regimen of cyclophosphamide.

The study aims to assess the safety of the proposed therapy and to determine the recommended Phase II dose. This study also will evaluate the activity of the CD123R(EQ)28ζ/EGFRt+ T cells in the form of disease response, T-cell persistence, and immunogenicity.

### **B. Written Reviews by RAC Members**

Nine RAC members voted for in-depth review and public discussion of the protocol. Key issues included that it will be the first trial to employ a CD123-specific CAR. Off-target effects could occur because this molecule is expressed on a subset of pluripotent progenitor cells.

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

Ms. Dresser focused her review on the informed consent document (ICD). She noted that the document refers to the study intervention as “treatment,” characterization that could result in patients believing that the intervention has a good chance of benefitting them, which is unlikely. She suggested using the terms “study drug,” “investigational drug,” or “experimental product.” Ms. Dresser stated that some of the material in the document could be omitted to make it easier to navigate. She noted that the dosages in the table on page five would be meaningless to nonscientist readers, and suggested that the investigators include an explanation of what cytokine release syndrome involves. Ms. Dresser stated that the information about withdrawal from the study should include that it is not possible to remove the infusion of genetically modified cells once they have been infused into the body, but that it is possible to minimize the effects of the genetically modified cells through the use of cetuximab and other drugs. She encouraged the investigators to simplify the language in the ICD because the current version would be difficult for prospective participants to follow, and she suggested rewriting the document at an eighth-grade reading level, with short sentences and paragraphs and using the active voice.

Noting that this protocol is well written, Dr. Kiem asked the investigators to discuss why they expect the CAR cells to work on CD123-expressing leukemia when two trials using anti-CD123 antibodies (including one linked to diphtheria toxin) did not show significant responses, and whether they would expect the toxicity profile to be different. Because CD123 is expressed on other tissues, he requested information about which *in vivo* studies were performed to evaluate the potential for on-target, off-tumor effects and potential toxicities from the CAR cells binding to non-AML tissue. Dr. Kiem asked for discussion about the optional cetuximab administration, particularly to clarify the criteria as to when this treatment would be employed and whether research participants would be able to move to alloSCT without CAR depletion. He suggested that the ICD include information about the impact on the alloSCT if CD123 CAR cells still

persist at significant levels, the rationale and risks of the T-cell ablation, whether a particular CAR level is acceptable before alloSCT, when the investigators would use a second cetuximab infusion, and what has been their experience with CAR depletion with cetuximab. Dr. Kiem asked the investigators to clarify to what extent normal hematopoiesis would be analyzed and studied, how it would be part of the dose escalation and de-escalation scheme especially in light of the cyclophosphamide conditioning, and how soon after reinduction, cyclophosphamide would be given. He also requested clarification as to (1) whether alloSCT would be conducted before 60 days and, if progression occurs, whether alternative therapy would be discussed before a second dose is offered; (2) the eligibility criteria for moving forward with an alloSCT if a response occurs, especially with regard to the likely increased risk for relapse and impact on survival; and (3) how and when the regulatory T cells (Tregs) would be depleted.

Dr. Sadelain asked that the investigators provide and discuss data indicating that normal hematopoietic stem/progenitor cells are spared in leukemia-bearing mice undergoing CD123 CAR T-cell therapy. He asked whether *in vivo* data are available that show the efficacy and kinetics of CD123 CAR T-cell elimination by cetuximab. In addition, Dr. Sadelain requested further clarification of the quantitative criteria for cetuximab administration to research participants.

### C. RAC Discussion

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

- Dr. Hammarskjöld noted that using a self-inactivating lentivirus vector, as planned, could be safer than using a Moloney virus. She asked whether the investigators plan to look at integration patterns, the results of which could be useful for the scientific and therapeutic communities.
- Dr. Atkins asked what would happen if the experimental treatment does not work and if the stem cells cannot be eliminated. He also asked whether the investigators expect to be able to enroll the appropriate number of subjects willing to take cetuximab and how many subjects would need to receive cetuximab to be able to adequately test the question as to whether it can eliminate CAR T cells.

### D. Investigator Response

#### 1. Written Responses to RAC Reviews

The investigators stated that the efficacy of CD123 T cells in the clinical setting is unknown. However, based on the potent anti-leukemic activity observed with the CAR123 T cells, the impressive 70 to 90 percent complete response seen in recent clinical trials using CD19 CAR T cells that contain the same CD28 costimulatory domain in treating acute lymphoblastic leukemia, and cumulative studies that demonstrate CD123 is a well-characterized leukemia-associated antigen, the investigators believe that CD123-specific CAR T-cell adoptive immunotherapy is a promising approach in treating AML and warrants clinical testing. The two published clinical trials testing CSL360 (a neutralizing anti-CD123 antibody) and SL401 (a diphtheria toxin and human interleukin-3 conjugate) are Phase I studies in which efficacy was not the primary objective. An improved version of CSL360 with enhanced antibody-dependent cell-mediated cytotoxicity activity, CSL362, currently is being studied in a multicenter clinical trial. SL401 was tested in a Phase IB clinical trial of patients with CD123+ blastic plasmacytoid dendritic cell neoplasm. The SL401 dosing schedule was based on the dose-finding results from the previous Phase I clinical trial. Five of seven evaluable subjects achieved CR, confirming that potent clinical anti-tumor activity can be achieved by targeting CD123. The investigators expect that this CAR T-cell therapy would have an overlapping but different toxicity profile, based in part on the mechanistic differences between cell-based therapy and antibody or receptor-drug conjugate mediated therapy. The investigators expect to see similar on-target toxicities including possible reduced hematopoiesis, reduced numbers of basophils, monocytes, plasmacytoid dendritic cells, and natural killer cells, as well as similar off-target toxicities such as infusion reactions. They also expect to see toxicities that are unique to T-cell therapy, such as cytokine release syndrome and macrophage activation syndrome. The abnormal liver function seen in subjects treated with SL401 is likely due to nonspecific liver uptake and damage by the drug. There is no CD123 expression on Kupffer cells or hepatocytes.

Low-level expression of CD123 is found on a subset of CD34+CD38-hematopoietic stem/progenitor cells. It is also expressed at high levels on plasmacytoid dendritic cells and basophils and at low levels on monocytes, eosinophils, and myeloid dendritic cells. Only patients with an identified donor stem cell source are eligible to enroll on this proposed study. Therefore, in the event of prolonged severe cytopenia, an alloSCT will restore hematopoiesis.

The proposed clinical protocol describes when cetuximab will be used for CAR+ T-cell ablation, which includes prolonged neutropenia, and optional ablation prior to the start of conditioning for alloSCT. Cetuximab will be offered to research participants prior to alloSCT, but will not be required for two reasons: (1) The study team recognizes that administration of cetuximab introduces the potential for additional side effects while the ability to ablate CAR+ T cells with cetuximab in humans is still theoretical, and (2) since the manufacturing platform used in this proposed protocol has not endowed the CAR+ T cells with any survival advantages, the investigators believe the CAR+ T cells will follow the same fate as unmanipulated T cells through myeloablative conditioning. Any level of CAR+ T cells detected prior to alloSCT is acceptable, and all participants, regardless of percentage of detectable CAR+ T cells or cetuximab ablation, will move on to alloSCT, which is the standard of care. This protocol provides an opportunity to assess the clinical efficacy of cetuximab in ablating the CAR+ T cells, which is one of the exploratory objectives. The ICD has been revised to include reasons why CAR+ T cells might be ablated.

Because the investigators acknowledge the difficulty of predicting to what extent normal hematopoiesis would be affected by the CD123 CAR+ T cells, they added exploratory objectives that include impact on hematopoiesis. A few preclinical studies and two Phase I clinical trials indicate that normal hematopoiesis might be mildly affected when targeting CD123. The investigators propose to analyze the hematopoietic stem/progenitor cell compartments using flow cytometric analysis and immunohistochemistry of bone marrow samples in order to follow numbers of subsets of blood cells in the peripheral blood at various time points after T-cell infusion. Because all participants are expected to move on to receive alloSCT with an available stem-cell source, hematopoiesis capacity is not included as one of the determining factors in the dose-finding design. The cyclophosphamide dose as a lymphodepletion regimen is modest, at 1.5 mg/m<sup>2</sup>, which is not myelosuppressive at this dose level. In the proposed participant population, cyclophosphamide treatment might transiently worsen the extent of myelosuppression caused by prior systemic chemotherapies; therefore, collection of bone and blood samples is required prior to cyclophosphamide administration to document the hematopoietic function at baseline. The investigators also propose to assess hematopoietic function at day 28 post T-cell infusion. If hematopoiesis worsens at that point, it would most likely be due to effects from CAR+ T cells rather than from cyclophosphamide.

