

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 717-783-2548.

1. **Grantee Institution:** The Trustees of the University of Pennsylvania
2. **Reporting Period (start and end date of grant award period):** 1/1/2010-12/31/2013
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Gearline R. Robinson-Hall, BSF
4. **Grant Contact Person’s Telephone Number:** 215-746-6821
5. **Grant SAP Number:** 4100050912
6. **Project Number and Title of Research Project:** 4 - *The Role of CCR5 Blockade on the Prevention of Graft-Vs-Host Disease*
7. **Start and End Date of Research Project:** 1/1/2010 – 12/31/2013
8. **Name of Principal Investigator for the Research Project:** David L. Porter, 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:

\$ 602,609.98

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
Reshef	Asst.Prof.	32% Yr4	\$53,922.87
Gao	Clinical Res. Coordinator	25% Yr4	\$14,535.00
Vassilev	Clinical Res. Assistant	27% Yr1; 88% Yr2; 100% Yr.3	\$78,411.96
Jemison	Clinical Practice Nurse	50% Yr3	\$30,257.24

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
Porter, David L	PI	10%

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:

Pfizer (research grant) \$20,000

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 _____

My colleague, Dr Ran Reshef was able to compete for and received additional funding as noted below.

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 to be awarded:
Lymphocyte Trafficking Blockade in Allogeneic Stem-Cell Transplantation	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)		\$161,800/yr x 3	\$161,800/yr x 3
Separating the graft-versus-host and graft-versus-tumor responses by blocking lymphocyte chemotaxis	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input checked="" type="checkbox"/> Nonfederal source (specify: American Society of Clinical Oncology)		\$62,467/yr x 3	\$62,467/yr x 3
Control of Human Graft-Versus-Host Disease by Modulation of Lymphocyte Trafficking	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input checked="" type="checkbox"/> Nonfederal source (specify: National Marrow Donor Program, Amy Strelzer Manasevit Research Program)		\$74,074/yr x 3	\$74,074/yr x 3

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

Yes x No _____

If yes, please describe your plans:

Additional funding and sources will depend on the results of our current phase II trial. Ultimately we hope a project studying blockade of lymphocyte trafficking to prevent graft-versus-host disease can be funded under an RO1, R23, or possibly even a program project mechanism.

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

We have initiated a follow up trial studying maraviroc in patients who had the most significant benefit in our pilot trial. We are performing a phase 2 study of extending exposure of maraviroc to 90 days and limiting enrollment only to recipients of unrelated donor stem cell grafts. We have 12 of a planned 32 patients on this clinical trial. Furthermore the use of maraviroc to prevent GVHD will be one of 3 arms on a planned national randomized phase II trial run through the blood and marrow transplant clinical trials network (BMT-CTN). We are planning a number of correlate to scientific assays to study the impact of maraviroc on immune reconstitution. We are looking at T-cell number and function and identifying differentiation phenotype of T cells in patients who were or were not exposed to maraviroc. We are trying to identify recent thymic emigrants to see if maraviroc impacts trafficking to the thymus. We are also studying CCR 5 haplotype as well as CCR 5 level of expression in donor T cells to see if this will impact either graft versus host disease or protection for graft-versus-host disease by maraviroc.

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 had a dramatic impact on our infrastructure. We were able to build a comprehensive data base for this trial using these funds to partially support a research coordinator/data manager. This data base was then leveraged and expanded to support our entire allogeneic SCT program (using other funds to support this part of that project). This had an immediate impact on our program in terms of quality management but also in research capability. Furthermore we were able to partially support a practice nurse (RN) to help with research subjects. Using an RN in this model was new to our group and was tremendously successful providing expert, timely and appropriate care to these patients. This model has now been expanded to other areas of our program and has expanded our research capability and quality ensuring timely visits, testing, assessments, etc.

