RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 8, 2011

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

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[Note: The latest Human Gene Transfer Protocol List can be found at the Office of Biotechnology Activities' 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[1]

March 8, 2011

The Recombinant DNA Advisory Committee (RAC) was convened for its 124th meeting at 11:00 a.m. on March 8, 2011, at the Marriott Suites Hotel in Bethesda, Maryland. Dr. John Zaia (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 11:00 a.m. until 3:00 p.m. on March 8. The following individuals were present for all or part of the March 2011 RAC meeting.

Committee Members

Andrew D. Badley, Mayo Clinic and Foundation
Jeffrey S. Bartlett, Nationwide Children's Hospital/Ohio State University
Michael J. Buchmeier, University of California, Irvine *(via teleconference)*
E. Antonio Chiocca, Ohio State University Medical Center
Hung Y. Fan, University of California, Irvine
Yuman Fong, Memorial Sloan-Kettering Cancer Center
Norman Fost, University of Wisconsin–Madison *(via teleconference)*
Jeffrey P. Kahn, University of Minnesota
Joseph A. Kanabrocki, University of Chicago
Walter J. Koch, Thomas Jefferson University
Margaret S. Mallino, University Park, Maryland
David A. Ornelles, Wake Forest University School of Medicine
Bernard Roizman, The University of Chicago *(via teleconference)*
Susan R. Ross, University of Pennsylvania
Marcella Sarzotti-Kelsoe, Duke University Medical Center *(via teleconference)*
Marshall Strome, St. Luke's–Roosevelt Hospital Center/New York Head & Neck Institute
James R. Yankaskas, University of North Carolina at Chapel Hill
John A. Zaia, City of Hope (RAC Chair)

Office of Biotechnology Activities (OBA)

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

Additional Speakers

Scott J. Antonia, University of South Florida *(via teleconference)*
Soraya Bekkali, Sanofi-Aventis
Mark Creager, Brigham and Women's Hospital
Caroline DeSurmont-Ruchaud, Sanofi-Aventis
Jhanelle Gray, Moffitt Cancer Center and Research Institute
Joanna Haas, Genzyme Corporation
William R. Hiatt, University of Colorado School of Medicine *(via teleconference)*
William E. Janssen, Moffitt Cancer Center and Research Institute *(via teleconference)*
Pablo Tebas, University of Pennsylvania
James Streisand, Genzyme Corporation
Lee-Jen Wei, Harvard University *(via teleconference)*

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

Non-voting Agency Representatives

Lisa A. Rooney, Office for Human Research Protections, U.S. Department of Health and Human Services (DHHS)

NIH/OD/OBA Staff Members

Chezelle L. George
Linda Gargiulo
Robert Jambou
Maureen Montgomery
Marina O'Reilly
Gene Rosenthal
Thomas Y. Shih

Attendees

There were 16 attendees at this 1-day RAC meeting.

Attachments

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

I. Call to Order and Opening Remarks

Dr. Zaia, RAC Chair, called the meeting to order at 11:00 a.m. on March 8, 2011. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on February 9, 2011 (76 FR 7224). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of the RAC), public review and discussion of one gene transfer protocol, and updates on two previously reviewed clinical trials that have now been completed.

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

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

II. Minutes of the December 2010 RAC Meeting

RAC Reviewers: Drs. Sarzotti-Kelsoe and Yankaskas

Dr. Sarzotti-Kelsoe stated that she and Dr. Yankaskas had reviewed the minutes document in detail and found that the document accurately recorded the details of the December 7-8, 2010, RAC meeting. They forwarded five corrections to the executive secretary and recommended that the minutes be accepted as written.

A. Committee Motion 1

Dr. Sarzotti-Kelsoe moved and Dr. Yankaskas seconded that the minutes of the December 7-8, 2010, RAC meeting be accepted. The motion was approved unanimously by voice vote.

III. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Chiocca, Fong, Kohn, Strome, Yankaskas, and Zaia

Dr. Yankaskas reported that 10 protocol submissions were received by the OBA in the past 3 months, 9 of which were not selected for public review at this RAC meeting. Of the nine protocols not selected for public review, seven were oncology protocols, one was for a monogenic disease, and one was for an infectious disease. In these nine protocols, two used plasmid vectors, two used adenovirus vectors, two used lentivirus vectors, one used a listeria monocytogenes vector, one used a vaccinia virus vector, and one used a retrovirus vector.

For eighteen protocols, Appendix M follow-up information was submitted indicating their enrollment. Of trials that had initiated enrollment in the past 3 months, nine protocols had been reviewed by the RAC at previous public meetings and five warranted public notation:

- Protocol #813, "A Pilot Study of Haploidentical Natural Killer Cell Infusions for B Cell Lineage Lymphoblastic Leukemia," was reviewed by the RAC in December 2006. The principal investigator submitted a protocol amendment that will replace the retroviral vector with electroporation of mRNA for the anti-CD19 chimeric antigen receptor (CAR). It was found that electroporation can result in high expression of the CAR that then declines over 48 hours and is almost undetectable after 96 hours.

