

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): 1/1/2009 - 12/31/2009**
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees): John T. Lonsdale, PhD**
4. **Grant Contact Person’s Telephone Number: 800-222-6374 ext. 271**
5. **Grant ME Number or SAP Number: SAP4100047642**
6. **Project Number and Title of Research Project: Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes**
7. **Start and End Date of Research Project: 1/1/2009 – 12/31/2009**
8. **Name of Principal Investigator for the Research Project: John T. 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:

\$ \$58,338_____

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
Montross	HBDI Manager	25% (1/09-4/09)	\$5,123
Tang	HBDI Coordinator	40% (1/09-12/09)	\$16,074
Miller	HBDI Director	10% (9/09-12/09)	\$2,294

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	Principal Investigator	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	None	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

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:
An International Network for Microvascular Complications in Type 1 Diabetes: Incidence and Genetic Susceptibility	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input checked="" type="checkbox"/> Nonfederal source (specify: <u>Bando Venerdi (Italy)</u>)	11/2009	\$451,716	Pending
Monogenic Diabetes Registry	<input checked="" type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _____)	2/2009	\$185,000	Not funded
	<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: We plan to submit an R21 in response to RFA: PA-06-151 - Secondary Analyses in Obesity, Diabetes, Digestive and Kidney Diseases. We have submitted a grant to the Iacocca Family Foundation (03/01/2010).

12. Future of Research Project. What are the future plans for this research project? We intend to continue our analyses on the genetic information obtained utilizing funds from this granting period as well as expand our detailed analyses from microvascular complications (retinopathy, neuropathy, and nephropathy) to include autoimmune diseases and the genetics of glycemic control.

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 _____

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 _____

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 _____ No _____

If yes, please describe the collaborations: We continued our productive collaboration with Maria Cristina Monti, PhD and David Greenberg, PhD of the University of Columbia.

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

Yes _____ No _____

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 _____

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 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.

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). DO NOT DELETE THESE INSTRUCTIONS.

Specific Aims:

Aim 1. Explore the genetic susceptibility among T1D patients to microvascular complications using:

- a. Case-control association analysis nested on the HBDI T1D cohort. "Cases" are defined as T1D patients with retinopathy or nephropathy or neuropathy, and "controls" are defined as patients with at least a 20 year history of T1D but without complications and without 1st degree relatives with complications.
- b. Family-based association analysis. Because we have family data, we can additionally test any statistically significant results from the case-control study using family-based association.
- c. Multipoint linkage analysis to determine if a locus found for the complication is actually related to the complication alone or to T1D.

Aim 2. 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.

Aim 3. To confirm novel associations with diabetic microvascular complications by constructing a dense SNP map. SNPs which show significant association or linkage with the microvascular complications, particularly those that are not linked to T1D susceptibility itself, will be further evaluated through a SNP saturation study to identify the gene responsible for the observed genetic signal.

Summary of Research Completed

Specific Aim 1 – Data Exploration for Genetic Susceptibility Among Type 1 Diabetic Patients to Microvascular Complications

The Human Biological Data Interchange's (HBDI) data were collected from American families ascertained through the presence of at least one type 1 diabetic subject (proband), although multiplex families were preferentially sought. The follow-up protocol requests updated information about development of complications and a copy of all medical records of relevance to the diabetes and complications history. Depending on the phenotype of interest, three types of cases were created: Type 1 diabetic patients with retinopathy, nephropathy or neuropathy. "Controls" were defined as patients with at least a 20 year history of type 1 diabetes but without complications and without first degree relatives with complications. A large number of SNPs were typed in candidate genes for type 1 diabetics by the Type 1 Diabetes Genetic Consortium (T1DGC) CIDR, RR1 AND RR2 genotyping projects. These data were provided to HBDI, which links the genotype with the subject's epidemiological and clinical information.

Statistical Analysis: Exploratory analysis for each phenotype of interest was performed. Allelic and genotypic tests were aimed at detecting candidate signals (at $\alpha = 0.05$) for retinopathy, nephropathy and neuropathy. Because all the HBDI families used in this study are Caucasians, of similar socioeconomic status and geographical origin, population stratification issues are minimized.