For research participants who receive salvage chemotherapy, cyclophosphamide will be given only after a response assessment is completed and treatment-related toxicities have been assessed adequately. This statement has been added to the proposed clinical protocol.

The investigators have revised the language in the proposed clinical protocol to allow initiation of alloSCT workup any time beginning 28 days post T-cell infusion; the second T-cell infusion is optional and exploratory in nature. The study team will discuss with the participant other alternative treatment options prior to the second T-cell infusion.

Subjects can proceed to alloSCT 28 days after T-cell infusion, with eligibility determined by standard of care and the treating physician. The investigators have modified the proposed clinical protocol accordingly.

Tregs will only be depleted *in vivo* through lymphodepletion and will not be depleted from the cellular product. However, the study team acknowledged a typographical error in the clinical protocol that may have misinformed the reviewers suggesting that CD25+ Tregs would be depleted from the cellular product. The study will use bulk T cells collected from participants without subset selection.

The anti-leukemic efficacy and hematologic on-target toxicity of CD123 CAR cells have not been assessed in mice bearing both leukemia cells and a humanized immune system. Two groups of

researchers have examined the impact of CAR cells on hematopoiesis in non-leukemia-bearing humanized NOD-skid gamma (NSG) mice, finding no significant impact of CD123 CAR cytokine-induced killer cells on the normal longterm repopulating cells derived from either umbilical cord blood cells or normal adult bone marrow cells. One other result reported that treatment with CD123 CAR+ T cells led to significant reduction of numbers of CD34+CD38- platelets and B cells in mice that were engrafted with fetal liver CD34+ cells. The discrepancy between results from these two studies might be explained by the differences in CAR design and the stem cell source; the CD123 CAR proposed for this trial is different from both of those CARs. The investigators chose not to perform mouse experiments for this proposed protocol, because (1) the humanized NSG model is limited in its ability to predict accurately the impact on hematopoiesis in humans, and mouse models in general have not been effective in predicting toxicities due to intrinsic differences between various murine strains and *Homo sapiens*; and (2) the proposed study is designed as a bridge to alloSCT independent of the impact of T-cell therapy on regeneration of marrow function and blood counts. This study provides an opportunity to assess directly the impact of the proposed CD123 CAR on hematopoiesis in the pre-transplant stage by providing a safe setting to better understand the effects of the investigational drug for future applications of this therapy.

Regarding the efficacy and kinetics of CD123 CAR T-cell elimination by cetuximab, the investigators explained that one investigator has reported effective deletion of more than 95 percent of mouse T cells bearing EGFRt after daily cetuximab injection for six days. Recently, the investigators' colleagues observed up to 95 percent deletion of human CD19CAR-EGFRt T cells after daily cetuximab treatment for four consecutive days. The investigators reported that they have not tested the ablation ability of cetuximab on CD123 CAR-EGFRt T cells. All of this information will be disclosed to research participants who elect to have transferred T cells removed using cetuximab.

The primary use of cetuximab in this study is to explore its capacity to ablate EGFRt+ CAR T cells in the setting of an optional infusion prior to alloSCT. Research participants will proceed to alloSCT at or after 28 days post T-cell infusion. Participants who elect optional cetuximab prior to alloSCT will receive a single infusion of cetuximab. Researchers will analyze peripheral blood samples at baseline, within 24 hours, and at seven and 14 days after cetuximab for adverse events and EGFRt+ CAR T cells. The investigators agreed to revise the protocol and ICD to emphasize this plan.

The secondary use of cetuximab in this study is for managing toxicities such as prolonged neutropenia and if a lymphoproliferative disorder occurs from an infused, genetically modified T cell. The cetuximab dosing schedule for this use is modeled after the FDA-approved schedule for treating patients with head and neck cancer.

The investigators agreed to revise and update the ICD to reflect suggestions by the RAC reviewers, including simplifying or clarifying terms, descriptions of procedures, and sentence structure.

## **2. Responses to RAC Discussion Questions**

Regarding the lentiviral vector integration effects, Dr. Forman explained that the investigators are obliged to submit samples of their product for analysis. If they see persistence, they will conduct their own studies of clonality, T-cell receptor diversity, and proliferation to discern whether mutagenesis is occurring as a secondary malignancy. However, in the investigators' experience, mutagenesis has not been seen under these circumstances.

If the experimental treatment does not work and the leukemia is not in remission, Dr. Forman stated that the investigators would recommend proceeding directly to transplant via enrollment in one of the protocols at City of Hope specifically for that purpose. In the presence of persistent T cells and persistent disease, the investigators likely would eliminate the T cells with cetuximab, explaining to the subject that they want to be sure that the experimental T cells do not get in the way of the efficacy of another therapy. Dr. Forman said that he would take Dr. Atkins' suggestion—that the investigators should look at the cetuximab in patients who have residual T cells and residual leukemia before transplantation—to his colleagues for consideration.

Dr. Forman noted that it would only take three to six research participants to answer the question of whether the cetuximab can eliminate the CAR T cells. He was unsure whether the clinical situation would define the responses to cetuximab, because the T-cell binding the antibody would be true regardless of the clinical situation. However, he agreed to discuss this question with the statistician associated with this proposed protocol.

#### **E. Public Comment**

No comments from the public were offered.

#### **F. Synopsis of RAC Discussion and RAC Observations and Recommendations**

##### Clinical and Trial Design Issues

- The protocol proposes to use cetuximab to test whether the EGFRt can be used to eliminate the modified T cells. Research participants will be asked to undergo cetuximab infusion prior to alloSCT to test the ability of this system to ablate anti-CD123+ CAR T cells in vivo. It is not clear that there will be a clinical benefit to participants from the elimination of the T cells, especially since the T cells likely would be eliminated by the pre-transplant conditioning. However, most of the anticipated risks of such a procedure could be justified if the procedure will answer an important scientific question. Therefore, it is important to provide the scientific rationale and articulate, from a statistical perspective, how many participants would need to receive cetuximab to answer this question. Also, the investigators should consider whether this approach should be tested first in individuals who do not have a complete leukemic response, rather than in those who enter CR and can quickly proceed to transplant.

##### Ethical/Legal/Social Issues

- The ICD should more clearly emphasize to potential participants that this study is designed to be a bridge to allogeneic stem cell transplant and should not be considered as therapy in lieu of transplant.

#### **G. Committee Motion 2**

Dr. Kiem summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. Dr. Kiem moved and Dr. Ornelles seconded that the RAC vote on these summarized recommendations, which the RAC approved by a vote of 12 in favor, 0 opposed, 0 abstentions, and 3 recusals.

*(At this point, Dr. Kohn resumed chairing the March 2014 RAC meeting.)*

#### **IV. Review and Discussion of Human Gene Transfer Protocol #1401-1288: Phase I Study To Determine the Effects of Mesenchymal Stem Cells Secreting Interferon Beta in Patients with Advanced Ovarian Cancer**

Principal Investigator: Amanda Olson, M.D., University of Texas MD Anderson Cancer Center (MDACC)  
Additional Presenters: Michael Andreeff, M.D., Ph.D., MDACC; Frank Marini, Ph.D., MDACC (*via teleconference*); Ian K. McNiece, Ph.D., MDACC; Elizabeth J. Shpall, M.D., MDACC; Shannon Westin, M.D., M.P.H., MDACC; and Eric S. Yvon, Ph.D., MDACC  
RAC Reviewers: Drs. Kohn, Sarzotti-Kelsoe, and Zoloth

Drs. Atkins and Ornelles recused themselves from consideration of this protocol due to conflicts of interest.

## A. Protocol Summary

The goal of this study is to evaluate the safety and feasibility of administering mesenchymal progenitor cells (MSCs) transfected with a plasmid to express interferon beta (INF- $\beta$ ) in women with advanced refractory epithelial ovarian cancer. The MSCs will be genetically modified to secrete interferon, which may exert an anti-tumor effect. The MSCs will travel preferentially to sites of tumors and become tumor-associated fibroblasts.

The investigators have reported anti-tumor effects in breast and ovarian cancers and gliomas in preclinical studies. The genetically modified MSCs that secrete INF- $\beta$  at the tumor site should exert limited systemic toxicity and should decrease tumor progression. Therefore, the investigators hypothesize that donor-derived, genetically modified MSCs could engraft preferentially at tumor sites and promote anti-tumor effects via local production of INF- $\beta$ . The MSCs will be administered on an outpatient basis directly into the abdomen via a port placed in the abdomen for infusion. Three research participants will be administered escalating dose levels and will be monitored closely for adverse events.