- Protocol #807, "A Phase I Trial of Intratumoral Administration of Secondary Lymphoid Chemokine Gene Modified Autologous Dendritic Cells in Advanced Non-Small Cell Lung Cancer," also was reviewed by the RAC in December 2006. The protocol was amended in response to two RAC recommendations. Because the balance between immunosuppression and immunostimulation might shift toward immunosuppression as CCL-21 levels increase, detailed immunologic characterization of T-cell populations will be performed. In response to concern that stimulation of the cells with keyhole limpet hemocyanin (KLH) could result in KLH being the primary antigen presented by the dendritic cells, KLH stimulation of the final product will be eliminated.

- Protocol #848, "A Phase I Study of Intratumoral Administration of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Alloclone-002 Modified for Glucocorticoid Resistance and Interleukin-2," was reviewed by the RAC in June 2007. Data was submitted to show that expression of a truncated glucocorticoid receptor protein that results from disruption of the glucocorticoid receptor by the zinc finger nuclease (ZFN) does not have an effect on genome-wide gene expression profiles. Data also was submitted to support the safety of the ZFN.

- Protocol #950, "Gene Therapy for SCID-X1 Using a Self-Inactivated Gamma Retroviral Vector," was reviewed by the RAC in December 2008. In response to a request, additional animal studies were conducted to compare the potential genotoxicity of the self-inactivated vector with retroviral vectors similar to those used in the French and British X-SCID trials. Data were provided from secondary transplant studies in mice along with updated *in vitro* immortalization assays and integration-site analysis.

- Protocol #1061, "A Phase I Dose Escalation Safety Study of Subretinally Injected RetinoStat®, a Lentiviral Vector Expressing Endostatin and Angiostatin, in Patients with Advanced Neovascular Age-Related Macular Degeneration," was reviewed by the RAC in September 2010. The sponsor clarified that the data and safety monitoring board has the final decision as to the continuation of the study and also clarified language within the informed consent document regarding the potential use of participants' samples.

A total of 16 serious adverse events (SAEs) were reviewed by the GTSAB from 14 protocols, including initial and followup reports. After analysis of these events, the GTSAB concluded that no reports needed additional public discussion.

Dr. Yankaskas discussed some recent new results for Protocol #843, "A Phase I Study of Autologous T Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nuclease SB-728 in HIV-Infected Patients." The sponsor, Dr. Carl June, and principal investigator, Dr. Pablo Tebas, both from the University of Pennsylvania, presented partial results of this protocol at the 18th Conference of Retroviruses and Opportunistic Infections in Boston on March 2, 2011. Infusion of up to 10×10^9 cells in nine evaluable participants was well tolerated and the ZFN-CCR5 modified cells persisted in the peripheral blood for more than 1 year. Clinically, participants showed improvement in CD4+ T-cell counts and the CD4/CD8 ratios improved in a number of participants. Data to support these findings were presented. Webcast of this presentation can be accessed at http://www.retroconference.org/2011/data/files/webcast_2011.htm.

IV. Gene Transfer Using Growth Factors for Peripheral Vascular Disease: Updates on Two Recent Trials

A. Introduction

Dr. Zaia introduced this discussion by noting that the use of growth factors in gene transfer trials has been of concern to the RAC. The concern was whether continuous exposure to growth factors might have deleterious effects, such as carcinogenesis. He reviewed the background of growth factor use, noting that a variety of growth factors transgenes have been used with the majority of protocols using the vascular endothelial growth factor (VEGF), and he provided analysis of RAC-reviewed protocols by:

- Targeted disease – cardiovascular disease and peripheral vascular disease are most prevalent
- Delivery system – plasmids represent nearly 60 percent and adenoviruses approximately one-third of all studies
- Phase – Phase I trials represent 55 percent, and 36 percent are Phase II
- Current status – 83 percent of gene transfer trials are closed or were never initiated, whereas 16 percent remain open

Questions for consideration regarding what can be learned about the use of growth factors from the two trials under discussion were:

- Is failure to see clinical effect related to failure of transgene expression and angiogenesis, or is there angiogenesis without clinical effect?
- Were the animal models predictive of the clinical effect?
- Could vector choice have been a factor?
- As angiogenesis is a key physiologic process in tumor growth, was there any difference in malignancy rates between those who received active agent and those who received placebo?
- Were there unanticipated problems?

B. Protocol #0709-838 titled: A Randomized Double-Blind Placebo-Controlled Parallel Group Study of the Efficacy and Safety of XRP0038/NV1FGF on Amputation or Any Death in Critical Limb Ischemia Patients with Skin Lesions

Presenters: Soraya Bekkali, M.D., Sanofi-Aventis, Paris, France; Caroline DeSurmont-Ruchaud, Ph.D., Sanofi-Aventis, Paris, France; and William R. Hiatt, M.D., University of Colorado School of Medicine *(via teleconference)*

Dr. DeSurmont-Ruchaud presented an overview of the project, including a description of the product, a plasmid expressing human acidic fibroblast growth factor (FGF1), target indication (peripheral artery disease [PAD]), dose and regime. The mechanism of action of the expressed FGF1 was pro-angiogenic, resulting in capillary formation and maturation to arterioles. She also provided information about the pharmacology of NV1FGF, results of NV1FGF in the hypercholesterolemic hamster model of PAD, and the preclinical development that showed no evidence of risk as tested in rats.