Among the 6,626 HBDI extended families there is a subset of families in which all members were genotyped by the T1DGC: 2532 T1D Caucasian patients, from 424 nuclear families. 411 T1D subjects (16%) had at least one confirmable diabetic complication. We have performed a preliminary study using 5943 SNPs from the CIDR, 398 from the RR1 and 1536 from the RR2 T1DGC-Genome Scans. Index cases from 260 families were used for the analysis. Table 1 shows the number of significant SNPs ($p < 0.05$) for association with retinopathy, nephropathy or neuropathy.

Table 1. Number of significant SNPs for the three projects and the three phenotypes. N=total number of SNPs; $N(p < 0.05)$ =number of significant SNPs; $N(OR > 1)$ =number of high-risk SNPs, with an Odds Ratio > 1 .

Project	SNPs	Retinopathy		Nephropathy		Neuropathy	
		$N(p < 0.05)$	$N(OR > 1)$	$N(p < 0.05)$	$N(OR > 1)$	$N(p < 0.05)$	$N(OR > 1)$
CIDR	5943	273	134	288	140	296	156
RR1	398	34	12	25	6	17	14
RR2	1536	82	31	76	33	72	35

Interestingly, we found, for example, SNPs in a region of chromosome 8 associated with a higher risk ($OR > 2$) of retinopathy and nephropathy using CIDR data, while using RR1 and RR2 data, SNPs in the IL2RA and IL15RA genes (chromosome 10) seem protective ($OR < 0.5$) for retinopathy and nephropathy.

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).

Specific Aim 2 – Continuation of Annual Follow-Up and Database Updates

953 questionnaires were printed and mailed out to families selected from the Human Biological Data Interchange's (HBDI) database. The Crystal Reports XI software was used to create the personalized questionnaire. Within the questionnaire packet, we included a cover letter and the questionnaire with a postage-paid return envelope. The questionnaires were mailed to the proband of the family. If the proband of the family is a minor, the questionnaire was mailed to the parent. The questionnaire collects updated information on family members diagnosed with diabetes within the past 10 years, family members who have diabetic complications (neuropathy, nephropathy or retinopathy). In addition, the questionnaire collected information on members affected by diabetes who have been free from neuropathy, nephropathy, retinopathy and heart disease for the past 20 years. We have already received 102 update questionnaires. Six families have refused to participate in filling out the questionnaire. There were also 139 questionnaires that were returned in the mail due to invalid addresses or due to the family's unknown relocation. In cases when a questionnaire was returned in the mail, we attempted to send the questionnaire to another family member with a validated address. Tracking on each sent out questionnaire is maintained in an Access database. Follow-up through phone calls to the families was initiated.

Specific Aim 3 – SNP saturation study on the most promising genomic region

The chromosomal region selected for the SNP saturation study had 40 SNPs genotyped in the HBDI sample by T1D consortium, thus we chose an additional 30 SNPs to be genotyped providing an excellent coverage for a case-control analysis. To perform the SNP saturation study, a set of 191 cases and 128 controls were selected from the HBDI cohort genotyped by T1DGC. Cases were defined as patients with retinopathy, while controls were T1D patients without any complications after 20 years with T1D and without family history of complications in T1D siblings. Multivariate models that incorporated a cluster function to account for potential confounders such as age, duration of diabetes, sex, and clinical relevant information were carried out. These samples were sent to the University of Pennsylvania Molecular Diagnostics Laboratory for additional SNP determination within this chromosomal region which had been demonstrated to be associated with development of retinopathy in Specific Aim 1. These 30 additional SNPs were selected based on minimum allele frequency, linkage disequilibrium and distance from one another. Additionally, a thorough investigation of which of these SNPs had been previously significantly associated with any disease process was done. All SNPs are located within a specific gene as well as its promoter and 3' UTR regions. We are currently awaiting the conclusion of the SNP assay processing by the University of Pennsylvania Molecular Diagnostics Laboratory in order to perform the analysis.

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. **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.				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published
2.				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published
3.				<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 from the SNP determination, 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 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, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	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. 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

B. 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-actylmuramyl-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 Qui 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 -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.

C. 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.

Principal Investigator/Program Director (Last, First, Middle): Lonsdale, John

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 diseases

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

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

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.

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.

BIOGRAPHICAL SKETCH

NAME Miller, Cathie G.	POSITION TITLE HBDI Director		
eRA COMMONS USER NAME cmiller1			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	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

A. 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

B. 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 C57BL/6 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 Bögl. 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.

C. 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.