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 X _____ No _____

If yes, please describe the collaborations:

Given our success with this project, this approach has been adapted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) as one of 3 arms on a planned national multicenter randomized Phase 2 study. Dr Reshef from Penn will be one of the national Principal Investigators on this trial. In addition, because of this work Penn was asked to join a consortium with University of Michigan to study biomarkers as predictors of GVHD.

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 (\square) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Project Overview

Based on compelling clinical observations and our preliminary data, we pursued a clinical trial to determine the feasibility, efficacy and safety of Maraviroc, a CCR5 inhibitor, as part of GVHD prophylaxis in patients undergoing reduced-intensity conditioned (RIC) allogeneic SCT. We explored correlative immunologic studies to assess immune reconstitution after transplant. This project was designed to test the role of CCR5 inhibition on GVHD prophylaxis, and to enhance the understanding of the role of lymphocyte trafficking in clinical transplantation. The specific aims of the current project were:

Aim 1: Determine the dosing, safety, and feasibility of the oral CCR5 inhibitor Maraviroc in combination with conventional tacrolimus and methotrexate (tac/mtx) as GVHD prophylaxis in patients undergoing reduced intensity (RIC) allogeneic SCT. This was a prospective phase I/II, single arm, single-center trial.

Patients received Maraviroc beginning after the last dose of the conditioning regimen (day-2) until day +30 in addition to a standard GVHD prophylaxis regimen of tac/mtx. Patients will undergo a 7 time point detailed pharmacokinetic analysis. Toxicity will be monitored and recorded using the NCI CTCAE 3.0 criteria.

Aim 2: To assess the efficacy of the CCR5 inhibitor Maraviroc as GVHD prevention in combination with conventional tac/mtx during RIC allogeneic SCT. This aim tests the hypothesis that inhibition of lymphocyte trafficking through CCR5 inhibition early after allogeneic SCT will decrease the incidence of acute GVHD.

Aim 3: To explore the effect of CCR5 inhibition on post-transplant immune reconstitution and on biological surrogates for GVT activity, and identify additional candidate chemokine receptors that can be used as therapeutic targets in GVHD prevention.

Subaim 3a: Determine the effect of the CCR5 inhibition on immune reconstitution after RIC SCT to test the hypothesis that the CCR5 inhibitor Maraviroc promotes immune reconstitution following RIC SCT.

Subaim 3b: Determine the effect of Maraviroc on in vitro surrogates for graft-vs-tumor (GVT) activity. We hypothesize that CCR5 inhibition preserves the GVT effect after allogeneic SCT. We will identify and compare induction of tumor-specific immunity in patients undergoing RIC SCT with and without the CCR5 inhibitor Maraviroc using: 1) antigen-specific T-cell assays; 2) functional T-cell studies; 3) tumor-specific T-cell assays.

Aim 1 of this project has been completed and results published in abstract and by peer review manuscript. Unfortunately, his publication did not acknowledge the PA Department of Health purely by oversight and through an editing error. It was picked up after the final galleys came through and the editors would not permit modification at that point. This was indeed an error on our part. The PA Department of Health will be acknowledged in all future publications. Through June, 2012 we enrolled a total of 38 subjects on our clinical trial titled *The Role of*

CCR5 Blockade on the Prevention of Graft-Vs-Host Disease. Our results showed this therapy was both safe and feasible. The initial pharmacokinetic analysis portion of the study involved the first 12 patients and this phase of the project was completed and analyzed. It was feasible to administer drug to all patients. There was no toxicity directly attributable to the drug and we picked the higher dose level to move forward with for our phase II study. This further confirms feasibility and safety of the drug. The drug was temporarily held in 7 patients due to grade 3 LFT abnormalities (n=2) or grade 3-4 mucositis (n=5). LFT abnormalities did not recur when the drug was restarted in both patients. The adverse event profile was similar to the expected toxicity observed in patients undergoing RIC SCT.