Dr. Bekkali presented data and results regarding the proof of concept of local transgene expression in critical limb ischemia (CLI) amputated subjects, individual data that showed high variability from one subject to another (as observed previously in animals), the clinical development program, and the NV1FGF Phase II study, called the TALISMAN study, which was designed to assess clinical efficacy. Promising preliminary results from the Phase II trial led to designing a Phase III trial (called the TAMARIS trial) to assess clinical efficacy in a larger population. The TAMARIS trial was conducted in 30 countries at 171 sites, which reflects the rarity of this stage in the PAD population. The Phase III trial replicated the Phase II trial including dosing, except with the addition of a placebo arm.

Dr. Bekkali provided information and data about the TARAMIS study's trial design, endpoints, baseline demographics, subgroup analysis, extent of exposure, and safety issues. Following the negative study results, the investigators performed an in-depth analysis of the Phase III results with the help of the steering committee. No indication of efficacy was suggested by any of the in-depth analyses, including the secondary analysis that looked at hemodynamic parameters such as leg pressure, and various subgroup analyses by demographics, medical history, geographic region, renal impairment, and disease stage (trying to identify whether a subgroup of patients could be identified as a responder group). Additional substudies were negative. The TAMARIS study design and rigorous conduct of the trial makes this data fully reliable, and this trial is considered conclusive. The size of the trial was appropriate, the investigators performed regular audits, and careful oversight was provided by the steering committee.

Dr. DeSurmont-Ruchaud stated that causes of the differing outcomes that could be related to the investigational product also were evaluated. Results indicated that the treatment allocation process occurred with no errors and that the *in vivo* expression profile was not impacted by the manufacturing changes between the Phase II lots and the Phase III lots.

Overall conclusions related to the TAMARIS trial were that:

- The Phase III study, given its robust features, provides a reliable assessment of NV1FGF efficacy and safety at 1 year; longterm safety followup is ongoing.
- Though intramuscular administration of NV1FGF was proven in a Phase I study to lead to FGF-1 expression in participants' muscles, the study drug at the tested dose of 4 mg x 4 every 2 weeks seemed ineffective, as compared to placebo, in translating the FGF-1 protein expression into a meaningful and sustained clinical benefit for the CLI patients.
- No formulation change or treatment mix-up could explain the TAMARIS results.
- The significant difference in the secondary endpoint observed in the small TALISMAN Phase II trial in favor of NV1FGF was probably a chance finding.
- TAMARIS results may question the concept of gene-based therapeutic angiogenesis applied to CLI in extrapolating from the impressive results seen in small animals into humans suffering from complex and chronic vascular disease.

C. Protocol #0407-661 titled: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 in Patients with Intermittent Claudication

Presenters: Mark Creager, M.D., Brigham and Women's Hospital; Joanna Haas, Ph.D., M.S., Genzyme Corporation; James Streisand, M.D., Genzyme Corporation; and Lee-Jen Wei, Ph.D., Harvard University (former RAC member) *(via teleconference)*

Dr. Creager presented the results of this Phase II trial. A total of 35 sites participated in this study – 27 from the United States, 4 from the United Kingdom, and 4 from Germany. PAD is primarily an atherosclerotic disorder that involves significant stenosis or occlusion affecting the aorta or an artery that supplies the limb. Some patients are asymptomatic but about 30 percent of patients have symptoms of intermittent claudication, which is the development of a discomfort, ache, cramp, or pain in the leg or from the calf that occurs with walking and resolves with rest. Few medical therapies are available to treat these patients. Only two drugs are approved by the U.S. Food and Drug Administration (FDA), and

revascularization therapy is usually reserved for those patients with the most disabling symptoms of claudication or those with CLI.

Therapeutic angiogenesis using gene transfer has the potential to improve symptoms of claudication by forming new blood vessels and improving blood flow to the affected limbs of patients with PAD. In preclinical models of high limb ischemia, HIF-1α/VP16 increases collateral blood vessel formation as well as blood flow. In a Phase I trial of participants with CLI, HIF-1α/VP16 was shown to be safe and associated with resolution of rest pain and, in some research participants, healing. For the Phase II study, the investigators hypothesized that intramuscular administration of Ad2 HIF-1α/VP16, which is an engineered recombinant Type 2 adenovirus vector encoding constitutively active HIF-1a, would improve peak walking time in patients with PAD and intermittent claudication. The objectives were to assess the efficacy of HIF-1α/VP16 compared to placebo in treating severe intermittent claudication and to assess the safety and tolerability of HIF-1α/VP16 compared to placebo. Dr. Creager described the inclusion and exclusion criteria and the efficacy and safety endpoints for this study.

