

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:** National Disease Research Interchange
2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2010
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Lonsdale, PhD
4. **Grant Contact Person’s Telephone Number:** 800-222-6374 x 271
5. **Grant SAP Number:** 4100050902
6. **Project Number and Title of Research Project:** 1 - Fine Mapping of Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes
7. **Start and End Date of Research Project:** 1/1/2010 – 12/31/2010
8. **Name of Principal Investigator for the Research Project:** John Lonsdale, PhD
9. **Research Project Expenses.**

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

\$73,679

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
Miller	Director	10%	\$ 9,230
Tang	Manager	45%	\$19,226

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	Position Title	% of Effort on Project
Lonsdale	PI	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 _____ No X _____

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

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 _____ No X _____

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:
None	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)		\$	\$

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:

With our collaborators at Columbia University, we are submitting a proposal for the Type 1 Diabetes Impact Award (DP3). This submission is due March 11th, 2011. NDRI will provide subcontract support for this proposal. The proposal will continue our work exploring the genetic contributions to the development of complications in individuals with diabetes.

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

We are continuing to explore the genetic contributions to the development of complications in individuals with diabetes. Specifically, we are exploring the availability of confirmation datasets with similar data points and DNA availability to confirm our previous report on significant SNPs demonstrated to be protective to the development of complications. Additionally, with this years grant we are examining functional differences from normal retinas, diabetic normal retinas and diabetic retinopathy affected retinas. This work will not only provide functional confirmation of the importance of the SNPs demonstrated to be protective from our previous analysis, but will lead to potentially additional genetic targets to explore. Also, family follow-up on a yearly basis as to the vital information including new family members, newly diagnosed individuals with diabetes (type 1, type 2 and monogenic forms), and development or absence of complications will continue.

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 X No _____

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female	1		1	
Unknown				
Total	1		1	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1		1	
Unknown				
Total	1		1	

	Undergraduate	Masters	Pre-doc	Post-doc
White			1	
Black				
Asian	1			
Other				
Unknown				
Total	1		1	

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 _____ No X _____

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

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:

We have developed a collaboration with the University of Pennsylvania's Microarray and DNA Sequencing Facility. The facility carries out all our sequencing and microarray work.

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 X _____ No _____

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

Due to our interest in growing the National Genetics Family Registry to provide additional families eligible for enrollment in these studies, we have continued to reach out to the diabetic community through individual diabetes educators, diabetes on-line communities, and JDRF chapters. We have recruited over 20 families in the last 6 months alone to enroll in the Registry.

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

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. 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.

The overall goal of this project is to find specific genes responsible for the devastating diabetes complications. Our specific aims are to: 1) Analyze the SNP data using case-control association analysis (typing for which was supported by the 2008 PA Formula grant), 2) Genotype representative SNPs on new members selected in the HBDI families to be able to perform family-based association and linkage analyses (typing for which will be funded in this PA Formula grant) and confirm the results from the case-control analysis, 3) Continue our annual program of participant follow-up using the updated family questionnaire to track any development or progression of microvascular complications among patients with both T1D and T2D, 4) Plan more genotyping and execute more analyses on other specific genes found to be significant in the development of retinopathy complications in the HBDI T1D patients identified from funds from the 2008 PA Formula Grant.

Aim 1. Analyze the SNP data generated with support of the 2008 PA Formula grant (*SNP saturation study*). The goal is to confirm and better define the role of a specific gene (on chromosome 12) found to be significantly associated to diabetic retinopathy by our group. The SNP data were obtained on a subgroup of HBDI subjects already genotyped by T1DGC. Definition and selection of cases and controls for the saturation study was guided by the same criteria of the original study: "cases" were defined as T1D patients with retinopathy and "controls" were defined as patients with at least a 20-year history of T1D but without complications and without 1st degree relatives with complications.

A set of 95 cases with retinopathy, 38 cases with nephropathy, 31 cases with neuropathy and 167 controls without microvascular diabetic complications were selected from the HBDI cohort genotyped by T1DGC. These samples were sent to the University of Pennsylvania Molecular Diagnostics Laboratory. 29 additional SNPs were selected within the gene, based on minimum allele frequency, linkage disequilibrium and distance from one another. They are located in the gene and in the promoter and 3' UTR regions.

The gene selected for the SNP saturation study already had 40 SNPs genotyped in the HBDI sample by T1D consortium, giving an excellent coverage to better define a possible region inside the gene associated to retinopathy.