Although maraviroc is not associated with an increase in infections or hematologic toxicity in HIV patients, to further assess safety we studied whether CCR5 blockade inhibits effector T-cell responses or hematopoietic activity that might negatively impact non-HIV patients undergoing HSCT. First, we tested whether the presence of maraviroc affected T-cell performance in a series of functional assays and found that pharmacologic doses of maraviroc (0.5-5 μ M) had no effect on T-cell proliferation and cytokine secretion in response to cognate viral peptide (CMV) stimulation; moreover, there was no diminution of specific T-cell cytotoxicity against CMV peptide-loaded T2 cells.

Second, to investigate the potential effect of maraviroc on hematopoiesis, we plated fresh normal donor PBMC in methylcellulose in the presence of appropriate cytokines and demonstrated that formation of myeloid and erythroid colonies was not significantly affected by the presence of maraviroc compared to untreated cells. These results are in agreement with clinical observations that failure of engraftment was never reported to be associated with SCT from Δ 32-CCR5 carriers.

All evaluable patients had adequate neutrophil engraftment (ANC>500/ μ L) at a median time of 15 days (range 10-27); one subject was not evaluable due to death on day 12 from sepsis. The median time to platelet engraftment (platelet count>20,000/ μ L without transfusions) was 19 days (range 9-84) and 1 patient failed to achieve independence from platelet transfusions in the setting of early relapse of his T-cell lymphoma.

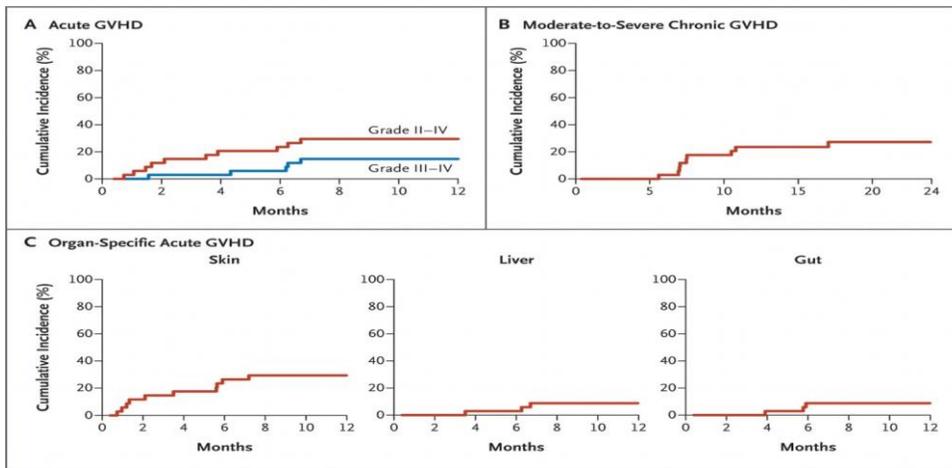
We have seen no increase in unexpected infections. In as yet unpublished data we compared outcomes on this clinical trial to a group of similar concurrent control patients. The incidence and type of infection are shown below. There was no difference in infection risk for recipients of maraviroc compared to recipients of more traditional GVHD prophylaxis.

Infection (up to day 100)	Tac/MTX+MVC N (%)	Tac/MTX N (%)
Bacteremia	8 (21)	11 (23)
CMV reactivation (up to day 180)	7 (18)	9 (19)
UTI	3 (8)	7 (15)
C. Diff. colitis	5 (13)	6 (13)
Pneumonia	2 (5)	1 (2)
Viral infections	0 (0)	2 (4)
Fungal Infections	0 (0)	3 (6)
Others:		
Soft tissue infection	1 (3)	1 (3)
Cholecystitis	1 (3)	2 (4)
Infected prosthetic joint	1 (3)	0 (0)
Sinusitis	0	1 (3)
Peritonitis	0	1 (3)

