

Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is “None”, please specify “None” as your response. “Not applicable” is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** University of Pittsburgh- of the Commonwealth System of Higher Education
2. **Reporting Period (start and end date of grant award period):** 1/1/2011 - 12/31/2014
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Margaret C. McDonald, PhD
4. **Grant Contact Person’s Telephone Number:** 412-383-7474
5. **Grant SAP Number:** 4100054875
6. **Project Number and Title of Research Project:** 05 – Melanoma Vaccine Clinical Trial
7. **Start and End Date of Research Project:** 1/1/2011 - 12/31/2012
8. **Name of Principal Investigator for the Research Project:** John M. Kirkwood, MD
9. **Research Project Expenses.**

9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

\$ 488,481.97

9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
DeBlasio	Clinical Research Coordinator	76% January 2011-March 2011; 100% November 2011-May 2012; 100% July 2012-December 2012	\$143,981.33
Simonetta	Clinical Research Coordinator	75% January 2011-December 2011	\$116,988.42
Merriman	Clinical Research Associate	100% November 2011-December 2012	\$102,487.66
Rose	Clinical Research Coordinator	100% January 2012-December 2012	\$114,193.03
Gassette	Senior Regulatory Specialist	41% October 2012-December 2012	\$10,831.52

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Kirkwood, John	Principal Investigator	10%
Moschos, Stergios	Co-Principal Investigator	10%
Kalinski, Pawel	Co-Investigator	10%
Tarhini, Ahmad	Co-Investigator	5%
Gooding, William	Biostatistician	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes X No _____

If yes, please indicate the source and amount of other funds:

NCI P50 CA121973 SPORE in Skin Cancer—Project 3, “Dendritic Cells Guide Melanoma-Specific T cells” \$480,000

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes X No

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
SPORE in Skin Cancer (renewal)	X NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	September 2012	\$12,500,000	\$11,334,561

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes No X

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

Based on experience gained from this trial, we are developing new and enhanced dendritic cell (DC)-based vaccines for melanoma. For example, a new trial, “Multiple Antigen-Engineered DC Immunization and IFN α Boost for Metastatic Melanoma,” currently underway, is supported by the UPCI Skin Cancer SPORE. Another example includes a new randomized, phase II study examining the efficacy of DC vaccines that incorporate six tumor blood vessel antigen (TBVA)-derived peptides, in combination with dasatinib, in patients with metastatic melanoma. The improved methodology developed during this research project, as well as the knowledge gained, are being applied to enhance the effectiveness of the next generation of DC-based vaccines.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes _____ No X

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of-State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes _____ No X

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes X No _____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This project provided essential support for key clinical research staff and has, therefore,

contributed to improved clinical research infrastructure at the University of Pittsburgh Cancer Institute (UPCI).

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes _____ No X

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes _____ No X

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes _____ No X

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (β) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The overall goal of this project is to examine the safety and efficacy of novel therapeutic cancer vaccines designed to improve patient outcomes. We will examine multi-epitope anti-melanoma vaccines based on polarized alpha dendritic cells (α DC1s), comparing α DC1s to standard DCs in patients with advanced (stage III/IV) melanoma (UPCI 03-118). This study was designed to evaluate the ability of both types of DCs to induce different sets of chemokine receptors on tumor-specific CD8⁺ T cells.

Methods:

The treatment protocol involved two courses of intralymphatic (I.L.) vaccination on Week 1 and Week 6, with a four-week interval between the courses. The duration of each I.L. vaccination course was planned as four days (Tuesday through Friday) of treatment. The primary objective of this study is to evaluate the safety of I.L. vaccination with either type-1-polarized dendritic cells (α DC1) or with control mature non-polarized DC (cDC) loaded with melanoma-associated peptides and tumor-unrelated "heterologous helper antigens" in both cases. Based on past experiences from UPCI and other cancer centers performing DC-based vaccinations, our primary hypothesis was that vaccination with either DC type will be well-tolerated and not associated with serious adverse events. The secondary objective of this study is to evaluate immunity to melanoma resulting from I.L. immunization with these vaccines.