Using a case-control association analysis we analyzed the 29 extra SNPs; a significant association of 3 SNPs with retinopathy was confirmed (p-values ranging from 0.0002391 – 0.009694, OR 1.69-1.864). They are in the same intronic region of the SNPs found to be significant among the original 40 SNPs genotyped by the T1DGC.

Multivariate models that incorporated potential confounders as age, duration of diabetes, and sex and Groups were stratified to determine whether some markers were specifically associated with subgroups defined by presence/absence of other complications (retinopathy, nephropathy, neuropathy, hypertension, and cardiac conditions). Haplotypic analysis will be carried out as well.

These results provide strong preliminary evidence for genetic association with diabetic microvascular complications. Our results suggest that genes predisposing to T1D may also be involved specifically in complications development (or lack of development) and will be submitted for publication soon.

Aim 2. Perform SNP analysis of additional family members to allow for family-based association and linkage analyses. New members of the families analyzed for aim 1 (families of cases and families of controls) will be selected and SNPs representative of the region of interest of the gene determined in Aim 1 will be genotyped.

Because we have family data, we can additionally test any statistically significant results from the case-control study using family-based association. Multipoint linkage analysis, besides, is able to determine if a locus found for the complication is actually related to the complication alone or to T1D.

Analysis of each family genotyped by T1DGC was done to select informative families to allow for family-based association and linkage analysis. 392 individuals from 88 families were selected for additional SNP analysis. The selection of informative families included families with affected children who were discordant for development of complications. Due to updated family information from returned completed questionnaires, an additional 6 families were eligible for inclusion (Table 1). Individuals noted as absent of complication were included only upon either medical record review or other confirmation from the individual's physician.

<i>N. of HBDI Families</i>	retinopathy	nephropathy	neuropathy	any complication
At least 1 sibling with and at least 1 sibling without:	88	77	42	88
At least 2 siblings with:	49	17	11	65
At least 2 siblings without:	318	356	357	222
Trios: two parents and 1 affected sibling with:	144	79	63	249

Table 1. Description of type 1 diabetes HBDI families with at least 1 sibling without retinopathy, nephropathy or neuropathy.

Validation analysis of markers significantly associated to retinopathy (after applying Bonferroni multiple testing correction) in the case-control study design is being carried out using family based genetic association analysis (TDT – transmission disequilibrium test and the PDT – pedigree disequilibrium test) with the above individuals.

We are looking for loci that “protect” against the development of the complication or that increase the risk for the onset or a rapid progression. In order to use linkage analysis, families must have at least one sib with the trait (lack of complication) and one sib without the trait (presence of complication). Because all sibs in the analysis have T1D, the only way to differentiate linkage to the target phenotype from T1D is to have at least one T1D sib without the trait and one with the trait. There are 88 families that fit the classification of at least one sib with the trait (without complication) and one sib without the trait (with complication).

In order to distinguish loci that may predispose to complications from loci that predispose to diabetes, we performed additional analysis on 200 families which do not overlap the 88 families who have members who lack complications. These families were used to examine linkage at loci with complications protection determined from the first analysis of the 88 families discordant for complications. If the T1D+ complication analysis indicates linkage at the same loci that the protection analysis indicates, then the locus is not specific for complications. If no linkage is indicated in the T1D+ complications group, then the locus may be specific for complications.

We are currently finalizing the analysis. Preliminary results demonstrate a confirmation of the previously identified region as specific for retinopathy.

Aim 3. Continue our annual program of participant follow-up using the updated family questionnaire to track development or progression of microvascular complications among patients with both T1D and T2D. Data gathered will be an essential component of our primary aim.

Our goal was to continue the annual program of participant follow-up using an updated family questionnaire to track development/progression or lack of development/progression of microvascular complications among patients with both T1D and T2D. To this end, we sent 1000 questionnaires to participants in 2010. To date, we have received 228 completed

questionnaires/updates from individual participants. The information in these updates provides information on 4,298 individuals in the HBDI National Genetics Family Registry. Seventy questionnaires were returned due to incorrect addresses. Of these, we were able to send questionnaires to different family members in 47 cases, thus only 23 families have been confirmed lost to follow-up. Furthermore, we instituted a program of follow-up contact through email and phone calls. To date, we have attempted to contact 1,253 individuals, with success on 778 cases (62.1%). We continue to follow-up with these families in order to maintain the ability to track development/progression or lack of development/progression of microvascular complications. Of note, in three years (2008-2010) we have updated 11,891 individuals from the National Genetics Family Registry. In regards to the participants who have been immortalized in the NDRI National Genetics Family Repository, we have updated 1,323 (49%) of these individuals in the last 3 years. Thus, our continued effort to perform annual updates has led to a significant rate of follow-up with participants and has resulted in continued interest and enhanced the usefulness of our database and repository.