## 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 use of genetically modified MSCs expressing INF- $\beta$ , a potent cytokine with the potential for systemic activity and toxicity.

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

Dr. Kohn asked the investigators to describe the EF1-HTLV mini promoter in the expression plasmid; to state whether the Amaxa electroporation device will be able to effectively treat  $7 \times 10^8$  cells in a single cycle or reasonable numbers of cycles (as proposed for the third dose level in a typical 70 kg research participant); and to present additional data on the amounts and time course of INF- $\beta$  expression produced from the specific MSC line to be electroporated with the specific expression plasmid. He noted that the dose level to be tested ( $1 \times 10^7$  cells/kg) is approximately one-fifth of the effective dose in the preclinical data, where mice were treated with approximately  $5 \times 10^7$  cells/kg. Dr. Kohn queried as to whether the potential immune responses to allogeneic MSCs, such as those that will be used in the proposed clinical trial, have been assessed to determine if they further limit the net amounts of INF- $\beta$  delivered to the tumor. With regard to informed consent issues, Dr. Kohn suggested that all implications of possible benefit to research participants should be reworded more realistically, risks such as intra-abdominal infection associated with the presence of the indwelling catheter over the course of four weeks should be stated more fully, and the ICD should state that an autopsy will be requested if the research participant dies.

Dr. Sarzotti-Kelsoe noted that the investigators used an adeno-associated vector in their preliminary animal studies to express INF- $\beta$  in MSCs, although they proposed in this protocol to use transient transfection of MSCs with plasmid DNA for INF- $\beta$ ; she asked for an explanation of how the two expression methods compared in terms of potency, safety, and biodistribution. She asked the investigators to discuss the rationale behind using the intraperitoneal (IP) route for the proposed protocol, noting that most of the preclinical and clinical trials listed in support of this protocol used intravenous (IV) injection of MSCs. Dr. Sarzotti-Kelsoe requested that the investigators provide the following information:

- How the MSCs are derived and cryopreserved, and the health screening tests that will be done on the donor of MSCs
- How the transfection efficiency is controlled for consistency before research participants' infusion of the MSCs and how the 50 percent efficiency rate is confirmed before each infusion
- The fate of the infused MSCs *in vivo*, how their persistence and potential toxicity would be tested, and whether these cells could be eliminated if they produce unwarranted effects
- Alternative therapies that exist at other cancer centers

- How the investigators intend to demonstrate that the plasmid DNA-transfected, infused MSCs will home to the ovarian cancer sites and not to other organs or normal cell sites with the potential to cause toxicity
- Details of the type of serum cytokines tested after the first two doses of MSCs
- How long the follow-up period will continue

Dr. Zoloth focused her review on ethical issues related to this proposed protocol. With regard to the ICD, she noted that it does not explain clearly why the participant is being asked to participate, and the standard form refers to 15-year follow-up and admonitions to avoid pregnancy, references that may not be appropriate for these critically ill women. Dr. Zoloth remarked that there is a reference in the protocol to an ombudsman at the Cancer Center who acts as an advocate in clinical trials, but this is not mentioned in the ICD. She suggested that the information that INF- $\beta$  infusions, when tried, only affected the blood chemistry and not the actual disease process should be explained clearly. Other suggested explanations or clarifications included the source of the cell (male) and why male cells are used. Regarding the process of home care, Dr. Zoloth asked the investigators to discuss the pros and cons of the proposed informal monitoring system in which the research participant is sent home after the infusion is delivered at the medical center, particularly in light of potential side effects. She asked whether the investigators assume that each participant will have a support system to provide post-infusion monitoring, and opined that no woman should be excluded from participation in this trial because she lives alone. She also noted that effective home care would be improved by including additional description and care of the required indwelling abdominal catheter. Noting that the MSCs are proposed to be administered into the peritoneum and the cells then are expected to home to the tumor, Dr. Zoloth requested that the investigators discuss whether the cells can migrate and engraft in other places and how this risk was contained in the animal model. She asked for explanation as to why the list of side effects includes "suicide" and how the MSCs would be monitored *in vivo*.

### C. RAC Discussion

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

- Dr. Hammarskjöld requested clarification about the duration of expression of the INF- $\beta$ . She suggested that other viral vectors might provide longer-term expression.
- Dr. Sadelain asked the investigators to discuss whether there have been multiple infusions of an allogeneic cell line (MSCs) to patients of any disease, in conjunction with an immunosuppressive regimen.
- Dr. Sarzotti-Kelsoe suggested that the investigators watch for the possibility that interferon could increase the expression of Class I molecules that would make MSCs more antigenic.
- Dr. Kohn suggested that the investigators could look for inflammatory cells, since they will be conducting biopsies at the end of the experimental treatment. Since a catheter will already be in place for each research participant, the investigators also could sample peritoneal fluids to look for inflammatory cells.
- Dr. Kiem asked about the persistence of the allogeneic MSCs in other tumors.

### D. Investigator Response

#### 1. Written Responses to RAC Reviews

The investigators reported that they have tested a number of promoters in MSCs and found the proposed composite promoter to be small, efficient, and constitutive in MSCs.

This protocol will use human platelet lysate (PLTMax®) in place of fetal calf serum for the expansion of the allogeneic MSCs. Platelet lysate will also be used during the generation of MSCs expressing IFN- $\beta$ .

Regarding the fact that the highest dose level to be tested in this protocol is approximately one-fifth of the effective dose reported in the preclinical data, the investigators explained that responses vary and

depend on many factors, including molecular features of the targeted tumor, biodistribution of injected MSCs, and their IFN- $\beta$  production kinetics. Not all of these factors can be modeled in mice, which is also a factor in proposing IP, rather than systemic, injection. If the investigators see tumor homing of MSCs and some evidence of anti-tumor activity, it will be possible to increase the dose of injected cells, hopefully without risking increased systemic toxicity. Depending on experimental conditions, responses have been seen at lower dose levels.

The investigators saw no evidence of immune rejection when they infused the human MSCs into the NSG mice. From cardiac studies, the investigators know that unmanipulated allogeneic MSCs were as effective as autologous MSCs at improving cardiac function.

The investigators stated that they have modified an existing institutional patient education resource to provide to participants in this trial. This document provides information on the definition of intraperitoneal therapy, placement of the catheter, and care of the catheter during the trial. In addition, participants will have individual consent in person by institutional repository collaborators, who will discuss the procedure fully. The information about risks has been expanded and modified to include the long-term risk of the indwelling catheter.

The investigators explained that their decision to use a plasmid-based delivery system was based on:

- Safety. The immunogenicity issues associated with adenovirus may have precluded second and third injections, or rendered them ineffective. They preferred not to use viral-based delivery due to the higher complexity of these systems in the clinical setting.
- Simplicity. This plasmid-based system is small, has robust expression of IFN- $\beta$ , and after electroporation generates excellent expression levels for three to seven days.
- Bioequivalence. Although adenoviral infection is more efficient in infecting MSCs, its high level expression of IFN- $\beta$  (up to 50,000 IU) could increase toxicity.
- Distribution. The investigators have found no differences in the systemic or IP distribution of MSCs transfected with either adenoviral delivery or electroporation with a plasmid. The cells still home to tumors, although IP injection was superior to systemic injection in ovarian cancers.

Regarding using the IP route, safety and efficacy were the primary considerations. With regard to safety, the delivery of MSCs systemically results in a first pass through the lungs that could introduce IFN- $\beta$  into lung tissue. Although human MSCs have been demonstrated to remain in lungs for up to three hours, the investigators did not want any cell loss due to trapping. With regard to efficacy, because this is an ovarian cancer trial, by performing IP injections, the MSC-IFN- $\beta$  would have the greatest amount of successful engraftment by having the highest concentration of cells in the peritoneum where the tumor is located. The preclinical animal data in which MSCs were injected IP further demonstrated the above two points: minimal-to-no distribution of MSCs outside the peritoneum and increased numbers of engrafted MSCs in the tumor tissue, as compared with systemic delivery in mouse models in which less than 10 percent of the injected cell population was detectable at the tumor site.