Each type of DC was generated from patients' monocytes in eight-day-long cultures, supplemented with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4), but were exposed to different maturation cocktails, respectively, interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF α), polyinosinic-polycytidylic acid (poly-I:C), alpha interferon (IFN α) and gamma interferon (IFN γ) (in case of α DC1), or IL-1 β , TNF α , interleukin-6 (IL-6) and prostaglandin E2 (PGE2) (in case of cDC). The increase in the frequency of melanoma-specific cytotoxic T-lymphocytes (CTL) was determined (the cumulative increase in the IFN γ -producing cells to each of HLA-A2-restricted peptides present in the vaccines). In addition, as tertiary endpoints, we planned to analyze the character of the anti-melanoma immune responses and the frequency, character, and duration of any clinical responses to vaccination with α DC1 or cDC.

Our secondary hypothesis, based on our preliminary data at study inception, was that enhanced Th1 and CTL anti-melanoma immunity would be promoted by immunization with both α DC1 and cDC. We further hypothesized that the level of augmented antitumor responses in patients

treated with α DC1 would exceed those observed for patients treated with vaccines containing nonpolarized DC, which represented the current “gold” standard of DC used in cancer immunotherapies at the time our study began.

Results:

A total of 22 patients were enrolled to this trial (Table 1), which was closed to accrual in January 2012. All 22 patients received at least one vaccination, and 21 were evaluable for toxicity and for clinical response. Among these, 15 received at least two vaccinations and six received only one vaccination. The median age of the 21 patients treated was 68 years (range 31-85).

Table 1. Patient data: gender, ethnicity, and race of subjects

Ethnic Category	Sex/Gender		
	Male	Female	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	4	8
Not Reported/Unknown	6	8	14
Total :	10	12	22
Racial Category			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Reported/Unknown/More than one race	1	0	1
White	9	12	21
Total :	10	12	22

Safety: Tables 2 and 3 summarize adverse events for all cycles.

Table 2: Worst Grade Adverse Event (AE) rate per patient (all cycles)

	N *	(%)
No AE	12	<i>57.1</i>
Grade 1	7	<i>33.3</i>
Grade 2	2	<i>9.5</i>
Grade 3	0	<i>0</i>
Grade 4	0	<i>0</i>
Grade 5	0	<i>0</i>
Total	21	<i>100</i>

* *Each patient is counted once.*

Table 3: Adverse Events (AEs) and number of patients by Worse Grade AE (all cycles)

Category	Type of Adverse Event	Grade					Total *
		1	2	3	4	5	
General Disorders and Administration Site Conditions	Fatigue	1	0	0	0	0	1
	Injection Site Reaction	4	0	0	0	0	4
	Pain	1	1	0	0	0	2
Metabolism and Nutrition Disorders	Hyperglycemia	1	0	0	0	0	1
Musculoskeletal and Connective Tissue Disorders	Arthralgia	1	0	0	0	0	1
	Pain In Extremity	1	0	0	0	0	1
Nervous System Disorders	Dizziness	1	0	0	0	0	1
	Headache	2	0	0	0	0	2
	Tremor	1	0	0	0	0	1
Psychiatric Disorders	Anxiety	0	1	0	0	0	1
	Insomnia	1	0	0	0	0	1
Respiratory, Thoracic, and Mediastinal Disorders	Allergic Rhinitis	1	0	0	0	0	1
	Wheezing	1	0	0	0	0	1
Skin and Subcutaneous Tissue Disorders	Pruritus	1	0	0	0	0	1
	Skin and Subcutaneous Tissue Disorders	1	0	0	0	0	1
Vascular Disorders	Hypertension	0	1	0	0	0	1

* Each patient is counted at most once within each type of adverse event.

