Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814-935-1081

5. **Grant SAP Number:** # 4100047645

6. **Project Number and Title of Research Project:** 17 - The Interaction of Environmental Agents and LDL-Cholesterol in Parkinson's Disease

7. **Start and End Date of Research Project:** 5/1/2009 – 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Richard B. Mailman, Ph.D.

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

   $ 992,594

   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
Lindsay	Research Technician	22% Yr 1; 17% Yr 2	$14,987
Kocher	Research Technician	29.5% Yr 2	$14,114

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
Mailman	Professor, PI	2
Huang	Associate Professor	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
NextGen Sequencing system	Provides capacity for whole genome/exome studies of clinical and other populations	$901,172

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_____X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds

to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

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

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Parkinson’s Study Group	☐NIH ☐Other federal (specify:_____) ☒Nonfederal source (specify: Parkinson’s Study Group _)	08/03/09	$25,000	$25,000
Multimodal MRI markers of nigrostriatal pathology in parkinson's disease	☒NIH ☐Other federal (specify:____) ☐Nonfederal source (specify:_)	5/23/12	$649,506	$649,506

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:

This research has provided the foundation for one project of an NIH program project that is being worked on for submission in 2013.

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

This research has provided the foundation for one project of an NIH program project that is being worked on for submission in 2013.

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

Yes_____ No___X____

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

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

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

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

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

    Yes_____ No___X____

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

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

    Yes___X____ No_____

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

This project has helped our institution develop a critical mass of active research related to Parkinson's Disease. This provides the basis for a new Program Project Grant application on Parkinson's that is currently under development and will further expand our research base in the neurosciences.

The NextGen sequencing instrumentation capacities added through this project will have an ever-expanding role as a crucial part of our new Institute of Personalized Medicine and Genome Sciences facility. The sequencing instrumentation benefits Penn State Hershey researchers across the research enterprise and facilitates both basic and clinical research. Over the past five years a large number (sixty-one) of the research laboratories at Hershey have used the Genome Sciences Facility, but nationally "traditional" methods of genotyping of known SNPs such as microarrays are being augmented by whole genome and exome sequencing methods which can reveal new mutations associated with a disease or condition. The additional capacities provided by the HiSeq and MiSeq instruments have already been used for example to obtain results for extensive population studies of autism (Complete genome sequencing of 30 twins with autism and their families using the HiSeq - Dr. Daniel Notterman); RNA-Seq studies of Diabetic Retinopathy (HiSeq - National Eye Institute study funding to Dr. Willard Freeman), and for DNA methylation studies of the epigenetic basis of drug craving (MiSeq –National Institute on Drug Abuse funding – Dr. Willard Freeman, Dr. Sue Grigson). With the variety of molecular biological approaches possible with this instrumentation, investigators across a number of Clinical and Basic Science Departments and Divisions will be aided by the addition of this capability.

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:

This project has led to new collaborations with experts in the field, including Drs. Alberto Arturuo and Michael Schwartzchild of Harvard Medical School, Dr. Honglei Chen of the NIEHS, Dr. Tom Mosley (ARIC PI at the University of Mississippi, Jackson) and Dr. Alvaro Alonson (University of Minnesota).

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

Yes_____ No___X_____

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

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

Yes_____ No___X_____

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

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

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

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

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

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

This project is based on our earlier findings (supported by data from other groups) that associated increased prevalence of Parkinson's disease with lower cholesterol and presence of the apolipoprotein E ε2 allele (both of the latter generally considered "good" characteristics. This project involving the collaboration of a PD specialist and a basic neuroscientist is to develop more data that, if consistent with our central hypotheses, will set the stage for extramural NIH grants to study these issues further. We had two original specific aims, both of which were expanded/modified as the work progressed.

Aim 1: Test the central hypothesis further in the "Atherosclerosis Risk in the Communities" (ARIC) prospective cohort.

The ARIC cohort of ~16,000 participants, with baseline fasting lipid profiles since 1986, could provide a rigorous test of our central hypothesis supported by four prior studies. We

have gained approval from ARIC Committee to gather preliminary data in this cohort by identifying potential PD cases through self-reporting, medication history, and death records. Initial analysis of the relationship between potential PD subjects and cholesterol levels did not show a significant association between the occurrence of PD and fasting cholesterol profiles (both at baseline and follow-ups). A major problem, however, is that potential PD subjects identified by self-report, or by medication, or death records can be confounded by high rate of false positive diagnosis. For example, self reported Parkinson's disease may include many subjects with Parkinson's look-alike diseases such as Progressive Supranuclear Palsy (PSP), multisystem atrophy (MSA), normal pressure hydrocephalous, essential tremor, or stroke-related parkinsonism, etc. Moreover, potential cases identified by medication also can be confounded by a restless leg syndrome (RLS) that recently became a popular diagnosis and uses similar medication to Parkinson's disease, but with very different pathoetiology.