In preclinical studies, IFN- $\beta$  can be detected in cell culture supernatant of IFN- $\beta$ -transfected MSCs up to five days after transfection, indicating that live cells contain the IFN- $\beta$  plasmid. However, the investigators reported that they cannot confirm that the transfected cells are all viable. Because the electroporation method used to introduce the IFN- $\beta$  plasmid into the MSCs results in membrane permeability, which negates traditional methods for determination of viability, the investigators stated that they will culture an aliquot of the transfected cells overnight and assess the viability of the cells at that time point. Therefore, MSC viability will not be part of the release criteria. The transfection efficiency will not be controlled before research participants' infusion, because infusion will occur immediately after transfection. However, a fraction of the transfected cells will be kept in culture and supernatant collected after 24 hours for IFN- $\beta$  evaluation using ELISA assay and retrospective analysis.

In all animal models tested (mice, rats, and dogs), the investigators explained that the MSCs are found exclusively in the tumor. Their data demonstrated that other peritoneal organs do not have detectable MSCs. Whether MSCs last long term is unknown but biopsy will be conducted post-infusion and fluorescence *in situ* hybridization for Y chromosomes will be done to detect donor cells. As tumor size

decreases, the number of MSCs decreases in mouse models. There is not currently a way to eliminate these cells; the use of a suicide gene such as herpes simplex virus thymidine kinase is immunogenic and has been abandoned. Caspase constructs will be evaluated if needed. Steroids and immunosuppression will be given to any research participant experiencing grade 3 or grade 4 toxicity attributable to the experimental treatment.

Regarding alternative therapies for these patients, the National Comprehensive Cancer Network recommends participation in clinical trials. During the last ten years, the average new agent has achieved response rates of only 5 to 10 percent and progression-free survival averages two months; therefore, the need for novel therapies and mechanisms for therapy administration is paramount. Alternative therapies for this patient population include early-phase trials that do not place a limit on number of prior therapies. The number of these trials that are relevant to the ovarian cancer population typically range between zero and ten, and relevant trials may be available at other institutions. Potential participants will be made aware of other resources, including the National Cancer Institute's Clinical Trials Search Engine, to review their options.

In preliminary experiments, the investigators have seen no evidence of engraftment to normal organs. The investigators will conduct pre- and post-MSD infusion biopsies in which they will harvest tumor cells and then subject these cells to immunohistochemistry to detect MSC markers using fluorescence *in situ* hybridization.

In extensive testing in murine models, the investigators have not detected or seen any pathological consequences, even in their fully syngeneic system.

The investigators stated that cytokines will not be tested in this protocol.

With regard to testing for the possibility that interferon will increase the expression of Class I major histocompatibility complex (MHC) molecules on the tumor-associated fibroblasts, making them a more allogeneic target for T-cell-mediated responses, the investigators stated that they do not have this information but plan to evaluate the expression of Class I MHC molecules on the MSCs following electroporation with the IFN- $\beta$  construct.

Yearly safety evaluations will be conducted for 15 years for research participants who receive this experimental treatment. These individuals will be enrolled simultaneously on MDACC's Long Term Follow Up for Gene Therapy IRB #2006-0676 at time of enrollment, per the guidelines of the FDA Biologic Response Modifiers Advisory Committee.

The investigators reported that patient advocates are available to research participants; they generally serve as a liaison between the care team and the patient to bridge situations of concern. The investigators have added appropriate explanatory language to the ICD.

Given the minimal and limited side effects noted in millions of rheumatoid arthritis patients who receive interferon systemically and the thousands of patients who have been treated with MSCs for cardiac ischemia and graft-versus-host disease, the investigators explained that they do not expect the current participants to require additional monitoring beyond their institution's standard policies for Phase I trials. It is possible (but unlikely) that the genetically modified MSCs secreting IFN- $\beta$  will result in unexpected side effects. Instructions, which will be reiterated by the infusion center staff, state that the participant should report to the emergency center immediately if experiencing anything out of the ordinary.

The effects of IFN- $\beta$  are threefold: (1) it has direct cytotoxic effects on cells as it activates caspases; (2) it disrupts the cellular milieu by recruiting a number of immune cells that now recognize the tumor microenvironment as hostile; and (3) it modulates the local immune responses. The MSCs were not found in other organs in postmortem mouse specimens. As the tumor shrinks, the investigators have shown that the number of MSCs also decreases.

Suicide and depression have been reported as possible side effects of IFN- $\beta$ . Therefore, the investigators have included a collaborating psychiatrist in this protocol and have incorporated depression screening into this protocol to be administered as a screening for new symptoms weekly while participants are receiving the experimental treatment.

The MSCs have been shown to travel to sites of inflammation, which the investigators have documented in published papers. This possible result will be monitored by post-dosing biopsies.

The investigators agreed to revise and update the ICD to reflect suggestions by the RAC reviewers, including simplifying or clarifying terms.

## **2. Responses to RAC Discussion Questions**

Regarding duration of expression of the INF- $\beta$ , Dr. Andreeff explained that, after five days, 2,000 picograms are still present, which is approximately what is needed. The next dose is administered at one week. Although the investigators do not know what happens to the previous dose, they have seen low-level expression up to 14 days. Dr. Marini confirmed that five to seven days of expression occurs and then expression drops off, and added that shorter-term expression is safer and, the investigators believe, currently the best choice.

Dr. Shpall responded that the investigators have had experience with MSC infusion in graft-versus-host disease in which infusions were given twice weekly for four weeks with immunosuppressants, with continued responses in about 40 percent of the research participants. For example, MSCs were given once with cord blood expansions; those patients are also on prophylactic immunosuppression. Dr. McNiece added that in the cardiology setting, at the University of Miami, he and colleagues did a direct head-to-head comparison of autologous versus allogeneic MSCs; no difference in safety was seen, immunological tests showed no reaction, and results were published in *JAMA* in 2013. Dr. McNiece clarified that this comparison was only a single injection, and he further clarified that multiple infusions of allogeneic MSCs to non-immunocompromised recipients have not been done. Dr. Shpall added that multiple MSC infusions have been given for Crohn's disease where the patients were not on immunosuppression with preliminary positive results, multiple infusions have been given for peripheral vascular disease, and two or three infusions have been given in diabetics for wound healing in whom immunosuppression was not used and no untoward effects were seen. The investigators said they will watch carefully for any kind of cytokine storm.

Dr. Shpall said that the investigators' future preclinical studies will look at Class I molecules on the MSCs after electroporation.

Dr. Shpall agreed that, since the investigators will be doing biopsies at the end of the experimental treatment, they could look for inflammatory cells at that time. They also could sample peritoneal fluids to look for inflammatory cells since they will be draining fluids via the catheter.

Regarding persistence of allogeneic MSCs in other tumors, Dr. Andreeff explained that if there is no tumor, there is no MSC, because the MSCs need the tumor to survive; when the investigators have planted MSCs only, the MSCs do not proliferate and they die. Therefore, once a major anti-tumor response occurs, the survival factors for MSCs are withdrawn. Long-term information is not available; the investigators have sacrificed mice and found MSCs, but it is unknown what would happen after long periods of time and this research has not been conducted in humans.

## **E. Public Comment**

No comments from the public were offered.

## F. Synopsis of RAC Discussion and RAC Observations and Recommendations

### Preclinical Issue

- This protocol proposes the use of allogeneic cells from male donors, which will allow the MSCs to be tracked after administration; however, the survival of allogeneic cells may be limited due to immune-mediated elimination. If this approach shows promise, it may be appropriate to consider the use of autologous cells in order to avoid any potential immune responses. To advance the potential development of an autologous cell-based product, it would be helpful to conduct murine studies using autologous MSCs and compare the results in an allogeneic mouse model.

### Clinical and Trial Design Issues

- Any transfected MSCs that fail to express IFN- $\beta$  or stop producing IFN- $\beta$  after administration may have the potential to differentiate into tumor-supporting fibroblasts. In the planned tumor biopsies, it would be informative to look for evidence of tumor enhancement to evaluate for this effect.
- Although MSC administration has been studied in other research settings, including for cardiac disease, there is limited data regarding the effect of repeat infusions of allogeneic MSCs in immunocompetent research participants. It may be useful to monitor fluid samples from the peritoneal space for inflammatory markers or MSC-specific immune cells.
- The protocol should clarify the time that it will take from the introduction of the plasmids by electroporation to infusion. As written, it is not clear that this process will likely take 3 to 4 hours, as stated at the RAC meeting, especially when 70 independent electroporations will be done in parallel for the high-dose MSC infusions.