Immunologic efficacy: Only 11 patients received the protocol-mandated two courses of intralymphatic treatment and were evaluable. Two of the four patients among the initial cohort exhibited either antitumor effects or autoimmune anti-pigment immune responses, while four of a total of 11 efficacy-evaluable patients demonstrated immune responses against at least one of the four vaccine-associated CTL epitopes (gp100, tyrosinase, MART1, EphA2; see Table 4). These early data were interpreted as early proof-of-concept. However, overall immunologic and clinical time-to-progression (TTP) analyses did not reveal statistically significant differences between the study groups (see below).

Table 4. DC type and total antigen (Ag) response count

# responsive Ags	DC Type	Total Antigen (Ag) Response			
		0	1	2	3
	αDC1	3	0	2	1
	Standard DC	4	1	0	0

*Cochran-Armitage Trend Test: $p=0.1818$

Clinical observations: The treated patients who received both cycles of vaccination (N = 11) were followed for progression-free survival (PFS) and overall survival (OS). An analysis of the partial results available to date has not revealed any differences related to either DC type or vaccine dose. The best overall clinical responses seen by response evaluation criteria in solid tumors (RECIST) were stable disease in four patients. Among 21 patients who received at least one vaccination, median PFS was 8.9 weeks, with 95 percent CI (7.4, 9.9). Current vital status includes two patients alive and 19 deceased.

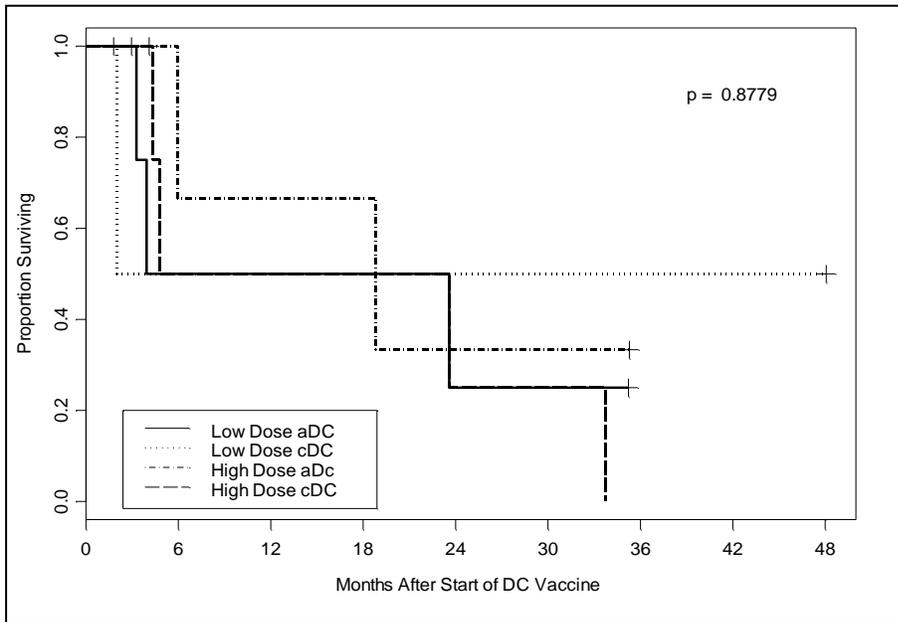


Figure 1. Overall survival by arm

Interestingly, one patient treated developed involution of all melanoma-in-transit lesions (Figure 2). He was not formally considered as a responder by RECIST criteria adopted by the study protocol.