We have also completed Aim 2. Among 35 evaluable patients (3 were not evaluable for primary endpoint since they were treated on the phase I portion with low levels of MVC below our defined threshold), the cumulative incidences of grade II-IV and grade III-IV acute GVHD at day 100 were $14.7 \pm 6.1\%$ (rate \pm standard error) (95%CI [5.3, 28.7]) and $2.9 \pm 2.9\%$ (95%CI [0.2, 13.2]) respectively (Figure 1a). These rates were 2-3 fold lower than those reported in other studies of RIC SCT. Importantly, in the first 100 days, there were no cases of acute GVHD involving the liver or intestine, strikingly similar to the findings in mouse models in which a CCR5 antibody ameliorated GVHD of the liver and gut. The only cases of acute GVHD that we observed up to day 100 were limited to the skin. At day 180, the cumulative incidence of grade II-IV acute GvHD was $23.6 \pm 7.4\%$, and organ involvement remained largely confined to the skin with low rates of liver ($2.9 \pm 2.9\%$) and gut ($8.8 \pm 5.0\%$) GvHD. The cumulative incidence of grade III-IV GvHD was only $5.9 \pm 4.1\%$ at day 180, largely attributable to low incidence rates of gut and liver GvHD, which were absent before day 100 and remained infrequent up to day

180. In evaluable participants who received a graft from their HLA-matched sibling (n=11), there were no cases of GVHD prior to day-100 and only one case of acute GVHD prior to day-180. Outcomes are shown here:

Rate (%)	Severe GvHD (Gr. 3-4)		Acute GvHD (Gr. 2-4)	
	Day 100	Day 180	Day 100	Day 180
Tac/MTX+MVC	2.9	5.9	14.7	23.6



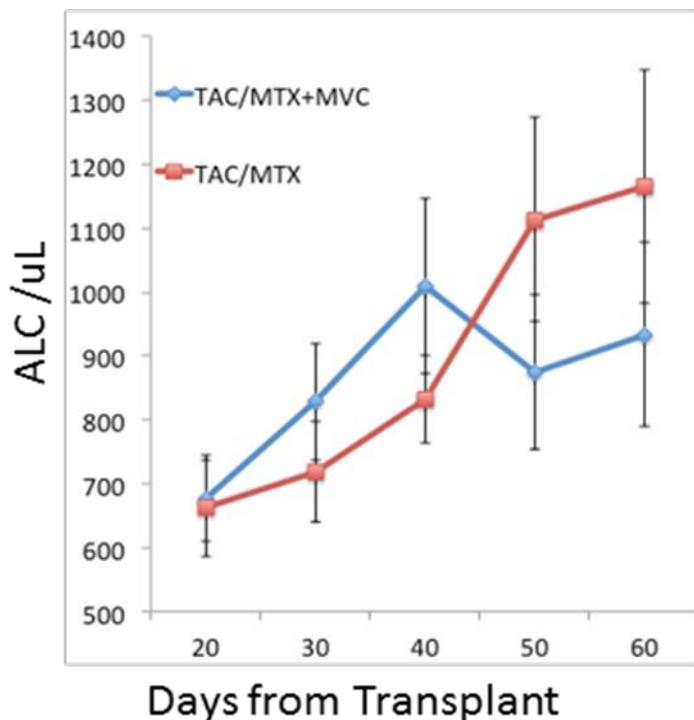
Furthermore, non-relapse mortality was quite low as seen below:

Rate (%)	NRM	
	6 mo.	12 mo.
Tac/MTX+MVC (N=35)	2.9	11.7

The cumulative incidence of relapse in recipients of maraviroc was $55.9 \pm 8.8\%$ at 1 year, which is not higher than expected considering the disease characteristics and the reduced intensity conditioning regimen, which is associated with high risk for relapse. A subset analysis of patients with AML/MDS and lymphoid malignancies did not reveal any significant differences in relapse rates (data not shown). The estimated 2-year survival rate was $47.1 \pm 8.6\%$.