### Ethical/Legal/Social Issues

- Because the patients who are eligible for enrollment in this protocol have an incurable disease, it is important that research participants understand that this trial is not likely to provide direct benefit to them. The ICD should state clearly that this is a first-in-human trial in which the primary objective is to test safety and not efficacy.
- The ICD includes statements regarding protecting against pregnancy. Given that the treatment for this disease likely precludes pregnancy, these references seem unnecessary and possibly upsetting to potential research participants. Although the investigators' institutional review board (IRB) may require certain standard language, the RAC urges the investigators to discuss this issue with them in the context of this specific disease. The ICD also includes language regarding the requirement for long-term follow-up of at least 15 years, which may be misleading for research participants with a disease with such limited survival. First, it may be helpful to clarify with the regulatory authorities whether 15 year follow-up is actually required for MSCs transduced with a plasmid-based vector, because the most recent FDA Guidance indicates that not all gene-transfer products require 15-year follow-up (Guidance for Industry Gene Therapy Clinical Trials- Observing Subjects for Delayed Adverse Events: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>). Any statement about long-term follow-up should be clarified to explain why this language is included and that it is not indicative of the investigators' expectations regarding the potential efficacy of this approach.
- The table of potential infusion side effects in the revised ICD lists suicide and depression and these side effects are noted as being "based on studies of patients with immune/heart disease who have received normal MSCs by vein." If the psychiatric side effects listed are associated with IFN- $\beta$  and have not been observed in studies with non-genetically-modified MSCs, this should be clarified. In addition, given the relative rarity of this side effect with IFN- $\beta$  and the fact that delivery

will be by IP infusion, the risk of severe psychiatric side effects should be low. It would be helpful to provide potential participants more information about the likelihood of some of these risks and inform them that there will be active monitoring by an appropriate mental health professional.

### **G. Committee Motion 3**

Dr. Kohn summarized the RAC recommendations to be included in the letter to the investigators, expressing the RAC's comments and concerns. Dr. Kohn asked for a vote on these summarized recommendations, which the RAC approved by a vote of 13 in favor, 0 opposed, 0 abstentions, and 2 recusals.

### **V. Review and Discussion of Human Gene Transfer Protocol #1401-1289: Phase I/II Gene Transfer Clinical Trial of rAAV9.MCV.hNAGLU for Mucopolysaccharidosis (MPS) IIIB**

Principal Investigator:	Kevin M. Flanigan, M.D., The Research Institute at Nationwide Children's Hospital
Additional Presenters:	K. Reed Clark, Ph.D., Nationwide Children's Hospital; Haiyan Fu, M.D., Nationwide Children's Hospital; Doug McCarty, Ph.D., Nationwide Children's Hospital; Tim Miller, Ph.D., Abeona Therapeutics, Inc.
Sponsor	Abeona Therapeutics, Inc.
RAC Reviewers:	Drs. Atkins, Chatterjee, and Fost

#### **A. Protocol Summary**

The investigators propose a study to establish whether gene transfer in patients with mucopolysaccharidosis IIIB (MPS IIIB, also known as Sanfilippo syndrome) is safe and whether it can potentially improve the behavioral skills and intellectual ability and increase the survival rate in patients receiving a gene replacement therapy. In this condition, a build-up of glucosaminoglycans (GAGs) in the central nervous system (CNS) and other organs is directly related to the malfunction of the  $\alpha$ -N-acetylglucosaminidase (NAGLU) enzyme, resulting in dramatic loss of intellectual ability and a high rate of premature death. In this study, the defective NAGLU gene will be replaced with a functional gene carried by an adeno-associated virus (AAV). AAV is often found naturally in humans and is not known to cause any human disease.

Presently there is no treatment for MPS IIIB; only supportive care is currently possible.

Research participants with MPS IIIB will receive a single IV injection of the NAGLU gene. The participants will be evaluated at specified intervals and up to two years post-injection. The primary outcome for this clinical trial is safety, and participants will be monitored carefully for any side effects of the experimental treatment. Motor function and intellectual ability will be assessed throughout the study. Cerebrospinal fluid (CSF) markers of inflammation and enzyme activity will be assessed at baseline, one month, six months, and one year. Blood and urine tests as well as physical examination will be conducted during the screening visits and on days 0, 1, 2, and 7, and then at 1, 3, 6, 12, 18, and 24 months following the injection for a total of two years to ensure there are no side effects from the gene injections.

#### **B. Written Reviews by RAC Members**

Twelve RAC members voted for in-depth review and public discussion of the protocol. Key issues included the first systemic IV administration of AAV9 in children. The safety of administering relatively high doses of the vector (up to  $5 \times 10^{13}$  viral genomes[vg]/kg) to children was deemed to deserve further discussion. In addition, given that many children with this disease are expected to survive into young adulthood, the risks and benefits of this approach for children as young as two years, with respect to the durability of expression and vector persistence, was determined to deserve further discussion.

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

Dr. Atkins noted that this well-designed study would attempt to treat a devastating and untreatable genetic illness that is the consequence of the absence of function of a single gene. The efficacy of the preliminary animal model data using the same vector is compelling and showed no toxicity. This vector has been used previously in humans and has proven to be tolerable and to cross the blood-brain barrier. He asked the investigators to discuss the variability of NAGLU levels in the CSF over time in a particular patient, noting that if the level is detectable and varies over time, it is possible that changes on a given CSF specimen relative to baseline might be difficult to interpret. Dr. Atkins suggested that repeat baseline levels might need to be obtained, and more than one follow-up CSF sample within the first six months also might need to be obtained.

Dr. Chatterjee requested that the investigators comment on the justification of the two doses chosen for this study, noting some concern about the high doses of AAV9 that would be administered systemically to potentially very young subjects. She noted that the mice appeared to perform as well or better at the lower dose as compared with the higher dose in two key tests, and differences in survival were not marked. Dr. Chatterjee expressed concern about the overall durability of the experimental treatment and vector persistence. She noted that reductions in NAGLU levels were observed at 12 months post-infusion in the mouse and asked whether long-term studies looking at durability of transduction had been done in nonhuman primates and what the implications would be for treatment durability in humans. In addition, if there is loss of NAGLU later in life, she asked whether disease pathology would be attenuated due to correction of the defect during early development. Dr. Chatterjee asked the investigators to discuss what is known about the long-term levels of NAGLU expression required for a cure, whether overexpression of NAGLU is harmful particularly because supraphysiologic levels were observed in some cases, and whether the immune responses seen against NAGLU in nonhuman primates precipitated autoimmune responses. She stated that it would be important for precautions to be in place to avoid inadvertent transduction of caregivers. Although AAV is non-pathogenic and has an excellent safety record, the use of high doses of vector, particularly in young research participants, could lead to shedding and possible bystander transduction.

Noting that four lumbar punctures (LPs) are planned (at baseline, one month, six months, and 12 months) to assess for enzyme levels and signs of an inflammatory response, Dr. Fost asked the investigators to clarify the scientific rationale for the six-month LP and to explain what would be learned from that LP that could not be gleaned from the others. With regard to the Data Safety Monitoring Board (DSMB), he requested that the investigators consider including someone experienced in clinical ethics, preferably research ethics. Regarding the ICD, Dr. Fost offered several observations:

- The introduction uses the term “treatment,” which should generally be avoided in Phase I studies as it suggests a known benefit; he suggested substituting more accurate descriptive terms, because clinical benefit is unknown and unlikely.
- At several other points in the ICD, language indicates more knowledge and optimism for this approach in humans than is warranted; wording should be altered appropriately.
- The investigators should clarify whether anesthesia will be used for the LPs planned for days 7 and 30 (visits 3 and 4).
- The list of people authorized to use, disclose, and receive identifiable protected health information (PHI) is overly inclusive.
- Regarding the use of samples and data for research, a third choice should be added that would offer the participants (or their representatives) the option of asking that they be informed of specific future research studies as they arise, so they can decide at that time whether or not to participate.

### **C. RAC Discussion**

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

- Dr. Hammarskjöld asked about the potential for integration with AAV9, and suggested that the investigators look at that, since they will already have DNA.

- Noting that the total planned enrollment for this protocol is six, with participants between the ages of two and ten years, Dr. Hammarskjöld expressed concern about the differences among children in that age range and how those differences might affect evaluation of a safe dose.
- Regarding the need for the six-month LP, Dr. Atkins asked, if there were high NAGLU levels in the CSF at one month and NAGLU was absent at 12 months, whether the investigators would consider administering repeat dosing in the future and whether they would use an intermediate value to help decide the time interval for repeat dosing.
- In order not to promote unrealistic hope among the parents of these children, Ms. Dresser suggested adding wording to the ICD that says, “It is unusual for participants in an early safety study like this to benefit.”
- Dr. Zoloth commented that the introduction to the ICD is particularly clear and well written.
- Dr. Chatterjee asked about the frequency of the disease and how difficult it would be for the investigators to accrue six participants.
- Dr. Zoloth asked the investigators to explain why they have set the minimum age for inclusion at two years.
- Dr. Kohn suggested monitoring liver function and other potential signs of an immune response to virus-containing cells more frequently in the early months of this protocol.
- Dr. Kohn asked about the status of newborn screening for this disease and other MPS diseases, noting that newborn screening for severe combined immunodeficiency disease has been instituted in the last few years on a state-by-state basis.