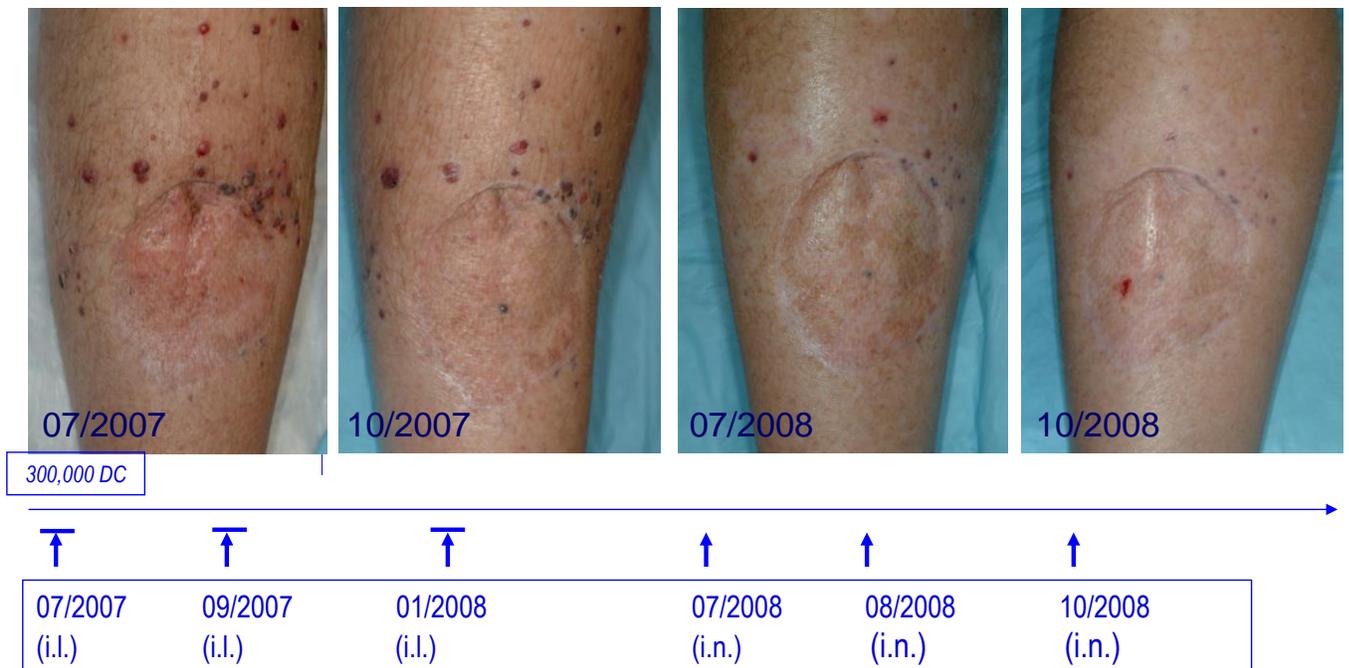


Figure 2. One patient developed involution of all melanoma-in-transit lesions.

Another patient demonstrated signs of disseminated vitiligo (Figure 3).