The results showed that intramuscular administration of Ad2 HIF-1α/VP16 to participants with intermittent claudication secondary to PAD did not improve peak walking time, did not improve claudication onset time, did not change the ankle brachial index, and did not alter quality of life by the walking impairment questionnaire. In addition, during the 104 weeks of followup of cancer development, no participants in the placebo group developed lung cancer; however, one participant in the low-dose group, one in the intermediate-dose group, and four (6.2 percent) in the high-dose group developed lung cancer. A posthoc statistical analysis showed a significant difference in the number of lung cancers in the high-dose group compared to placebo.

Taking all the results into consideration, the investigators concluded that gene transfer with intramuscular administration of HIF-1α is not an effective therapy for patients with PAD and severe intermittent claudication.

D. RAC Discussion

Dr. Chiocca commented about the difficulty of reporting negative results. However, he noted the educational value of publishing negative results along with analysis of a trial's failures.

Dr. Hiatt explained that, for large clinical trials, no appropriate surrogate endpoints are available that would improve interpretation of the positive and negative data.

Dr. Creager discussed the finding that the biologic activity seen in preclinical models was not realized when growth factors are administered to people. Age may make a difference – the animals are young and do not have disease while the research participants are older and do have disease. It is unknown whether downstream recruitment of the important substances needed for angiogenesis would take place in an elderly human population that includes those with atherosclerosis. In addition, it is possible that the preclinical models are not the appropriate models.

In further possible explanation as to why the Phase II trial did not show positive results, Dr. Creager characterized as complex the events that must take place for blood vessels to form and line up adequately to ensure perfusion; administering a single agent might not be sufficient to integrate all the activities required for blood vessel development. He hypothesized further that the spacing of injections in humans might not be ideal – it might be too far apart; because animals are much smaller than humans, the same number of injections would be much closer together. In addition, the number of times each experimental compound was given (in both trials) might not have provided a sufficient duration of effect such that the effect could be captured by the investigators.

Dr. Fong suggested that future trials incorporate marker genes so more information can be learned about the process. Therefore, it would be possible, at an earlier stage, to determine if proceeding to a larger trial is warranted.

Regarding growth factors and cancer, Dr. Fong acknowledged the importance of understanding whether an increase in malignancies occurs when participants are given growth factors. He warned against concluding from these two trials that there is no risk of cancer, because it is unknown whether the gene was expressed or got to its target organ or to off-target organs.

In response to Dr. Fong's questions about biodistribution and local expression of the protein, Dr. Bekkali explained that their investigators have performed biodistribution studies in animals and in participants and have noted that the plasmid is rapidly degraded in the circulation. The half-life is three to five minutes, and products of plasmid degradation were detected afterward. The protein was only detected in the injected muscles, a finding that was confirmed in the animal trials that allowed for analysis of all the nontarget organs. After research participants' limbs were amputated, microbiopsies were performed and the protein was detected at the injection sites and not in the muscle area that was distant from the injection site. This biopsy result confirms that part of the biological process had begun and that the protein was present. Presence of this protein led to sustained new vector formation in the experimental animals, but that same result did not occur in the humans.

With regard to possible marker genes, Dr. Creager noted that, for HIF-1α, it would be ideal to demonstrate expression of downstream substances including VEGF or stromal derived factor in the skeletal muscle of the areas being injected. Ideally this could be done by biopsy, although it would only be possible in a small translational study because many participants would not consent to it. He suggested, generally, looking for local expression of downstream markers of whatever substance is administered, in a subset of research participants. In addition, he suggested that conducting proof-of-concept studies should be considered before conducting clinical outcome trials, although he acknowledged that such studies are difficult to do when looking at target endpoints.

In response to Dr. Zaia's query, Dr. Bekkali explained the role of the adjudication committee, a body that was recommended by the FDA for this Phase III trial. Its roles were 1) to review participant status regarding unsuitability for standard revascularization, which resulted in approximately 95 percent being judged unsuitable for revascularization; 2) to ensure that the major amputations that were part of the primary endpoint were justified, which resulted in 100 percent being justified based on the disease worsening; 3) to review causes of death; and 4) to analyze the diagnosis of acute ischemic events.

Dr. Zaia asked about subgroup analysis for the TAMARIS study. Dr. Streisand responded that subgroup analyses were performed – for example, participants who had diabetes versus those who did not have diabetes as well as by region – and no signals of efficacy were found in any of those subgroups.

Dr. Strome asked Dr. Creager to venture an opinion about why the high-dose group showed an increase in lung cancer. Dr. Creager suggested it was a chance happening, but stated it was not possible to know with certainty unless this result was examined more systematically in additional studies. All the participants who developed lung cancer smoked; of the six lung cancer patients, five had non-small cell carcinoma, which is a smoking-related cancer.