## D. Investigator Response

### 1. Written Responses to RAC Reviews

The investigators explained that the variability in CSF NAGLU levels over time in individual patients is unknown. Establishing this variability is one of the goals of the investigators’ ongoing natural history study, in which they will enroll 15 MPS IIIB patients. Each participant in the natural history study will undergo two LPs, at enrollment and 12 months later, that will provide intra- and inter-participant data allowing assessment of stability during that year.

Regarding the question of whether more than one baseline NAGLU level needs to be obtained, the investigators explained that they do not believe that multiple pre-treatment LPs are justified. It is mechanistically unlikely that significant changes in enzyme activity would occur, given that most mutations result in nearly absent enzyme function. Data from the nonhuman primate studies demonstrated that CSF NAGLU rises by fold-change amounts in response to therapy, and variations in baseline CSF levels, if present, would be minor. Additional LPs prior to gene transfer would add additional risk without providing additional benefit.

As to whether more than one followup CSF sample should be obtained within the first 6 months, the investigators noted that they plan to obtain LPs at day 30, in addition to six months and 12 months, in order to assess safety (including CSF cell count, protein, and opening pressure) and NAGLU expression.

The investigators explained that a majority of MPS IIIB patients die in their teens, and few will survive to their third decade. No specific treatment is currently available for this devastating disease. Their choice of proposed doses was influenced by two major factors. Preclinical data in MPS IIIB mice demonstrate that  $2 \times 10^{13}$  vg/kg is the minimum effective dose in animals at four to six months of age, which is the age at which cognitive defects in the mouse model become measurable. Because the majority of MPS IIIB patients are clinically diagnosed based on cognitive deficiencies, the investigators explained that they believe that these older mice are a better model of the clinical scenario, and they anticipate that a similar dose will be required for a significant therapeutic benefit in humans. Considering the severity of the disease outcome and the size of the patient population, a sub-therapeutic dose cohort could not be justified. The high dose of  $5 \times 10^{13}$  vg/kg is essential to the exploration of a dose range, which is intrinsic to a Phase I/II clinical trial. The preclinical data in nonhuman primates supports the safety of vector delivery at this dose.

As in other lysosomal enzyme–related diseases and disease models, NAGLU levels in heterozygotes are much lower than in wildtype (approximately half), though there is no difference in GAG levels between heterozygotes and wildtype. Not all cells in the CNS will be expressing the recombinant enzyme, and the majority will be corrected through the bystander effects of secreted enzyme. Thus, the overall expression levels of NAGLU may not accurately reflect the available enzyme for the majority of cells. The investigators explained that the doses proposed are based on their empirical data in mice showing that  $2 \times 10^{13}$  vg/kg is the minimal effective dose at the targeted stages of disease progression.

The vector is persistent in the majority of non-dividing tissues, including the brain, until the endpoint of the studies in mice (16.1 to 27.2 months). The durability of the experimental treatment in humans is unclear because no such information is currently available, but the investigators noted the persistence of vector genomes and NAGLU expression in nonhuman primates at the longest observation point of six months. The highest levels of enzyme expression may be needed immediately upon dosing to clear accumulated GAG, and lower levels could suffice at later times to maintain clearance. Based on the preclinical data, the investigators expect to maintain correction of disease pathology at later time points. The implication of late loss of NAGLU expression in all tissues is unknown. If that were to happen, the investigators speculated that disease pathology would probably re-occur, although this result is uncertain because it is not known whether these specific GAGs accumulate at constant rates throughout life.

Regarding the long-term levels of NAGLU expression required for a cure, the investigators stated that they can infer from heterozygote data that levels of approximately one-third to one-half of wildtype levels are completely protective. However, levels of restored enzyme expression may not exactly correlate with the clinical effects of lifelong low-level expression. All FDA-approved recombinant enzyme replacement therapies require weekly or biweekly infusion, which results in very high peak enzyme levels (greatly exceeding normal circulating levels) that decline rapidly following infusion. It is difficult to make an analogy to the proposed gene transfer in which enzyme levels may decline slowly over years.

The investigators reported that they found no evidence that overexpression of NAGLU is harmful. They did not observe any adverse events in their preclinical studies in either MPS IIIB mice or in nonhuman primates, both of which expressed supraphysiologic levels. Weekly and monthly hematology and blood chemistry studies in nonhuman primates did not show abnormal responses to treatment for up to six months, and histopathology did not show any treatment-related abnormalities. This safety profile is bolstered by data from enzyme replacement therapies in similar lysosomal storage diseases in which peak enzyme levels may be thousands of times above normal without adverse consequences.

Although an antibody response to human NAGLU in nonhuman primates was demonstrated, there was no evidence of autoimmune pathology in any tissues examined up to six months post-injection. Furthermore, MPS IIIB mice—which are null for NAGLU—did not show evidence of immune-mediated clearance of transduced cells over two years, despite demonstrating an antibody response. Although the investigators believe that an autoimmune response is unlikely, dosed participants will be monitored for development of NAGLU and recombinant AAV9 cytotoxic T-lymphocytes, as well as for signs and symptoms of autoimmune reactions.

Regarding inadvertent transduction of caregivers, the investigators explained that in mice, AAV9 persists in the blood for longer than most AAV serotypes, with a half-life in circulation of approximately four hours during the first ten hours post-injection, and approximately ten hours during the next three days post-injection. If this result is similar in humans, the investigators expect to go through approximately nine or ten half-lives of vector in circulation in three days, during which time the research participants can be maintained in the hospital under contact precautions. No information is currently available regarding human bystander transduction by vector shedding.

This Phase I trial will assess safety. The LP at six months is required to monitor for signs of CNS inflammation or immune response. The six-month LP will provide an additional data point for CSF NAGLU enzyme activity and GAG levels between early (one month) and late (12 month) assessments.

The investigators explained that they intend to include individuals with experience in clinical research and clinical trials on the DSMB. However, they will rely on their IRB to provide a review of the clinical and research ethics related to the study. At least one member of their IRB is an ethicist who participates in full committee reviews, and the IRB receives all DSMB reports and correspondence with the DSMB as part of their ongoing review of the study.

Many MPS IIIB patients exhibit impulsive behaviors that will prevent LPs being performed under local anesthetic alone. Therefore, the investigators will perform all LPs using sedation delivered under the care of anesthesiologists, who will determine the appropriate level of sedation for each individual. Based on experience to date in their ongoing natural history study, this sedation may consist of minimal IV propofol.

Although the need for any of the listed institutions to receive identifiable PHI is rare and typically not necessary, the language used in the ICD is required by the investigators' institution's IRB as part of their hospital's policy for when such a rare event occurs and PHI is required to be released to a governing party. Such event includes any possible audits or possible reporting of serious life-threatening events. The IRB policy is to cover the rare situations in which such an event could arise.

The investigators explained that it will be impractical to re-consent patients for each potential future study for which their de-identified samples might be used, and therefore declined to add a third choice regarding the use of samples and data for future research.

The investigators agreed to amend and update the ICD to reflect suggestions by the RAC reviewers.

## **2. Responses to RAC Discussion Questions**

With regard to the potential for integration, Dr. McCarty explained that AAV9 is as likely to integrate as any other AAV vector, and the investigators have no reason to believe that integration in this population would be different than any other. In the mouse model, several MPS IIIB animals had tumors but the same type of tumors were seen in the wildtype untreated animals; those tumors were checked for integrated genomes and were found to be negative. Because the greatest concern would be in the liver, the investigators plan to evaluate the livers using MRI at several timepoints after injection; there is no way to access the liver directly to test for vector integration.

Dr. Flanigan explained that the investigators believe that the natural history data will help guide the usefulness of the measurable outcomes across a range of ages. The investigators intend to keep in mind the possibility of safety outcome differences related to administering the proposed vector to a two-year-old compared with a ten-year-old.