The NDRI National Genetics Family Registry now includes epidemiologic and diagnostic data on 6,664 extended families (92,831 individuals). 8,948 subjects had type 1 diabetes (48% were females). 6,250 individuals reported type 2 diabetes, 3,429 had diabetes type unknown or unclassified (e.g., type 1 diabetes diagnosed after age 30), 44 patients had MODY (Maturity-Onset Diabetes of the Young), 126 patients had gestational diabetes and 74,034 subjects were not affected by diabetes. 90% of type 1 diabetes patients in the database were Caucasian, 1.8% were Hispanic, 0.6% American Indian, 1.8% Asian, 1.2% African-American, 0.2% bi-racial and 1.2% Pacific Islander.

A subset of 550 families were included in the HBDI genetic repository at the Coriell Institute in Camden, NJ. Blood was drawn from members of these families, cell lines were immortalized and DNA was extracted and stored. Among these are 424 nuclear families genotyped by the T1D Genetic Consortium: 2,532 Caucasian patients that were used as the study population for this study. The genetic data are provided to HBDI, which links the genotypes with the subjects' epidemiological and clinical information present in the HBDI database. Within this population, there are 895 T1D, including 424 probands and 471 affected siblings (Table 2). Of these 424 families, 408 are multiplex, with 2 or more affected siblings and unaffected parents. 861 of the T1D are living with a mean age of 42.3 +/- 12 years. The average age of onset for diabetes is 12.2 +/- 9.4 for all T1D affected individuals, with probands having an earlier age of onset (9.1 +/- 6.5 years) than affected siblings (13.9 +/- 8.35 years) as expected. The average duration of diabetes is 30.3 +/- 10 years for all T1D. Currently 221 individuals confirm presence of retinopathy, 94 confirm presence of neuropathy and 83 confirm presence of nephropathy.

Type 1 Individuals	N	Probands	Siblings
N of Subjects	895	424	471
No of Multiplex	408	na	na
Females	415	188	218
Living	861	381	455
Age (yr)	42.3 +/-12	42.2 +/- 11	41.3 +/- 11.7
Age of Onset (yr)	12.2 +/- 9.4	9.11 +/- 6.5	13.9 +/- 8.5
Duration of diabetes	30.3 +/- 10	32.9 +/- 9.7	27.6 +/- 8.9
Presence of Retinopathy	221	109	104
Presence of Neuropathy	94	48	42
Presence of Nephropathy	83	40	42

Table 2. Characteristics of type 1 diabetes patients and number of probands, siblings and parents only (description of the third or fourth degree relatives of probands are not included, as reliable information about presence of complications is not available). Data are n (%) or means±SD.

Aim 4. To perform a SNP saturation study on additional candidate genes associated with retinopathy. Beside the genomic region already explored through the support of the 2008 PA Formula grant, there are additional genes shown to be associated with retinopathy in our preliminary analyses. In depth gene SNP analysis studies could identify specific polymorphisms responsible for the observed genetic signal.

To comprehensively evaluate the most promising SNPs in a genetic region found to be significant for association or linkage with complications, an additional 15 SNPs were performed on 392 individuals from 88 families. Individual SNPs were selected based on previous analysis demonstrating significance to the development of, or protection from, the development of retinopathy. The individuals selected for further analysis were selected from the families genotyped by T1DGC. Informative families were selected to allow additional family-based association and linkage analysis. The selection of informative families included families with affected children who were discordant for complications.

For this aim, we will perform similar analysis as in Aim 2 above.

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?

_____ 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?

_____ Number of subjects originally targeted to be included in the study

_____ Number of subjects enrolled in the study

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

Gender:

_____ Males

_____ Females

_____ Unknown

Ethnicity:

_____ Latinos or Hispanics

_____ 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.)

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, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the “Cognition and MRI in Older Adults” research project (Project 1), and two publications for PI Zhang for the “Lung Cancer” research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI

Project 1 – Smith – Publication 2 – Cognition and MRI

Project 3 – Zhang – Publication 1 – Lung Cancer

Project 3 – Zhang – Publication 2 – Lung Cancer

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:

At the conclusion of the data analysis, we will submit an article for publication to a top tier journal detailing our findings on the role of specific SNPs within this chromosomal region in either protection from or contribution to the development of retinopathy related complications of T1D. Depending on the outcome of the data, additional articles may be submitted to additional journals.

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.