In response to Dr. Strome's query about how the investigators could capitalize on what they have learned from these failed trials that would inform further investigation, Dr. Creager responded that there is tremendous merit in looking at the efficacy of therapeutic angiogenesis in patients with PAD, but not enough is known at present. He suggested going back to the bench and establishing the combination of angiogenic factors that are required to orchestrate the development of new blood vessels that would provide collateral blood flow around stenotic areas. The effect of age must be studied, the effect of atherosclerosis should be studied, and more information about how to administer these drugs should be gathered. Dr. Creager stated that this field is still at the beginning of a long struggle to find effective therapy to improve blood supply and ameliorate symptoms in these patients. Drs. Hiatt and Bekkali concurred.

Dr. Badley noted the impressive results in the hamster model (from the TAMARIS study) that did not translate to the Phase III trial, and asked about efforts to improve model systems; he suggested aging the hamsters and/or including the smoking variable. Dr. Creager responded that a number of experimental

models are being tested at present, some more specific to PAD but none that manifest atherosclerosis. Studies are looking at older animals versus younger animals, but in one study with HIF-1α, no difference in efficacy occurred between older versus younger animals. A good animal model is needed, one that manifests atherosclerosis and is in old animals. Nearly every angiogenic growth factor, including VEGF, that has been looked at in a preclinical model has shown efficacy. To date, those results have not predicted what occurs in humans.

E. Public Comment

No public comment was offered.

V. Discussion of Human Gene Transfer Protocol #1101-1087 titled: A Randomized Phase I/II Trial using a GM-CSF Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) Vaccine in Combination with CCL21 for Patients with Stage IV Adenocarcinoma of the Lung

Principal Investigator:	Jhanelle Gray, M.D., Moffitt Cancer Center and Research Institute
Additional Presenters:	Scott J. Antonia, M.D., Ph.D., University of South Florida *(via teleconference)*, and William E. Janssen, Ph.D., Moffitt Cancer Center and Research Institute *(via teleconference)*
Sponsor:	Moffitt Cancer Center
RAC Reviewers:	Drs. Fost, Ornelles, and Strome

A. Protocol Summary

Treatment outcomes in patients with advanced adenocarcinoma of the lung remain poor despite numerous attempts to refine chemotherapeutic regimens for treating this disease. Novel treatment modalities, including immunotherapy, need to be developed given the lack of significant advances using conventional approaches.

A human bystander cell line that expresses both GM-CSF and CD40 ligand (GM.CD40L) has been created at the Moffitt Cancer Center; this cell line was utilized to generate an allogeneic tumor cell-based vaccine formulation. The bystander cells will help recruit (professional antigen presenting cells in the form of) dendritic cells (DCs) by secreting GM-CSF in the vaccine site microenvironment. Once activated by CD40L, DCs will take up apoptotic bodies from the irradiated tumor cells and will present tumor antigens in the context of MHC. Tumor-specific DCs will then migrate to the regional lymph nodes, where T cell activation can occur, leading to systemic tumor cell killing. CCL21 is a chemokine that helps to recruit T cells and leads to hyperresponsive T cells. CCL21 may amplify the results of the vaccine.

Based on this information, a phase I/II randomized study is proposed to evaluate two vaccine formulations (allogeneic tumor cells plus GM.CD40L bystander cells plus or minus CCL21L) in research participants with adenocarcinoma of the lung who have failed first-line therapy. The specific aims of the study are to evaluate: (1) safety and tolerability, (2) clinical efficacy and (3) the development of specific anti-tumor immune responses.

In the future, the information obtained from this project will serve as the basis for a phase III trial. The long-term goals are to develop a safe, feasible, and effective therapy that will improve the outcomes of individuals with adenocarcinoma of the lung. This project will provide insight into the role our immune system plays in the development of lung cancer and how it can be optimized to amplify its effectiveness against lung cancers.

B. Written Reviews by RAC Members

Seven RAC members voted for in-depth review and public discussion of the protocol. The key issue was the novelty of the construct.

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

Dr. Fost focused his review on the informed consent document. He noted that it was highly technical and was written significantly above a sixth-grade level, and that it could benefit from a half-page summary written in language a 12-year-old child could understand. He suggested including an explanation of the distinction between the Phase I and Phase II components that would include that: 1) a Phase I trial is intended primarily to look for adverse effects usually because the study involves a new product that has not been studied in humans before; and 2) to find the best dose for the later Phase II study, and 3) that clinical benefit is unusual in Phase I studies. The introduction of the benefits section should include in general terms a review of the results of prior studies using vaccines for this disease, providing potential participants with an understanding of what happened in prior related studies. Dr. Fost noted that the list of people who could receive private health information (on page 12 of the informed consent document) was unduly broad and should be revised.

Dr. Ornelles identified concerns in three categories: less substantive items including imprecision, incomplete information, and style issues; specific details regarding the adenovirus vector used in this protocol to express CCL21; and the larger issue of exposing cells of the immune system – such as dendritic cells and T cells – to replication incompetent adenoviruses. Viable adenovirus vector could be delivered along with the cellular vaccine, and questions remain about exactly what transpires during an infection with the E1-deleted adenovirus vector. Specific concerns included:

- What is the likelihood that infectious CCL21-expressing adenovirus particles would be released from the transduced and irradiated cells? Because it can be demonstrated experimentally that significant amounts of non-internalized virus remain cell-associated and infectious, it is likely that a variable amount of infectious Ad.CCL21 will be delivered to the research participant in association with the irradiated cells. In general, protocols using adenovirus vectors in such a context should consider the possibility that the viral vector affects the biology of the infected cell and that the viral vector could progress through a limited replicative cycle.