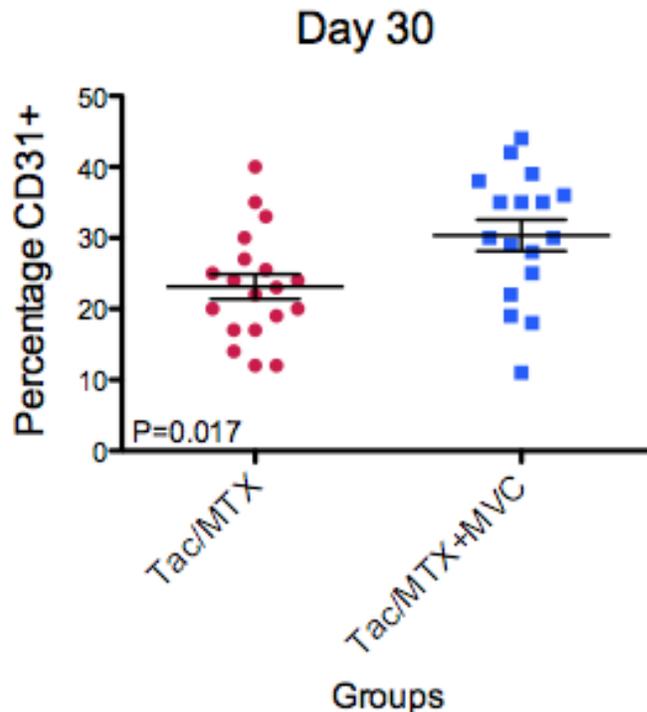
We have now compared outcomes in recipients of the experimental therapy (maraviroc) to a group of similar patients treated with conventional GVHD prophylaxis during a similar period of time (concurrent controls). These results are unpublished. Analysis is ongoing but initial data supports the conclusion that the addition of maraviroc significantly lowers the risk of acute GVHD without an increase in infection, non-relapse mortality, or relapse. We hope to complete the analysis and publish these results by the summer of 2014.

Aim 3 has been completed as well as we have now been able to study immune reconstitution and begin pulmonary studies involving other chemo kind receptors that may be used as targets for GVHD prevention. In aim 3a we studied immune constitution by looking at lymphocyte counts and recent thymic emigrants. We were able to compare these to a similar group of concurrent control patients treated in a similar way but without the addition of maraviroc for GVHD prophylaxis. Figures below suggest higher lymphocyte counts at day 30 and day 40. Available data suggests that rapid lymphocyte recovery is associated with lower risks of subsequent relapse.



Furthermore there was a higher percentage of recent thymic emigrants (as tested by studying the percentage of CD31 positive T cells at day 30) in recipients of maraviroc as shown below. This

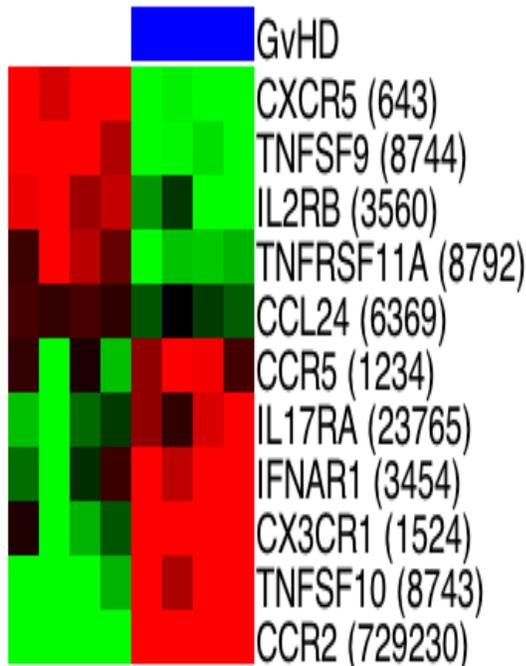
is logical since data suggests that CCR 5 prevents trafficking to the sinus. CCR 5 blockade might promote T cell trafficking to the thymus and enhance the immune recovery.