The data contained in the HBDI database is an immense and invaluable resource for the development and testing of hypotheses regarding genetic factors leading to susceptibility to diabetic complications. Improved methods of preventing, treating and curing diabetes will inevitably stem from a more thorough determination of which specific genetic factors contribute to the development of diabetic complications. The identification of type 1 diabetics who are genetically susceptible to retinopathy, neuropathy, and nephropathy will be of considerable benefit to society and will lead to a reduction in both the human and economic impact of these diseases.

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.

None

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. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

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 LONSDALE, John T.		POSITION TITLE Research Director, NDRI	
eRA COMMONS USER NAME (credential, e.g., agency login) JOHNLONSDALE			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/Y Y	FIELD OF STUDY
University of Newcastle Upon Tyne, England, UK	B.Sc (Double First Class Honors)	1981	Biochemistry & Microbiology
University of Newcastle Upon Tyne, England, UK	Ph.D.	1985	Microbial Biochemistry

A. Personal Statement

I am Director of Research at NDRI, the National Disease Research Interchange. As such, I have extensive experience in conduction research projects, providing administrative and scientific oversight. I am very familiar with NIH policies, as well as IRB and HIPAA policies.

B. Positions and Honors

- 1985-1995 Biochemistry Department, SmithKline Beecham Pharmaceuticals, Brockham Park, England, UK
- 1995-2001 Assistant Director, Anti-infectives Research, SmithKline Beecham Pharmaceuticals, Collegeville, PA USA
- 2001-2002 Director, Microbial Biochemistry - Antimicrobials and Host Defense CEDD, GlaxoSmithKline, Collegeville, PA, USA
- 2002 Director, Biochemistry - Microbial, Musculoskeletal and Proliferative Diseases CEDD, GlaxoSmithKline, Collegeville, PA, USA
- 2003- Present Research Director, NDRI, Philadelphia, PA, USA

A. Selected Peer-Reviewed Publications

1. Brandish PE. Burnham MK. Lonsdale JT. Southgate R. Inukai M. Bugg TDH. Slow binding inhibition of phospho-N-acetylmuramyl-pentapeptide translocase (*Escherichia coli*) by mureidomycin A. *Journal of Biological Chemistry*. 271 (13):7609-14, 1996.
2. Brandish PE. Kimura K. Inkai M. Southgate R. Lonsdale JT. Bugg TDH. Modes of action of tunicamycin, liposidomycin B, and mureidomycin A – Inhibition of phospho-N-acetylmuramyl-pentapeptide translocase from *Escherichia coli*. *Antimicrobial Agents & Chemotherapy*. 40(7):1640-44, 1996.
3. Salman M. Lonsdale JT. Besra GS. Brennan PJ. Phosphatidylinositol synthesis in mycobacteria. *Biochimica et Biophysica Acta-Molecular & Cell Biology of Lipids*. 1436(3):437-50, 1999
4. Salman M. Brennan PJ. Lonsdale JT. Synthesis of mycolic acids of mycobacteria: an assessment of the cell-free system in light of the whole genome. *Biochimica et Biophysica Acta-Molecular & Cell Biology of Lipids*. 1437(3):325-332, 1999.