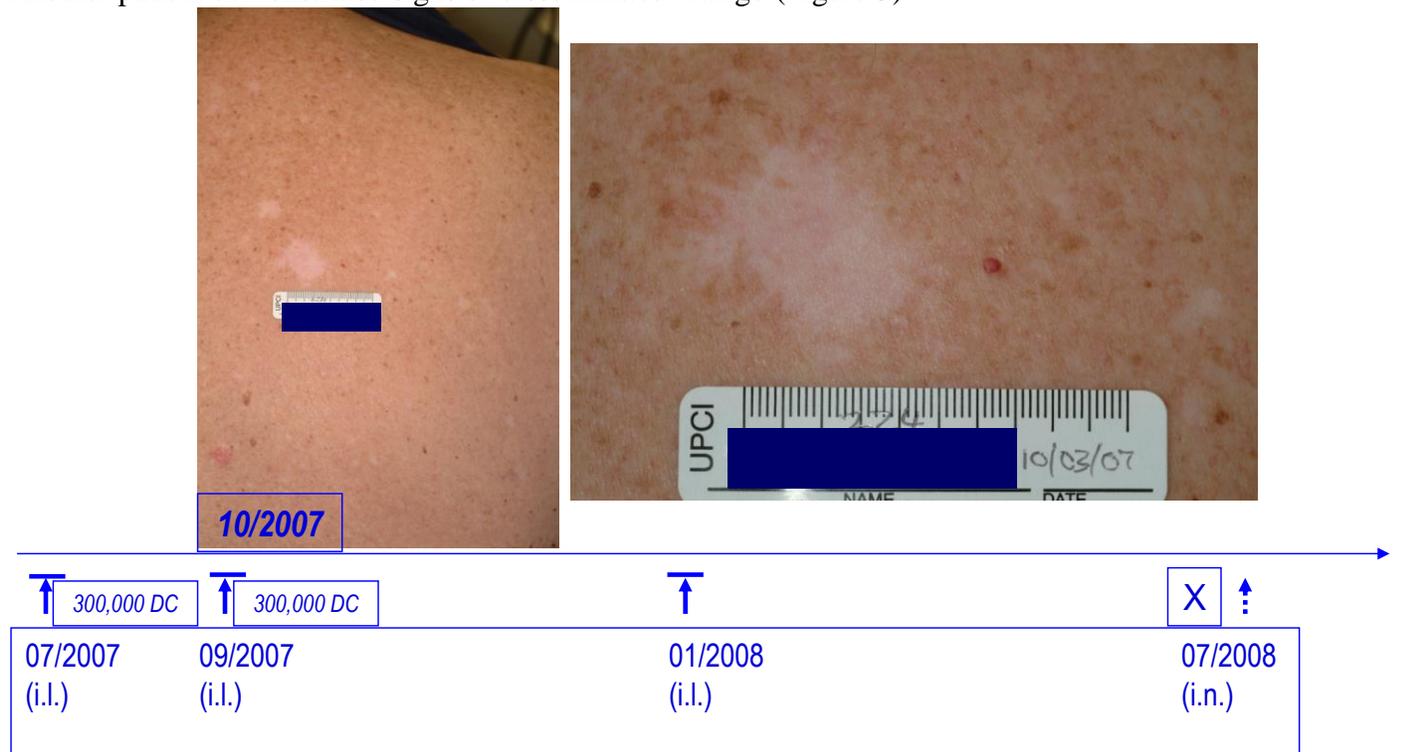


Figure 3. One patient demonstrated signs of disseminated vitiligo.

Caveats: The trial has been closed to accrual due to the technical challenges of intralymphatic cannulation and compounded by modest differences between the groups observed thus far (with the stipulation that only 11 of the planned/needed 28 patients received treatment sufficient to be evaluable for the primary endpoint of efficacy—the induction of melanoma-specific immune

responses). Assessment of trial results has been problematic because we systematically observed lower-than-anticipated levels of interleukin (IL)-12 produced by vaccines (on average, up to 10 times lower than seen in our preclinical studies and a concurrent melanoma trial completed by our collaborators in Heidelberg and Essen, Germany).

Our analyses indicated that this discrepancy may have been caused by a suboptimal combination of DC culture duration with the concentration of maturation-inducing factors and the type of culture medium used in the trial (the original medium used to develop the vaccine was discontinued). As a result, Dr. Kalinski's team has developed modified DC maturation protocols for use in our prospective trials. In addition, UPCI, in partnership with UPMC and the University of Pittsburgh, established the Immunotransplantation Center (ITC), which is led by Dr. Kalinski and serves as the current good manufacturing practice unit specializing in α DC1 therapies for cancer patients.

A clinical trial in melanoma (α DC1s loaded with alternative peptide antigens) and colorectal cancer (α DC1s loaded with autologous tumor material) based on the revised α DC1 protocols developed by our investigators were initiated in summer 2014. An additional ovarian cancer trial (α DC1s loaded with autologous tumor material) is expected to open in spring 2015.

Conclusions:

The demonstration of the feasibility of prolonged cannulation of lymphatic vessels for infusion of DC prepared *ex vivo* constitutes the major novelty of the current study, and the resulting improvement in methodology will be submitted for publication shortly. However, applicability of the technique is limited by logistic challenges. To date, there has also been no evidence of any significant advantage for this route compared to alternatives—at least as tested in the limited number of participants we enrolled.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be “No.”