Dr. Flanigan averred that any AAV repeat dosing is a challenge due to antibody responses generated from the initial dosing. Researchers from Nationwide Children's Hospital have shown that there is a route to re-dosing for AAV-mediated therapies in humans. However, if the outcome is one month with high expression and 12 months with no or low expression and no interim data is collected, that two-point data does not provide a curve and the investigators would like to collect more information than just two data points from this cohort of subjects.

Dr. Flanigan responded that the frequency of the disease is approximately 0.5 cases per 100,000 population. He stated that the investigators believe it will not be difficult to accrue six participants for the timeframe proposed for this trial.

Regarding the two-year-old minimum age for trial participation, Dr. Flanigan explained that diagnosis is generally made by the age of two when the loss of motor functions usually begins.

Dr. Flanigan reported that screening for MPS diseases is not done at birth but is done by clinicians at the time of symptom presentation. Dr. Fu added that some international groups are trying to make newborn screening available for MPS disorders. However, many clinicians believe there is no point to conduct newborn screening because no therapy is currently available.

## E. Public Comment

Four public comments were offered in support of this clinical trial. Comments presented by the following individuals are provided verbatim in Appendix A:

- Sue and Brad Wilson, Children's Medical Research Foundation
- Elizabeth and Randall Linton, San Filippo Children's Research Foundation, Canada
- Cara and Glenn O'Neill, Cure Sanfilippo Foundation
- Stuart and Jennifer Siedman, Sanfilippo Research Foundation

## F. Synopsis of RAC Discussion and RAC Observations and Recommendations

### Clinical and Trial Design Issues

- This protocol states that successful gene transfer will be demonstrated by human NAGLU expression in the CSF, and this will be used as a criterion, along with safety, to expand enrollment into the highest dose cohort. Although the investigators suspect that most participants will have limited, if any, hNAGLU production in the CSF, it is not yet known whether there could be variability in the levels of hNAGLU in the CSF. Since the decision to move forward will be based on the results from the first six participants, it may be important to consider whether this sample size can provide an accurate signal of safety and efficacy as defined by hNAGLU expression in the CSF. The investigators will only be able to assess reliably the safety of inducing hNAGLU expression in the CNS if they can verify that there actually is gene expression in the CSF, as demonstrated by an increase in hNAGLU levels compared with baseline. If there is significant variability in levels of hNAGLU in the CSF over time, such assessment of safety and efficacy will be challenging. The RAC suggests considering whether it is feasible to primarily enroll patients with close to undetectable levels of hNAGLU in the CSF so that it will be possible to verify that the gene transfer results in expression of hNAGLU in the CSF. The proposed natural history study may inform this question.
- In previous trials using AAV in hemophilia, immune responses to the vector in the liver were detected by a rise in liver enzymes that sometimes occurred from 5 to 8 weeks after dosing. These trials have used steroids to address this complication with continued transgene expression. Because the investigators propose to perform blood tests at 1 month and 3 months after the intervention, such a reaction could be missed if it occurs between 4 and 12 weeks afterward. Although the proposed AAV vector is a different serotype than that used in the hemophilia trial, the investigators should consider adding liver enzyme blood tests at more frequent intervals.

### Ethical/Legal/Social Issues

- The ICD addresses, and the clinical protocol offers, two options to participants regarding the use of their samples for future research studies: (1) to allow samples to be stored and used for research purposes in the future, or (2) to refuse to allow the samples to be stored and used. A third option to consider is to offer participants the alternative of having their samples stored in an identifiable manner and to be contacted so that they may decide whether to give specific consent for studies on these samples.
- The investigators have put together an impressive preclinical package and the RAC shares their hope that this approach will offer benefit to these children; however, it is an unfortunate reality that most Phase I studies do not lead to an efficacious therapy. To minimize the risk of overpromising the potential of this first-in-human trial, the investigators should consider revising the benefit section to state, "it is unusual for participants in an early safety study to benefit."

## G. Committee Motion 4

Dr. Kohn summarized the RAC recommendations to be included in the letter to the investigators, expressing the RAC's comments and concerns. Dr. Kohn asked for a vote on these summarized recommendations, which the RAC approved by a vote of 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

## VI. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Atkins, Curry, Kiem, Kohn, Pilewski, Sadelain, Strome, and Whitley

### A. GTSAB Report

Dr. Kohn presented the GTSAB report for the first quarter of 2014. Within the past three months, the OBA received 15 protocol submissions, 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 aromatic L-amino acid deficiency. In these 12 protocols, six used retroviruses, two used plasmids, two used lentiviruses, one used AAV, and one used pox virus. (Information about these trials was made available on the OBA website after this RAC meeting.)

The GTSAB reviewed initial and follow-up reports on 14 serious adverse events from eight protocols. After analyzing these events, the GTSAB concluded that none warranted public discussion at this RAC meeting.

During this quarter, the OBA received notification from investigators that 12 protocols were newly open to enrollment, five of which had been reviewed publicly by the RAC. One protocol had previously submitted responses to the issues raised and Dr. Kohn reviewed the responses of the other four protocols:

- OBA Protocol #827, reviewed by the RAC in March 2007: Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa (RDEB)
- OBA Protocol #1073, reviewed by the RAC in December 2010: An Open Label, Non-Randomized, Single Dose, Multi-Center Phase 2/3 Study of the Safety and Efficacy of Lenti-D Modified Autologous Stem Cells for the Treatment of Subjects with Childhood Cerebral Adrenoleukodystrophy
- OBA Protocol #1130, reviewed by the RAC in December 2011: An Adaptive Phase I/II Study of the Safety of CD4+ T Lymphocytes and CD34+ Hematopoietic Stem/Progenitor Cells Transduced with CAL-1, a Dual Anti-HIV Gene Transfer Construct, in Busulfan Conditioned HIV-Infected Adults Previously Exposed to ART
- OBA Protocol #1164, reviewed by the RAC in June 2012: A Phase 1/2, Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects with  $\beta$ -Thalassemia Major by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral  $\beta$ A-T87Q-Globin Vector

Dr. Kohn discussed a recent publication from OBA protocol #843, in the *New England Journal of Medicine*, titled "Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV." Twelve research participants received Zinc Finger Nuclease-modified autologous T cells, and six participants initiated a 12-week treatment interruption that was completed by four of the six participants. The modified T cells had an estimated mean half-life of 48 weeks and, during treatment interruption and the resultant viremia, the decline in the median number of circulating *CCR5*-modified T cells was significantly less than the decline in unmodified cells. The conclusion was the *CCR5*-modified autologous CD4 T-cell infusions are safe within the limits of this study.

Dr. Kohn announced a RAC workshop to be held on June 10, 2014, in Bethesda, Maryland, titled "Genomic Editing: Establishing Preclinical Toxicology Standards." This workshop will focus on the various genomic editing techniques (zinc finger nucleases, transcription activator-like effector nucleases,

meganucleases, and clustered regulatory interspaced short palindromic repeats (CRISPR)) and the development of preclinical assays to advance these promising technologies into the clinic.

**B. RAC Discussion**

No discussion occurred.

**C. Public Comment**

No public comments were offered.

**VII. Closing Remarks and Adjournment**

Dr. Kohn thanked the RAC members and the OBA staff and adjourned the March 2014 RAC meeting at 3:20 p.m. on March 12, 2014.

*(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: \_\_\_\_\_

\_\_\_\_\_  
Donald B. Kohn, M.D.  
Chair, Recombinant DNA Advisory Committee

**Attachment I:  
Recombinant DNA Advisory Committee Roster**

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#### **LIAISON REPRESENTATIVE**

**FAYL**, Gilbert, Ph.D.  
Secretary of External Affairs  
European Academy of Sciences and Arts  
Brussels, Belgium

**Attachment II:  
Public Attendees**

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*(This list includes only individuals who are not identified elsewhere in this document. It does not include two individuals whose names were illegible on the sign-in sheets.)*

P.J. Brooks, Office of Rare Disease Research, NIH  
Kathleen Buckley, Team Sanfilippo  
Nancy DiFranzo, National Heart, Lung, and Blood Institute, NIH  
Sharon Harris, NIH  
Carl S. Kapes, Team Sanfilippo  
William Merritt, National Cancer Institute, NIH  
Jenny Meshulam, Team Sanfilippo  
Karen Ross  
Patty Taormo, Team Sanfilippo  
Rachel Witt, FDA