For aim 3B we studied recovery of T cell chimerism as a surrogate for graft versus tumor activity. Maraviroc had no impact on recovery of donor T cells when compared to our control population. We were also able to show that T cells exposed to maraviroc retained functional activity using cytokine release assays and in vitro cell killing. We were not able to compare tumor-specific immunity however. This has been very difficult to do in this or other settings.

To complete aim 3 we have begun to study other potential candidate chemokine receptors that may be used as therapeutic targets in GVHD prevention. Using microarray analysis for gene expression profiling, we studied samples collected and banked from this trial from a small number of patients who had no GVHD at the time of sampling. Four of these patients went on to develop GVHD within 14 days and four of these patients had no GVHD for at least 2 months after sampling. We identified 879 differentially expressed genes. Among the highest differentially expressed genes in patients destined to develop GVHD were CCR 5 as well as CCR 2. CCR 2 is another important chemokine receptor necessary for lymphocyte trafficking. The differential expression profiles are shown here.

IMPORTANT LYMPHOCYTE TRAFFICKING GENES:



Based on these results, we performed hematopoietic stem cell transplant in mice using donors that were deficient in CCR2. Preliminary data confirmed older data in the literature showing that T cells that do not express CCR 2 resulted in less GVHD than control T cells. There is an available dual CCR 2/CCR 5 antagonist currently in phase II trials for the treatment of HIV. The drug is called cenicriviroc. We have been in discussions with the company that has rights to this compound, Tobira Therapeutics, about potential funding for future studies looking at dual inhibition of CCR 2/CCR 5. These discussions are ongoing at the time of this report.

Presentations and abstracts:

Prevention of Graft-Versus-Host Disease by Inhibition of Lymphocyte Trafficking Using a CCR5 Antagonist. Reshef et al. Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 673.

Inhibition of Lymphocyte Trafficking Using a CCR5 Antagonist – Final Results of a Phase I/II Study. Reshef et al, Blood (ASH Annual Meeting Abstracts), Nov 2011; 118: 1011.

Feasibility, Safety and Efficacy of Maraviroc, a CCR5 Antagonist, in Graft-Versus-Host Disease Prevention After Reduced intensity Conditioned (RIC) Allogeneic Stem Cell Transplant (SCT): a Phase I/II Study. Reshef et al. Biology of Blood and Marrow Transplantation Volume 17, Issue 2, Supplement , Page S331, February 2011.

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?

>8 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?

38 Number of subjects originally targeted to be included in the study
38 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:

15 Males
23 Females
 Unknown

Ethnicity:

 Latinos or Hispanics
38 Not Latinos or Hispanics
 Unknown

Race:

- American Indian or Alaska Native
 Asian
 Blacks or African American
 Native Hawaiian or Other Pacific Islander
 White
 Other, specify: _____
 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.)

Philadelphia, PA.

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
 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
- Project 04 – Bates – Neonatal intensive care

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:

We are planning to finish our analysis and write a manuscript that compares the outcome of these patients to our group of concurrent controls. We hope this will be completed by the summer of 2014.

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.

The major discovery as described above is the finding that the addition of maraviroc to standard GVHD prophylaxis results in a remarkably low incidence of severe graft versus host disease. We believe the mechanism is through inhibition of lymphocyte trafficking. Furthermore this activity does not result in increased infections or relapse implying preservation of graft versus tumor activity without an increase in immune suppression. We believe this has the potential to change the approach to allogeneic stem cell transplant and GVHD prevention. This discovery has allowed us to move forward with additional testing of this approach with plans for both single center and multicenter trials.