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

If “Yes” to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both “No.”)

18(C) How many hospital and health care professionals were involved in the research project?

10-15 Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

28 Number of subjects originally targeted to be included in the study
22 Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:

10 Males
12 Females
 Unknown

Ethnicity:

 Latinos or Hispanics
21 Not Latinos or Hispanics
1 Unknown

Race:

 American Indian or Alaska Native
 Asian
 Blacks or African American
 Native Hawaiian or Other Pacific Islander
21 White
 Other, specify: _____
1 Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

Allegheny County

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?

_____ Yes
 _____ **X** No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?

_____ Yes
 _____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

- Project 01 – Smith – Three cases of isolated
- Project 01 – Smith – Investigation of NEB1 deletions
- Project 03 – Zhang – Molecular profiling of aromatase

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes X No _____

If yes, please describe your plans:

Drs. Tarhini, Kalinski, Kirkwood, and other collaborators are preparing to submit the novelty of this study—demonstration of the feasibility of prolonged cannulation of lymphatic vessels for infusion of DC prepared *ex vivo*—for publication.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.

Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment.

Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

New methods for maturing dendritic cells (DCs) to produce more effective DC-based anticancer vaccines were developed.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes _____ No X

If “Yes” to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is “No.”)

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?

Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?

Yes_____ No____

If yes, indicate number of patent, title and date issued:

Patent number:

Title of patent:

Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

NAME Kirkwood, John M.	POSITION TITLE Professor of Medicine		
eRA COMMONS USER NAME kirkwoodjm@upmc.edu			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Oberlin College, Oberlin, OH	BA	06/69	Biochemistry
Yale University School of Medicine, New Haven, CT	MD	06/73	Medicine
Yale University School of Medicine, New Haven, CT	Int/Res	06/76	Internal Medicine
Harvard University, Boston, MA	Fellowship	06/78	Tumor Immunology

A. Personal Statement

I have directed the UPCI Melanoma Program since 1986, and the Melanoma Committee of the ECOG (now ECOG-ACRIN) since 1989, where our studies at UPCI have served as the impetus for new multicenter phase II and III trials in the national cooperative groups. My research has focused on the analysis of the immunobiology and molecular features of melanoma progression, in studies of advanced disease and high-risk operable disease. Our development of new therapies including the first effective adjuvant therapy of melanoma has included the assessment of biomarkers that may refine application of these therapies. Our translational investigations of immunotherapies and molecularly targeted agents combined with one another have included phase I-II and III studies of cytokines, IFNs and antibodies alone and in conjunction with protein/peptide vaccines. In the adjuvant sphere we have turned to more rapidly informative neoadjuvant study designs, completing the first such evaluations of IFN alfa-2b, ipilimumab, and now are evaluating the combination of these agents. This model has illuminated the mechanisms of immunotherapy and allowed the assessment of antitumor immunity in serum and tumor tissue over time. These neoadjuvant trial designs have moved from phase I-II into phase III trials, with the national and international cooperative groups. My increasing focus upon prevention, led to the formation of the Melanoma Prevention Working Group in ECOG-ACRIN, now involving interdisciplinary experts from all of the cooperative groups. Recent initiatives have focused upon earlier disease, including the precursor and risk marker lesion known as the atypical/dysplastic nevus, where we have initiated an education system wide internet education program for primary care physicians in 2014 at UPMC. This work has also recently included the development of an oral sulforaphane prevention trial (UPCI 10-114) to define PK/PD and signaling effects on STAT3 in atypical nevi. The investigative mission to understand the mechanism and optimal therapeutic application of new agents has throughout been coupled with the goal of mentoring medical and graduate students, postdoctoral fellows, and junior faculty physician-scientists facilitated through our newly funded T32.