- A shortcoming of the preclinical studies evaluating the efficacy of CCL21 is that the comparison was made against non-treated cells and not against cells treated with a null vector or presumably inert transgene.

- The use of the human cytomegalovirus (CMV) immediate early enhancer and promoter is another concerning feature of Ad.CCL21. Previous and recent work has established that inclusion of the CMV enhancer and promoter in an E1-deleted adenovirus contributes to a strong innate inflammatory response following infection, irrespective of the transgene. There exists a possibility that this effect in the research participant would obscure, confound, or synergize with expression of CCL21. However, by not including a null vector control, the experimental plan might miss such an effect.

- The reason for administering the tetanus vaccine (Decavac) should be represented more clearly in the informed consent document.

- While CCL21 is likely to act in the manner suggested by many preclinical studies, the studies proposed here may be misinterpreted by ascribing a function to CCL21 that is due to infection with adenovirus and not due to the transgene. Alternatively, these studies might conclude erroneously that CCL21 has no impact when, in fact, the consequence of infection with adenovirus negated effects of the secreted CCL21.

- How was the optimal concentration of adenovirus vector determined to be a multiplicity of infection (MOI) of 500? The E1-deleted vectors show multiplicity-dependent effects on cell cycle progression and the DNA damage response. Any of several possibilities could confound interpretation of results and obscure a meaningful beneficial result from the use of CCL21.

- Is it possible that repeated exposure to the complex cellular-plus-viral vaccine could lead to some form of tolerance or other immune dysfunction?

- What are the chances that the radiographic criteria used to judge efficacy could miss biological effects?

- While the investigators may have no evidence of expression of other genes from the Ad.CCL21 vector, other investigators have shown such expression. Although the consequences of expressing viral genes from the vector backbone (such as E4) are unknown, there is a reasonable probability that this will occur in the H1944 cells, which could influence the outcome in unanticipated ways.

Dr. Strome asked why the investigators decided not to selectively enroll participants with limited detectable disease and evidence of an ability to generate a tumor-specific immune response. He asked about a change in dose sequence from the prior study to this protocol and why the dosing intervals in the relevant animal study were not proposed in the human trial. Dr. Strome asked the investigators to state the rationale for changing from two injections at each of four sites in the prior study to one per site in this protocol, as well as the rationale for bypassing a Phase I trial in the investigators' original submission but not in the current one. With regard to the informed consent document, Dr. Strome asked about the procedures in place to assure all research participants receive similar information. He also opined that participants in this trial who are terminally ill should not have to pay for trial-related adverse events not covered by insurance, a point that should be made clear throughout the informed consent document.

C. RAC Discussion

During the meeting, the following additional questions, concerns, and issues were raised.

- Dr. Ross asked whether the investigators plan to conduct genetic testing of tumors prior to enrolling participants in the trial, in order to look for mutations.

- Dr. Fost clarified concerns about storing blood and tissue samples. Some research participants will agree to have their tissue used for tests that are directly relevant to the present study but do not want their tissue stored in perpetuity and made accessible for unrelated study. Therefore, if future uses are possible that are not necessary for the purposes of this study, collection of that tissue should be optional and it should be made clear to participants that their samples can be destroyed or de-identified after the study purposes are achieved.

D. Investigator Response

1. Written Responses to RAC Reviews

Dr. Gray explained that the list of people who could receive private health information is standard, as required by the sponsor's regulatory division, to ensure that participants understand that their data could be transmitted outside of Moffitt for safety and efficacy evaluations. As principal investigator of the study, she ensures that the information garnered from the study will be password protected in a secure database. An institutional policy for protected health information and an information technology systems confidentiality agreement will be enforced; both are available upon request.

In response to a query as to why the investigators decided not to selectively enroll individuals with limited detectable disease and evidence of an ability to generate a tumor-specific immune response, the investigators explained that the majority of patients with NSCLC present with late-stage disease. Individuals with no evidence of disease or minimal residual disease represent a minority of patients, and the investigators want to develop a vaccine therapy that would serve the largest number of patients.

The investigators changed from two injections at each of four sites in the prior study (in 2007) to one per site in this protocol because they realized they could safely administer the same volume of vaccine in one

injection at each site, thus improving participant comfort. The schedule used in the prior study was not well informed because information was not available at that time; however, the dosing schedule proposed in this trial appears to be the most effective and now is used in all Moffitt trials.

Compared to the prior submitted study, Phase I was included in this submission based on recommendations from the National Cancer Institute's NExT program and from OBA.

The procedures in place to assure all research participants are provided with similar information include a study initiation meeting arranged prior to enrolling in a study. This meeting would include the principal investigator, study coordinator, research nurses, and research pharmacists to ensure that all personnel involved with the study understand its intricacies. The policy at Moffitt is to assign the study to one clinical trial coordinator; this coordinator (as well as the backup coordinator) will be well versed in the consent and protocol procedures to make the process uniform.