5. Qiu XY. Janson CA. Konstantinidis AK. Nwagwu S. Silverman C. Smith WW. Khandekar S. Lonsdale J. Abdel-Meguid SS. Crystal structure of beta-ketoacyl-acyl carrier protein synthase III – A key condensing enzyme in bacterial fatty acid biosynthesis. *Journal of Biological Chemistry*. 274 (51):36465-71, 1999.
6. Khandekar SS. Konstantinidis AK. Silverman C. Janson CA. McNulty DE. Nwagwu S. Van Aller GS. Doyle ML. Kane JF. Qiu XY. Lonsdale J. Expression, purification, and crystallization of the *Escherichia coli* selenomethionyl beta-ketoacyl-acyl carrier protein synthase III. *Biochemical & Biophysical Research Communications*. 270(1):100-07, 2000.
7. Janson CA. Konstantinidis AK. Lonsdale JT. Qiu XY. Crystallization of *Escherichia coli* beta-ketoacyl-ACP synthase III and the use of a dry flash-cooling technique for data collection. *Acta Crystallographica Section D-Biological Crystallography*. 56(Part 6):747-48, 2000
8. Qiu X. Janson CA. Smith WW. Head M. Lonsdale J. Konstantinidis AK. Refined structures of beta-ketoacyl-acyl carrier protein synthase III. *Journal of Molecular Biology* 307 (1):341-56, 2001.
9. Payne DJ. Warren PV. Holmes DJ. Ji YD. Lonsdale JT. Bacterial fatty-acid biosynthesis: a genomics-driven target for antibacterial drug discovery. *Drug Discovery Today*. 6(10):537-544, 2001
10. Schaeffer ML. Agnihotri G. Kallender H. Brennan PJ. Lonsdale JT. Expression, purification, and characterization of the *Mycobacterium tuberculosis* acyl carrier protein, AcpM. *Biochimica et Biophysica Acta* 1532(1-2):67-78, 2001.
11. Khandekar SS. Gentry DR. Van Aller GS. Warren P. Xiang H. Silverman C. Doyle ML. Chambers PA. Konstantinidis AK. Brandt M. Daines RA. Lonsdale JT. Identification, substrate specificity, and inhibition of the *Streptococcus pneumoniae* beta-ketoacyl-acyl carrier protein synthase III (FabH). *Journal of Biological Chemistry* 276(32): 3024-30, 2001.
12. Throup JP. Zappacosta F. Lunsford RD. Annan RS. Carr SA. Lonsdale JT. Bryant AP. McDevitt D. Rosenberg M. Burnham MK. The srhSR gene pair from *Staphylococcus aureus*: genomic and proteomic approaches to the identification and characterization of gene function. *Biochemistry* 40(34):10392-401, 2001.
13. Schaeffer ML. Agnihotri G. Volker C. Kallender H. Brennan PJ. Lonsdale JT. Purification and biochemical characterization of the *Mycobacterium tuberculosis* beta-ketoacyl carrier protein synthases KasA and KasB. *Journal of Biological Chemistry* 276 (50):47029-37, 2001.
14. RA Daines, I Pendrak, K Sham, GS Van Aller, AK Konstantinidis, JT Lonsdale, CA Janson, X Qiu, M Brandt, SS Khandekar, C Silverman, and MS Head. First X-ray co-crystal structure of a bacterial FabH condensing enzyme and a small molecule inhibitor achieved using rational design and homology modeling. *J Med Chem* 46(1): 5-8. 2003.
15. SS Khandekar, RA Daines, and JT Lonsdale. Bacterial beta-ketoacyl-acyl carrier protein synthases as targets for antibacterial agents. *Curr Protein Pept Sci* 4(1): 21-9. 2003.
16. ML Schaeffer, JD Carson, H Kallender, and JT Lonsdale. Development of a scintillation proximity assay for the *Mycobacterium tuberculosis* KasA and KasB enzymes involved in mycolic acid biosynthesis. *Tuberculosis (Edinb)* 84(6): 353-60. 2004.
17. Edward A. Weinstein, Takahiro Yano, Lin-Sheng Li, David Avarbock, Andrew Avarbock, Douglas Helm, Andrew A. McColm, Ken Duncan, John T. Lonsdale, and Harvey Rubin.

- Inhibitors of type II NADH:menaquinone oxidoreductase represent a class of antitubercular drugs. *PNAS* 102: 4548 - 4553. 2005.
18. Xiayang Qiu, Anthony E. Choudhry, Cheryl A. Janson, Michael Grooms, Robert A. Daines, John T. Lonsdale, and Sanjay S. Khandekar. Crystal structure and substrate specificity of the β -ketoacyl-acyl carrier protein synthase III (FabH) from *Staphylococcus aureus*. *Protein Sci.* 14: 2087 - 2094. 2005.
 19. P Kim, YM Zhang, G Shenoy, QA Nguyen, HI Boshoff, UH Manjunatha, MB Goodwin, J Lonsdale, AC Price, DJ Miller, K Duncan, SW White, CO Rock, CE Barry 3rd, and CS Dowd. Structure-activity relationships at the 5-position of thiolactomycin: an intact (5R)-isoprene unit is required for activity against the condensing enzymes from *Mycobacterium tuberculosis* and *Escherichia coli*. *J Med Chem* 49(1): 159-71. 2006
 20. MC Monti, JT Lonsdale, C. Montomoli, R. Montross, E. Schlag and DA Greenberg. Familial risk factors for microvascular complications and differential male-female risk in a large cohort of American families with type 1 diabetes. *J Clin Endocrinol Metab* 92:4650-4655. 2007.

B. Completed Research Support

- Principal Investigator NIH/NIAID Drug Discovery Challenge Grant (1-UC1 AI49520-01). Evaluation and development of thiolactomycin derivatives as novel chemotherapies for tuberculosis. 2001-2003.
- Project leader NIH/NIAID/NCDDG-OI Drug Discovery Grant (PO1 AI46393). Cell wall of *Mycobacterium tuberculosis* as a target for drug discovery. 1996-2003.