### Attachment III: Abbreviations and Acronyms

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AAV	adeno-associated virus
alloSCT	allogeneic stem-cell transplantation
AML	acute myeloid leukemia
CAR	chimeric antigen receptor
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CSF	cerebrospinal fluid
DSMB	data safety monitoring board
EGFRt	truncated human epidermal growth factor
FDA	Food and Drug Administration, HHS
GAGs	glucosaminoglycans
GTSAB	Gene Transfer Safety Assessment Board
ICD	informed consent document
INF- $\beta$	interferon beta
IP	intraperitoneal
IRB	institutional review board
IV	intravenous
LP	lumbar puncture
MDACC	University of Texas MD Anderson Cancer Center
MHC	major histocompatibility complex
MPS	mucopolysaccharidosis
MSCs	mesenchymal progenitor cells
NAGLU	$\alpha$ -N-acetylglucosaminidase
NIH	National Institutes of Health
<i>NIH Guidelines</i>	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>
NK	natural killer
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PHI	protected health information
RAC	Recombinant DNA Advisory Committee
Treg	regulatory T cells
vg	viral genomes

**Appendix A:  
Public Comments on Human Gene Transfer Protocol #1401-1289:  
Phase I/II Gene Transfer Clinical Trial of rAAV9.MCV.hNAGLU for  
Mucopolysaccharidosis (MPS) IIIB**

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*[This testimony is provided verbatim, as reported in the transcript of the March 2014 RAC meeting.]*

**Testimony of Sue and Brad Wilson**

Hello. Our names are Sue and Brad Wilson. We're from Western Springs, Illinois. We represent the Children's Medical Research Foundation and our daughter, Kirby Wilson, afflicted with Sanfilippo.

A telephone call changed our lives. After giving me the devastating diagnosis on Kirby, I was told by our doctor that nothing could be done. We should enjoy her while we have her. She's the same little girl she was yesterday. And the person we were told to call, representing a support group, told us doctors didn't care. Buy a cage to contain her. We chose to challenge that doctor and that person, challenge our daughter's fate, form a foundation which was the first of its kind for Sanfilippo, and raise funds for science, a cure for Kirby.

And no, Kirby was not the same little girl she was yesterday. She was our almost four-year-old daughter that was about to define fortitude and show us what facing adversities with grace is all about. So with her little hand in ours, we set out on our journey, our hearts filled with hope for her future.

Since that time, almost 19 years ago to the day, we've devoted our lives to providing Kirby with the best opportunities possible. Our focus has always been her abilities, not her disabilities. Kirby's mission was song, dance, and happiness—happiness for all around her. Her smile was infectious and she asked just one thing of others "Happy? Mommy, happy? Kirby's happy." Her words, now lost, will live in our hearts forever.

Her message to find happiness in each day is something we strive to live by. Without words, she still speaks volumes. Our foundation has granted over \$3.7 million towards a cure. In 1997, it was our good fortune to meet Dr. Haiyan Fu and fund the initiation of this work.

Today, Brad and I stand before you, not to ask you to solve our problems or take away our daughter's pain. We're simply asking you to allow Nationwide to take this work to trial and to see it through to a successful conclusion. Hope will not keep our daughter and others like her alive. A therapy will.

You spoke today of risk to patients. I think all of our children inflicted with this devastating disease are indisputable proof of what doing nothing is, and we thank you very much for your consideration.

**Testimony of Elisabeth and Randall Linton**

Good afternoon, and thank you very much for allowing us to be here to share with you today. My name's Elisabeth Linton. My husband and I, Randall, have traveled from Toronto, Canada, to share our story about our life with our daughter, Elisa, and our passion for finding a treatment for Sanfilippo syndrome.

Almost 16 years ago, our youngest daughter, Elisa, was diagnosed with Sanfilippo syndrome at the age of four. She was a bright, vibrant, young girl, full of life and potential and full of dreams. Doctors at the Toronto Hospital for Sick Children told us of Elisa's fate. They told us to take her home and enjoy her every day, because there is no treatment to stop her progression, there is nothing to treat her symptoms, because there is no research in Canada, very little happening in the world, and that was because there was no money for research.

Soon after that, we connected with Brad and Sue Wilson, who just spoke. They inspired us with what they were doing in the United States by starting a foundation to raise awareness. We went back to Canada and we started a charity called the Sanfilippo Children's Research Foundation back in Canada.

So with faith and determination we have committed ourselves and everything about us to doing everything we could do to save our dear daughter, Elisa, and change the fate for other families with children diagnosed with Sanfilippo syndrome and change the state of research in this world.

I left my career and I started this foundation with my husband, and have dedicated my life for the last 15 years to raising funds to support research, out of the basement of our home, at the same time as caring for Elisa's ever-changing needs and raising our two other children to adulthood.

We are a true grassroots charity in Canada, the only one in Canada supporting research in the world. The SCRF is run solely by volunteer efforts, where 96 cents of every dollar raised has been committed to research. We have raised almost \$5 million to date.

This may not seem a lot in the scheme of research, and the cost and the money that goes into it, but I mention this only because it has supported 32 research projects around the world, and over 1 million of these dollars has been committed to supporting the research efforts of the amazing team of doctors at Nationwide Children's Hospital, because their work shows the most promise of moving closer to a treatment, we trust, in Elisa's lifetime.

It shows more promise than any other research project that we have been involved with globally. What a legacy her life is going to leave. Raising funds does not come easy at all. It has meant many sacrifices for our family and many involved with us.

It has involved a lot of prayers, blood, sweat, and tears over the years. We're not a large national charity at all, or a pharmaceutical company with a lot of funds to contribute. We're just a family with an amazing community of people around us who are determined and committed to making a difference in this world, to finding a treatment for Sanfilippo syndrome, moving research forward, so our children who are afflicted with this horrific disease will have a future, especially those that are yet to be born.

Over recent years a number of family foundations and fundraising efforts have been born in the U.S. and around the world because of the hope that has blossomed from the research efforts at Nationwide Children's Hospital, and a few of these families are represented here today.

We have dedicated our lives to getting research to the point that it's at today. We are asking you now to help us with this vital research in allowing it to continue to move forward from here, to the next level, with a decision to allow these gene therapy clinical trials to happen. We see promise, we see potential, and we see hope in the work that is presented at Nationwide.

Your decision today will not only impact the lives of Sanfilippo children and their families in the U.S., but those around the world, including our daughter, Elisa. We thank you in advance for working with us today, because tomorrow may be too late for our children. Thank you for your time.

#### **Testimony of Cara O'Neill**

Hello, and thank you for allowing me to speak here today. My name is Cara O'Neill. I've been a practicing pediatrician for the past 10 years. I'm an Assistant Professor at the University of South Carolina, where I care for children with special health care needs. I'm also Mom to my beautiful daughter, Eliza, who's four years old. She was just diagnosed this past July with Sanfilippo syndrome.

I want to speak very briefly on the unique risks that Sanfilippo families tolerate when looking at clinical trials, and specifically with this proposed clinical trial.

First, let me say that as parents we would not put our children in a situation to assume risks that are greater than the potential direct benefit offered by a treatment, simply because their condition is terminal. However, it cannot be ignored that our children do have a fatal disease with no available treatments.

It is also necessary to consider the rapidly progressive and disabling course of this disease when weighing how much preclinical data is enough data. Critical activities of daily living such as speech, mobility, and swallowing, can be lost in as short as a three- to six-month timespan.

As a community, we have educated ourselves on the science at hand. We accept the risks inherent in this gene therapy protocol. These risks are far outweighed by the possibility and potential of direct benefit to Sanfilippo children. The science is ready, the families are ready, and these children deserve a chance at life.

Thank you so much.

#### **Testimony of Stuart and Jennifer Siedman**

Thank you for letting us participate today. My name is Stuart Siedman. My wife, Jennifer, is here with me. We represent the Sanfilippo Research Foundation and our son, Benjamin. Benjamin, unlike many other children, was diagnosed at 18 months of age. In a week's time, our family will celebrate his 18th birthday.

Five weeks ago, Benjamin left us. He's not going to be here to celebrate.

In that intervening period, we watched him lose skills, mobility, speech, and cognitive capacity, but never the joy, the laughter, and the inspiration he brought our life. Also during that intervening time, we funded Dr. Fu and Dr. McCarty's research for over a decade. Our scientific advisory board reviewed many proposals of many other protocols. This is one that we continued to fund over that time.

It became apparent in Ben's life that there was a period where he would not benefit from this work, even if it went forward and were successful, but we still were here, we still continued our efforts. Benjamin is not with us. We're still here and we still continue our efforts, and we believe that it's an inspiration from our children, all of our children, and the children that are yet to be diagnosed, and Benjamin's brother and sister

who are carriers and need to think about their future, that this research be continued and allowed to move forward. Thank you for your time.