B. Positions and Honors

Positions and Employment

1967-1969	Senior Scholar in Tumor Immunology, Memorial Sloan Kettering, New York, NY
1976-1978	Assistant in Medicine, Peter Bent Brigham Hospital, Boston, MA
1978-1983	Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT
1978-1986	Attending Physician, Yale University School of Medicine
1978-1986	Consultant - Attending, West Haven VA Hospital, West Haven, CT
1983-1986	Associate Professor of Medicine and Dermatology, Yale University School of Medicine

1985-1986 Roosevelt Fellow/Visiting Scientist, Istituto per Tumori, Milan, Italy
 1986-1993 Associate Director for Medical Oncology, UPCI, Pittsburgh, PA
 1986-1996 Prof and Chief, Div. of Med. Oncol, Dept of Medicine, University of Pittsburgh, PA
 1993- Director, Melanoma Program, UPCI, Pittsburgh, PA
 1996-2006 Prof and Vice Chairman for Clinical Research, Dept of Med, University of Pittsburgh,
 Pittsburgh,
 2009- Prof of Clinical and Translational Science, University of Pittsburgh CTSI, Pittsburgh, PA

Honors

1980 Fellow of the Int'l Cancer Research Exchange Program, Sydney Univ Hosp, Australia
 1986 Roosevelt Fellow, American Cancer Society, NCI – Milan, Italy
 1989 Scientific Advisory Board, Cancer Research Institute, New York, NY
 1996 UPCI Scientific Leadership Award, UPCI, Pittsburgh, PA
 2000 ISICR Milstein Award, Amsterdam, The Netherlands
 2005 Wings of Hope Award, New York, NY
 2005 European Society of Cytokine Research Award
 2008 Donald Wade Waddell Award, University of Arizona
 2010 Wallace H. Clark Jr., MD Lecturer in Cutaneous Oncology

C. Selected Peer-Reviewed Publications (Selected from over 300 peer-reviewed publications)

Wang et al. (2008). Effects of high-dose IFN α 2b on regional lymph node metastases of human melanoma: modulation of STAT5, FOXP3, and IL-17. *Clin Cancer Res.* 14(24):8314-8320.

Tarhini et al. (2009). Prognostic significance of serum S100B protein in high-risk surgically resected melanoma patients participating in Intergroup Trial ECOG 1694. *J Clin Oncol.* 27(1):38-44.

Kirkwood et al. (2012). Immunotherapy of cancer in 2012. *CA Cancer J Clin.* 62(5):309-335.

Tarhini et al. (2012). Safety and efficacy of combination immunotherapy with interferon alfa-2b and tremelimumab in patients with stage IV melanoma. *J Clin Oncol.* 30(3):322-328.

Kirkwood et al. (2013). Comparative clinical benefits of systemic adjuvant therapy for paradigm solid tumors. *Cancer Treat Rev.* 39(1):27-43.

Slingluff et al. (2013). A randomized phase II trial of multiepitope vaccination with melanoma peptides for cytotoxic T cells and helper T cells for patients with metastatic melanoma (E1602). *Clin Cancer Res.* 19(15):4228-4238.

Ribas et al. (2013). Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. *J Clin Oncol.* 31(5):616-622.

Go et al. (2013). ECOG phase II trial of graded-dose peginterferon alpha-2b in patients with metastatic melanoma overexpressing basic fibroblast growth factor (E2602). *Clin Cancer Res.* 19(23):6597-6604.

Tarhini et al. (2014). A four-marker signature of TNF-RII, TGF- α , TIMP-1 and CRP is prognostic of worse survival in high-risk surgically resected melanoma. *J Transl Med.* 12:19.

Tarhini et al. (2014). Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. *PLoS One.* 9(2):e87705.

Fourcade et al. (2014). PD-1 and Tim-3 regulate the expansion of tumor antigen-specific CD8+ T cells induced by melanoma vaccines. *Cancer Res.* 74(4):1045-1055.

McArthur et al. (2014). Safety and efficacy of vemurafenib in BRAF and BRAF mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol.* 15(3):323-332.

Flaherty et al. (2014). Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. *Lancet Oncol.* 15(3):297-304.