BIOGRAPHICAL SKETCH

Provide the following information for the 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 Maria Cristina Monti		POSITION TITLE Associate Research Scientist, Columbia University, NY, USA & Research Scientist, University of Pavia, Italy	
eRA COMMONS USER NAME			
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
University of Pavia, Italy	MS	1995-2000	Biological Science
University of Pavia, School of Medical Statistics	PhD	2000-2003	Biostatistics
University of Pavia, School of Public Health, Faculty of Medicine	PhD	2003-2008	Public Health
IUSS- University Institute for Superior Studies in Pavia	Advanced Graduate International program	2001-2003	
Columbia University, New York, USA	training	2004-2008	Genetic complex

A. Positions and Honors

Employment

Research Scientist, University of Pavia and Associate Research Scientist at Department of Biostatistics, Columbia University, New York.

Consultant as a biostatistician at

- The National Disease Research Interchange (HBDI), Philadelphia, USA;
- Auxologic Institute, Milan, Italy;
- Department of Cardiology, Policlinico San Matteo Hospital, Pavia, Italy.

Employment History

2005-2007: Post-Doctoral fellowship, Columbia University, NY

2004-2007: Doctoral fellowship, University of Pavia

2002-2003: Annual Fellowships "Statistical and Epidemiological Analysis of SIDS (Sudden Infant Death Syndrome)", University of Pavia

2000-2001: Annual Fellowships: "Planning an Integrated Informative System for Drug Addiction", Prefettura di Pavia, & University of Pavia

Professional and Scientific Memberships

Fellow of the Italian Society for Medical Statistics and Clinical Epidemiology (SISMEC)

Fellow of the American Society of Human Genetics (ASHG)

Fellow of the European Society of Human Genetics (ESHG)

Honors

2001-2002-2003 Annual Awards by Advanced International Graduate Program (SAFI), Institute for Advanced Studies (IUSS), University of Pavia.

B. Selected Publications

1. Greenberg DA, Monti MC, Feenstra B, Zhang J, Hodge SE. The essence of linkage-based imprinting detection: Comparing power, type 1 error, and the effects of confounders in two different analysis approaches. Accettato per pubblicazione il 3 Gennaio 2010 in *Annals of Human Genetics*. IF: 2.2
2. Crotti L, Monti MC, Insolia R, Peljto A, Goosen A, Brink PA, Greenberg DA, Schwartz PJ, George AL. NOS1AP Is a Genetic Modifier of the Long-QT Syndrome. *Circulation*. 2009 Oct 27;120(17):1657-63. IF: 10.9
3. Menconi F, Monti MC, Greenberg DA, Oashi T, Osman R, Davies TF, Ban Y, Jacobson EM, Concepcion ES, Li CW, Tomer Y. Molecular amino acid signatures in the MHC class II peptide-binding pocket predispose to autoimmune thyroiditis in humans and in mice. *Proc Natl Acad Sci U S A*. 2008 Sep 16;105(37):14034-9. IF: 9.7
4. Carrà G, Montomoli C, Monti MC, Clerici M. Does HIV serostatus affect outcomes of dually diagnosed opiate dependents in residential treatment? *Epidemiol Psichiatr Soc*. 2008 Jan-Mar;17(1):77-81. IF: 2.9
5. Libetta C, Sepe V, Zucchi M, Pisacco P, Cosmai L, Meloni F, Campana C, Rampino T, Monti MC, Tavazzi L, Dal Canton A. Intermittent hemodiafiltration in refractory congestive heart failure: bnp and balance of inflammatory cytokines. *Nephrology, Dialysis and Transplantation*, 2007; 22:2013-9. IF: 3
6. Monti MC, Lonsdale JT, Montomoli C, Schlag E, Greenberg DA. A family study of type 1 diabetes microvascular complications. Evidence of familiarity, differential male-female risk, diabetes family history, and the risk for multiple complications. *J Clin Endocrinol Metab*, 2007; 92:4650-5. Epub 2007 Sep 18. IF: 5.8
7. Porrello E, Monti MC, Sinforiani E, Cairati M, Guaita A, Montomoli C, Govoni S, Racchi M. Estrogen Receptor α and APOE ϵ 4 polymorphisms interact to increase risk for sporadic AD in Italian females. *Eur. J. Neurol* 2006; 13:639-644. IF: 2.3
8. Carrà G, Scioli R, Monti MC, Marinoni A. Severity profiles of substance abusing patients in Italian community addiction facilities: influence of psychiatric concurrent disorders. *Eur Addict Res*. 2006;12:96-101. IF: 2.3
9. Bergamaschi R, Montomoli C, Candeloro E, Monti MC, Cioccale R, Bernardinelli L, Fratino P, Cosi V. Bayesian mapping of multiple sclerosis prevalence in the province of Pavia, northern Italy. *J Neurol Sci* 2006; 244:127-31. IF: 2
10. Montomoli C, Monti MC, Stramba-Badiale M, Marinoni A, Foglieni N, Carreri V, Amigoni M, Schwartz PJ. Mortality due to Sudden Infant Death Syndrome in Northern Italy, 1990-2000. A baseline for the assessment of prevention campaigns. *Paediatr Perinat Epidemiol* 2004. IF: 1.8
11. Monti MC, Montomoli C, Marinoni A, Stramba-Badiale M, Amigoni M, Carreri V, Schwartz PJ. Infant mortality and sudden crib death in Lombardy. *Epidemiol Prev* 2004; 28:13-19.