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

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME David L Porter	POSITION TITLE Professor of Medicine Director, Blood and Marrow Transplantation		
eRA COMMONS USER NAME (credential, e.g., agency login) DLPORTER			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Univ. of Rochester, Rochester, NY	B.A.	1981	Biochemistry
Brown Univ., Providence, RI	M.D.	1987	Medicine

B. Positions and Honors

Research and Professional Experience

- 1987-90 Intern, Resident, Univ. Hospital, Boston University Medical Center, Boston, MA (N Levinsky, Chief)
- 1990-91 Clinical Fellow in Medicine, Harvard Medical School, Boston, MA (R. Handin, Chief)
- 1990-91 Clinical Fellow in Medicine, Brigham & Women's Hospital, Boston, MA (R. Handin, Chief)
- 1991-93 Research Fellow in Medicine, Harvard Medical School (R. Handin, Chief)
- 1991-93 Research/Clinical Fellow in Medicine, Brigham & Women's Hospital (R. Handin, Chief)
- 1993-95 Instructor in Medicine, Harvard Medical School (R. Handin, Chief)
- 1996- Director, Allogeneic Bone Marrow Transplant and Immunotherapy, Univ. of PA (S. Emerson, Chief)
- 1996- Assoc. Director, Bone Marrow and Stem Cell Transplantation, Univ. of PA (S. Emerson, Chief)
- 1996-2002 Asst. Prof. of Medicine, Univ. of Pennsylvania Health System, Philadelphia, PA (S. Emerson, Chief)
- 2002-2008 Associate Prof. of Medicine, Univ. of Penn Health System, Philadelphia, PA (S. Emerson, Chief)
- 2008 Professor. of Medicine, Univ. of Penn Health System, Philadelphia, PA (L. Schuchter, Chief)
- 2008- Director, Blood and Marrow Stem Cell Transplantation, Univ. of PA (L. Schuchter, Chief)

C. Selected Peer-reviewed Publications (limit 15)

1. Paralkar VR, Nasta SD, Morrissey K, Smith J, Vassilev P, Martin ME, Goldstein SC, Loren A, Rook AH, Kim EJ, Porter DL.: Allogeneic hematopoietic stem cell transplantation for primary cutaneous T cell lymphomas. Bone Marrow Transplantation, 47: 940-945, 2012
2. Reshef R, Luger S, Hexner EO, Loren AW, Frey NV, Nasta SD, Goldstein SC, Stadmauer EA, Smith J, Bailey S, Mick R, Heitjan DF, Emerson SG, Hoxie JA, Vonderheide RH, Porter DL.: Effect of Blocking Lymphocyte Chemotaxis on Visceral Graft-vs-Host Disease. New England Journal of Medicine 367: 135-145, July 2012..

3. Anasetti, C, B. R. Logan, S. J. Lee, E. K. Waller, D. J. Weisdorf, J. R. Wingard, C. S. Cutler, P. Westervelt, A. Woolfrey, S. Couban, G. Ehninger, L. Johnston, R. T. Maziarz, M. A. Pulsipher, D. L. Porter, S. Mineishi, J. M. McCarty, S. P. Khan, P. Anderlini, W. I. Bensinger, S. F. Leitman, S. D. Rowley, C. Bredeson, S. L. Carter, M. M. Horowitz and D. L. Confer: Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors. New England Journal of Medicine 367: 1487-1496, Oct 2012.
4. Grupp, SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH.: Chimeric Antigen Receptor Modified T Cells for Acute Lymphoid Leukemia. New England Journal of Medicine 368: 1509-1518, April 2013

BIOGRAPHICAL SKETCH

NAME Ran Reshef, MD		POSITION TITLE Assistant Professor of Medicine	
eRA COMMONS USER NAME RESHEF		POSITION TITLE Instructor A	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Tel-Aviv University, Israel	B.Med.Sci.	1996	Medical Science
Tel-Aviv University, Israel	M.D.	2003	Medicine
University of Pennsylvania	M.Sc.	2011	Translational Research
Intern, Sourasky Tel-Aviv Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel		1997-1998	Rotating Internship
Resident in Medicine, Sourasky Tel-Aviv Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel		2003-2007	Internal Medicine
Clinical Fellow, University of Pennsylvania		2007-2009	Hematology & Oncology