In response to the question about participant expenses, the investigators explained that the trial will follow Medicare guidelines for reimbursement for participants on clinical trials. Per those guidelines, adverse events related or not related to the clinical trial are covered by the insurance policy. The policy specifically states: "Effective for items and services furnished on or after July 9, 2007, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials." An insurance company not paying for an adverse event is likely to be a policy-specific decision, and this potential situation is discussed by the clinical trial coordinator with the potential participant during the consenting process. Participants are encouraged to look into this coverage with their insurance companies prior to enrolling.

Regarding the possible association of adenovirus with the irradiated cells, washing of the cells will occur after the entire infection cycle. Cells will be initially infected at a high density, to maximize probability of virus-to-cell contact and adsorption. The cells will then be concentration-adjusted to a lower density, which is more favorable to the wellbeing of the cells, and will be allowed to incubate for at least 12 hours – allowing the virus time to internalize, unpackage, and initiate DNA replication and transcription, followed by protein synthesis. Afterward, the cells will be washed to remove unadsorbed free virus that may remain in the supernatant. The Ad.CCL21 is replication defective, so any amount produced by the transgene protein is anticipated to be short-lived and is unlikely to have significant biological effects. While a finite probability exists that viable virus that remains adsorbed onto the surface of the target cells might become injected, this study incorporates a Phase I component to monitor participants closely for safety.

The investigators acknowledge that the viral vector might produce an immune response, and they accept this possibility as a limitation of their proposed study. They considered the option of incorporating a null viral vector into the control arm, but concluded that doing so is not feasible because they do not have access to the vector, and because of cost and time prohibitions.

Regarding how the optimal concentration of adenovirus vector was determined to be an MOI of 500, the investigators explained that all the experiments performed involved a mock vaccine production to recapitulate what would occur during the clinical trial. The H1944 cells were infected, then irradiated, frozen, and thawed, and then used for experiments to demonstrate the feasibility in a clinical trial.

The investigators acknowledged that it is theoretically possible that repeated exposure to the complex cellular-plus-viral vaccine could lead to tolerance or other immune dysfunction. It is well accepted that the anti-tumor immune responses wane over time, and it is now well accepted that boosters are needed to maintain the immune responses.

Because of the chance that the radiographic criteria used to judge efficacy might miss biological effects, the investigators propose to use RECIST response criteria, which is the standard as currently accepted by the field of immunotherapy. In addition, they are using progression-free survival as their primary endpoint.

The investigators changed some language to make the protocol easier to understand. They noted that, following the RAC review, the informed consent document would be reviewed by their Institutional Review Board (IRB) for further input regarding language. In addition, the investigators agreed to modify the informed consent document to include the suggested clarifications and language modifications, and to decrease the chances of therapeutic misconception.

2. Responses to RAC Discussion Questions

Dr. Gray acknowledged that the investigators had changed from autologous cell lines in their prior study to allogeneic cell lines in this proposed study. The change was based on their ultimate goal to develop therapies that will have meaningful impact on the majority of lung cancer patients, which would require that pharmaceutical companies expand this study to a much larger patient population. The pharmaceutical companies are only interested in off-the-shelf (in this case, out-of-the-freezer) reagents or therapeutics that can be manufactured in bulk; they have no interest in pursuing an approach focused on autologous tumor cells.

Dr. Gray stated that many potential participants in this trial will have had their tumors tested for mutations, but doing so is not part of the current trial. Dr. Antonio explained that the investigators are not doing genetic testing on participants' tumor cells, but they might look for protein expression.

Regarding enrollment criteria, Dr. Gray explained that only participants who have failed prior therapeutic agents will be candidates for this trial.

Dr. Antonia explained that the investigators' intention is to perform the tests that have been stated explicitly in the protocol and then have no further access to participants' tissue or blood samples after that testing has been done. Dr. Gray agreed to make this intention clearer in the informed consent document.

Whether a participant is forced to leave the study after a research-related injury is, in part, mandated by the FDA or the IRB. However, Dr. Antonia stated that the investigators always advocate strongly to the regulatory agencies to continue a participant on trial if benefits are clearly outweighing the risks.

E. Public Comment

Ms. Rooney offered four comments about the informed consent document and the lay summary:

- Participants should be provided with a name and telephone number of someone to contact regarding human research participant questions; that contact is usually the IRB.
- With regard to the section entitled "What if you get sick or hurt while in study?" Ms. Rooney asked whether participants would be given some kind of "alert card" in the event they present to an emergency room but cannot communicate.
- The archival blood section and the tissue section were not clear about whether the stated additional procedures are necessary to answer the research question. If they are not, Ms. Rooney suggested that the investigators consider making these additional procedures not mandatory, as the current mandatory archiving of blood and tissue could appear coercive.
- The last page of the informed consent document includes the statement "I may have to leave the study without my consent for a variety of reasons," including if the participant has a study-related injury. Ms. Rooney expressed concern that participants might not notify the investigators about such injury or adverse event because they could then be taken out of the study, a situation that could affect the study results as well as not being in the best interests of the participant.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

<u>Clinical/Trial Design Issues</u>

- The allogeneic cells will be transduced with a replication-defective adenoviral vector and then irradiated. It is possible that irradiation may not inactivate all the viral particles in the transduced cells. As adenovirus can elicit immune responses, any analysis of immune responses or efficacy should consider the potential contribution of residual adenovirus.