C. Research Support

Grants ongoing

2007-2012: Co-investigator in the NIH Grant (National Institute of Health, United States) "Genetic Modifiers of Congenital Long QT Syndrome", PI: Alfred L. George, Jr., M.D;

2006-2008: Co-investigator in the Prin (National Italian Research Project) Grant "Morbidity and mortality in infancy: risk factors and incidence", PI: Cristina Montomoli, PhD

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 Miller, Cathie G.		POSITION TITLE HBDI Director	
eRA COMMONS USER NAME (credential, e.g., agency login) cmiller1			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.S.	1986-1990	Biology
University of Louisville, Louisville, KY	Ph.D.	1993-1997	Microbiology/Immunology
Wistar Institute, Philadelphia, PA	Post-Doc	1997-1998	Virology
University of Pennsylvania, Philadelphia, PA	Post-Doc	1998-2000	Virology/Cancer Therapeutics
University of Michigan, Ann Arbor, MI	B.S.	1986-1990	Biology

A. Personal Statement

I am Director of the HBDI, Human Biological Data Interchange. As such, I have extensive experience in database design and management as well as participant outreach and recruitment. I will be responsible for the organization and management of all participant outreach, overseeing data entry, database management, and data transfer. Furthermore, I will oversee the insurance of the maintenance of participants' confidentiality in compliance with applicable laws and regulations.

B. Positions and Honors

POSITIONS AND EMPLOYMENT:

1989-1990: Research Assistant, Extra-Corporeal Membrane Oxygenation Laboratory, Department of Surgery, University of Michigan, Ann Arbor, MI

1990-1993: Research Associate, Injury and Inflammation Laboratory, Division of Trauma, Burn, and Emergency Services, Department of Surgery, University of Michigan, Ann Arbor, MI

1993-1997: Graduate Student, Department of Microbiology and Immunology, School of Medicine, University of Louisville, Louisville, KY

1997-1998: Post-Doctoral Fellow, Wistar Institute, Philadelphia, PA

1998-2002: Post-Doctoral Fellow, Department of Microbiology, University of Pennsylvania School of Medicine, University of Pennsylvania, Philadelphia, PA

2002-2006: Senior Bioscientific Staff, Hermelin Brain Tumor Center, Henry Ford Health System, Detroit, MI

2006-2009: Instructor, Henry Ford Health System, Detroit, MI

2009-Present: Scientific Director of the Human Biological Data Interchange, National Disease Research Interchange, Philadelphia, PA

C. Selected peer-reviewed publications (in chronological order).

SELECTED PEER-REVIEWED PUBLICATIONS:

1. JL Rodriguez, **CG Miller**, LE DeForge, L Kelty, CJ Shanley, RH Bartlett, DG Remick. 1992. Local production of IL8 with nosocomial pneumonia. *J Trauma* 33 (7):74-82.
2. MK Eskandari, G Bolges, **CG Miller**, DG Remick, DJ Smith. 1992. Anti-TNF antibody therapy fails to prevent lethality after cecal ligation and puncture or endotoxemia. *J Immunol* 148:2742-2755.
3. JL Rodriguez, WL Garner, GO Till, **CG Miller**, NP Moore, PD Thompson, DG Remick, DJ Smith. 1993. Correlation of local and systemic cytokine response with clinical outcome following thermal injury. *J Trauma* 34(5):687-695.
4. WL Garner, JL Rodriguez, **CG Miller**, DG Remick, DJ Smith. 1994. Acute skin injury releases neutrophil chemoattractants. *Surgery* 116(1):42-48.
5. **CG Miller**, DE Justus, S Jayaraman, GJ Kotwal. 1995. Severe and prolonged inflammatory response to localized CPV infection in footpads of C5^{-/-} mice: Investigation of the role of host complement in poxvirus pathogenesis. *Cell Immunol* 162:326-332.
6. JR Shaywitz, **CG Miller**, KJ Johnson, JL Rodriguez. 1995. Multiple Organ Dysfunction Syndrome: End organ and systemic inflammatory response in a mouse model of nonseptic origin. *Shock* 4(6):389-396.
7. **CG Miller**, DN Cook, GJ Kotwal. 1996. Two chemotactic factors, C5a and MIP-1 alpha dramatically alter the mortality from zymosan-induced MODS: C5a promotes while MIP-1 alpha suppresses MODS. *Mol Immunol* 33: (14):1135-1137.
8. **CG Miller**, SN Shchelkunov, GJ Kotwal. 1997. Cowpox virus encoded homolog of the vaccinia virus complement control protein (VCP) is an inflammation modulatory protein (IMP). *Virology* 229: (1): 126-133.
9. GJ Kotwal, **CG Miller**, DE Justus. 1998. The inflammation modulatory protein (IMP) of cowpox virus drastically diminishes the tissue damage by down-regulating cellular infiltration resulting from complement activation. *Mol Cell Biochem* 185: (1-2) 39-46.
10. GJ Kotwal, **CG Miller**, DE Justus. 1998. Evasion of the consequences of C activation by IMP during CPV infection serves to preserve viral habitat. *Mol Immunol* 35: (6-7): 364-364.
11. **CG Miller**, NW Fraser. 2000. Role of the immune response during neuro-attenuated herpes simplex virus-mediated tumor destruction in a murine intracranial melanoma model. *Cancer Res* 60:5714-5722.
12. **CG Miller**, C Kummenacher, RJ Eisenberg, GH Cohen, P Spear, NW Fraser. 2000. Development of a syngenic B16 derived melanoma tumor susceptible to destruction by neuro-attenuated HSV-1. *Mol Ther* 3(2):160-168.
13. M Lock, **CG Miller**, NW Fraser. 2000. Analysis of protein expression from within the region encoding the 2.0 Kb latency associated transcript of HSV-1. *J Virol* 75(7):3413-3426.
14. H. Poptani, U. Duvvuri **CG Miller**, A. Mancuso, S. Charagundla, NW Fraser, JD Glickson, JS Leigh, R. Reddy. 2001. T1rho imaging of murine brain tumors at 4T. *Acad Radiol* 8(1):42-47.
15. M Ahmed, M Lock, **CG Miller**, NW Fraser. 2001. The 5' end of the stable 2-kb LAT intron and the exon 1 region of the latency associated transcript of HSV-1 protect cells from apoptosis *in vitro*, but not in neuronal cells *in vivo*. 2002. *J Virol* 76 (2):717-729.
16. **CG Miller**, NW Fraser. 2003. Requirement of an integrated immune response for

- successful neuro-attenuated HSV-1 therapy in an intracranial metastatic melanoma model. *Mol Ther* 7(6): 741-747.
17. J Kent, W Kang, **CG Miller**, NW Fraser. 2003. Herpes simplex virus latency-associated transcript gene function. *J Neurovirol* 9 (3):285-90.
 18. T Rosenzweig, A Ziv-Av, C Xiang, W Lu, S Cazacu, D Taler, **CG Miller**, R Reich, Y Shoshan, Y Anikster, G Kazimirsky, R Sarid, C Brodie. RTVP-1 is overexpressed in gliomas and regulates the growth, survival, and invasion of glioma cells. *Cancer Res.* 2006 Apr 15;66(8):4139-48.
 19. CA Billecke, S Finniss, L Tahash, **C Miller**, T Mikkelsen, N Farrell, and O Bögler. BBR3610 is more potent than cisplatin in the treatment of gliomas in vitro and in vivo and induces cell cycle arrest. *J. Neuro-Oncology.* 2006 Jul 8(3): 215-26.
 20. SA Rempel, RC Hawley, JA Gutierrez, E Mouzon, KR Bobbitt, N Lemke, CR Schultz, LR Schultz, W Golembieski, J Koblinski, S Vanosdol, **CG Miller**. Splenic and immune alterations of the Sparc-null mouse accompany a lack of immune response. *Genes Immun.* 2007 April 8(3):262-74.

D. Research Support

COMPLETED RESEARCH SUPPORT:

5 U01 CA062432-12: (Mikkelsen)

01/01/04 – 12/31/08

NIH/NCI (RFA: CA-04-001)

New Applications in Brain Tumor Therapy

[Johns Hopkins University]

Role: (Miller) Molecular Neuro-Oncology Investigator

To improve the therapeutic outcome of patients with primary brain tumors.