A. Personal Statement.

I am a physician scientist specializing in translational research in cellular therapy. My research focuses on two primary areas: 1. Investigating lymphocyte trafficking mechanisms that affect the immunologic outcomes of stem-cell transplantation, including graft-versus-host disease, graft-versus-leukemia responses and immune reconstitution. We pioneered the use of CCR5 blockade in allogeneic stem-cell transplantation, as recently published in the *New England Journal of Medicine*. 2. Identifying biomarkers for graft-versus-host disease and other outcomes of allogeneic transplants by analyzing genomic and phenotypic variables and using advanced computational biology methods for biomarker identification and validation.

B. Positions and Honors.

Positions, Employment

1999-2003	Medical Officer, Medical Corps, Israeli Defense Forces
2004-2005	Postdoctoral Research, Schwartz Lab, Department of Medicine, Sourasky Tel-Aviv Medical Center, Tel-Aviv University
2006	Postdoctoral Research, Reisner Lab, Department of Immunology, Weizmann Institute of Science
2009-2011	Instructor of Medicine, University of Pennsylvania Perelman School of Medicine
2008-2012	Postdoctoral Research Fellow, Vonderheide Lab, Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia
2009-present	Attending Physician, Heme malignancies and BMT service, Hospital of the University of Pennsylvania
2011-present	Assistant Professor of Medicine, University of Pennsylvania Perelman School of Medicine

Other Training

- 2008 Methods in Clinical Cancer Research Workshop, American Association for Cancer Research / American Society of Clinical Oncology. Vail, CO
- 2009 Clinical Research Training Institute, American Society of Hematology. La Jolla, CA

Board Certifications

- 2007 Internal Medicine (Israel)
- 2010 Hematology (Israel)

Editorial Positions

Ad Hoc Manuscript Reviewer (last 3 years): Nature Biotechnology, Biology of Blood and Marrow Transplantation, American Journal of Transplantation, Haematologica, Immunotherapy, Springer Science, American Journal of Hematology, Cancer Biology & Therapy, Expert Reviews of Hematology, Transplant Infectious Diseases, Transplant International, Annals of Transplantation.

Study Sections: NCI Provocative Questions (2011)

Abstract Reviewer: ASH Annual Meeting (2010, 2012)

Editorial Board: American Journal of Hematology (2012-)

C. Original peer-reviewed research articles (in chronological order).

1. Beatty GL, Smith JS, Reshef R, Patel KP, Colligon TA, Vance BA, Frey NV, Johnson FB, Porter DL, Vonderheide RH (2009). Functional unresponsiveness and replicative senescence of myeloid leukemia antigen- specific CD8+ T cells after allogeneic stem cell transplantation. Clin Cancer Res 15: 4944-53
2. Reshef R, Luskin MR, Kamoun M, Vardhanabhuti S, Tomaszewski JE, Stadtmauer EA, Porter DL, Heitjan DF, Tsai DE (2011). Association of HLA Polymorphisms with Post-Transplant Lymphoproliferative Disorder in Solid-Organ Transplant Recipients. Am J Transplant 11:817-25
3. Rager A, Frey N, Goldstein SC, Reshef R, Hexner EO, Loren A, Luger SM, Perl A, Tsai D, Davis J, Vozniak M, Smith J, Stadtmauer EA, Porter DL (2011). Inflammatory Cytokine Inhibition with Combination Daclizumab and Infliximab for Steroid Refractory Acute Graft-Versus-Host Disease. Bone Marrow Transplant 46:430-5
4. Reshef R, Vardhanabhuti S, Luskin MR, Heitjan DF, Hadjiliadis D, Goral S, Krok KL, Goldberg LR, Porter DL, Stadtmauer EA, Tsai DE (2011). Reduction of Immunosuppression as Initial Therapy for Post-Transplantation Lymphoproliferative Disorder. Am J Transplant 11: 336-47.