- In a Phase I trial (OBA Protocol # 0212-562) using a vaccine composed of GM.CD40L transduced autologous tumor cells, it took several months before an anti-tumor immune response was seen in participants who responded. That trial enrolled participants with metastatic melanoma, renal cell carcinoma, small-cell lung cancer, and mantle cell lymphoma [*Annals of Surgical Oncology*, 14(2):869-884 (2006)]. Given the potential time interval between dosing and development of an anti-tumor immune response, participants enrolled in this trial should ideally be those whose advanced disease is unlikely to progress significantly during the course of the trial. The investigators will be screening patients for eligibility for this single-site study and should take this into consideration. Ideally, to the extent possible, the inclusion/exclusion criteria should more precisely define criteria that would identify these participants.

- Participants will receive the vaccine once every two weeks for six weeks and then once every month for three months. This frequency of vaccine administration differs from that used in the Phase I GM.CD40L clinical trial. Of note in that trial, GM-CSF levels were detected within 24 hours of vaccination but returned to baseline after five days. Moreover, preclinical animal studies for this protocol used dosing intervals of three to four days. The rationale for the current dosing interval in light of the rapid decline in GM-CSF levels and the animal data should be explained in the protocol.

- In the previous Phase I study (OBA Protocol # 0212-562), the vaccine was administered by two injections at each of four sites (axilla and groin). This protocol proposes to use one injection per site because the same volume of vaccine can be safely administered in this manner, thus decreasing participant discomfort. However, as the goal is to elicit an immune response and dendritic cell migration to the lymph nodes, it is possible that administering more injections in varying sites could promote a better immunologic response. Consider whether this hypothesis should be tested in this study.

- The informed consent document requests that participants contact the investigators if they experience an adverse event. Because participants could present to an emergency room unaffiliated with the study and not be in a condition to contact the study team, the investigators may wish to consider developing a study card with summary information regarding the trial and the investigator's contact information that participants could carry with them to help ensure compliance with reporting.

<u>Ethical, Social, and Legal Issues</u>

- The informed consent document should be modified:
  - To include information regarding prior studies using vaccines for this disease
  - To include the name and contact information for an individual to be contacted regarding the rights of research participants
  - To clarify that, in order to enroll in the trial, participants are not required to consent to have any residual biopsy material analyzed

- The informed consent document notes that medical information could be disclosed to "[a]ny person who provides services or oversight responsibilities in connection with this study." The phrase "any person who provides services" is overly broad, as it could include almost anyone who provides non-clinical services to the Moffitt Cancer Center. Consider modifying this language to describe more accurately those persons who will likely need to have access to the participant's data.

- The informed consent document states that participants may have to leave the study without their consent if they experience a study-related injury. This language could inadvertently promote underreporting of adverse advents by participants. Consider either amending this language to explain more clearly the factors that would go into a decision to remove the participant or discuss this during the informed consent process.

G. Committee Motion 2

Dr. Zaia summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. It was moved by Dr. Yankaskas and seconded by Dr. Badley that the RAC approve these summarized recommendations. The vote was 20 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VI. Closing Remarks and Adjournment

Dr. Zaia thanked the RAC members and the OBA staff, and adjourned the March 2011 RAC meeting at 3:00 p.m. on March 8, 2011.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, actions 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: _____

_____
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Recombinant DNA Advisory Committee

Attachment I: RAC Roster
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Attachment II
Public Attendees

[This list includes only those individuals who are not elsewhere identified.]

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Pakwai Au, FDA
Mark Borigini, FDA
Mark Creager
Heather Embree, Lentigen
Marta Frisinger, Genzyme
Joanna Haas, Genzyme
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Tanya Krubit, GenVec
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Abigail Luo, FDA
John Scott, FDA
Jim Streisand, Genzyme
Steve Winitsky, FDA
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Attachment III
Abbreviations and Acronyms

CAR	chimeric antigen receptor
CD40L	CD40 ligand
CLI	critical limb ischemia
CMV	cytomegalovirus
DHHS	U.S. Department of Health and Human Services
FDA	Food and Drug Administration, DHHS
GM-CSF	granulocyte macrophage colony-stimulating factor
GTSAB	Gene Transfer Safety Assessment Board
HIF	hypoxia inducible factor
IRB	institutional review board
KLH	keyhole limpet hemocyanin
MOI	multiplicity of infection
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PAD	peripheral artery disease
pCOR	plasmid backbone with conditional origin of replication
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
VEGF	vascular endothelial growth factor
ZFN	zinc finger nuclease