To tease out the false diagnosis of Parkinson's disease from idiopathic Parkinson's disease, Dr. Huang has been working closely with Dr. Honglei Chen (from NIEHS), Dr. Tom Mosley (ARIC PI at Jackson, MI center), and Dr. Alvaro Alonson from Minnesota to develop a case-confirmation strategy. This strategy will include interviewing all potential PD subjects identified from the self report, or medication list. With each subject's permission, we are going to contact the treating physician and Dr. Huang will review the records of each of their potential subjects. This endeavor had gained approval from ARIC committee, and is partially funded by NIEHS. All the forms have been developed and in the process for IRB approval of each of the ARIC coordinating centers. The training of phone interviewers is expected to start within next month. I predict that this case confirmation process will be finished within the coming year, and will help us to clarify the relationship between PD and cholesterol.

In addition, we became aware of a second cohort that would allow prospective testing the hypothesis that lower plasma cholesterol may be associated with faster progression (in addition to prevalence) of PD. These cohorts were from the Parkinson's Study Group DATATOP and PRECEPT studies. Because there were no funds for this extension of Aim 1, we wrote an application to the PSG requesting access to this important dataset, as well as funds to perform needed analyses. This competitive application was funded (see above), and the work has been completed, and is an integral part of this Aim.

The DATATOP and PRECEPT data are important because they were two large neuroprotection studies that took place in two distinct epochs in relationship to the availability of statins. The DATATOP study started in late 1980's (pre-statin era), whereas PRECEPT began in the mid-2000's after FDA statins approvals in mid-late 1990's. This unique feature can help to explore potentially intriguing relationships among cholesterol and statins in relation to PD. Our initial case control studies found a negative association between statin usage and PD occurrences, a finding supported independently by two groups but contradicted by two others. The possible negative association between statin usage and PD occurrence, coupled with possible neuroprotective properties independent of its cholesterol lowering properties has prompted a data-mining effort by the epigenetic work group of the PSG.

The PSG analysis had three goals: 1) to explore the association prospectively of baseline serum cholesterol and the time to require levodopa therapy of PD subjects in both DATATOP and PRECEPT studies; 2) to explore the association prospectively between

baseline serum cholesterol and other important clinical landmark(s) of PD progression [i.e. time to freezing of gait, time to death] in the DATATOP Study; and 3) to explore the association between baseline serum cholesterol and both clinical (reflected at UPDRS scores) /radiographic progression [reflected as striatal uptake of [^{123}I]-2-β-carbomethoxy-3-β-(4-iodophenyl)tropanes] in PD in the PRECEPT study.

The results from the DATATOP study are shown in the following table, and provide new insights into this issue. All of the prior studies examined whether low cholesterol was associated with an increased the risk of getting Parkinson's disease. Here, for the first time, we provide evidence that low cholesterol is also associated with a faster progression of Parkinson's disease. These data beg the question of mechanism, but are another set of data consistent with the working hypothesis of this Aim.

Serum cholesterol quintile			Time Needing Levodopa Treatment	
	[cholesterol] mg/dL	N	Hazard Ratios (95% CI)	P values (one-tail)
1st	<=180.7	153	**1.0** (reference)	--
2nd	180.8-203.9	159	**0.82** (0.59-1.16)	0.130
3rd	204.0-222.8	153	**0.86** (0.62-1.20)	0.180
4th	222.9-246.7	156	**0.85** (0.60-1.19)	0.165
5th	>=246.8	153	**0.75** (0.52-1.09)	0.065
1 SD incr.	39.2	774	**0.91** (0.81-1.02)	0.045

* Models adjusted for gender, treatment group (deprenyl or not), baseline age, uric acid concentrations, PD subtype, and BMI

With these data showing the continued effects of cholesterol, we followed up on a study that formed one of the foundations of this project, to wit, a meta-analysis that suggested that ApoE4, a risk factor in Alzheimer's disease, was actually protective in PD. We addressed this by examining subjects in the PAGE cohort (a subset of the AARP Diet and Health Study cohort). Apolipoprotein E genotypes in relation to Parkinson's disease (PD) were examined in 786 cases and 1537 controls, all non-Hispanic Caucasian with adjustment for year of birth, sex, smoking status, daily caffeine intake, and family history of PD. Compared with participants with ApoE33, ApoE4 carriers had significantly lower odds for having PD, whereas ApoE2 carriers did not. Consistent with data on AD, however, in PD patients the prevalence of dementia appeared to be higher among ApoE4 carriers. These data are consistent with the fact that the ApoE4 allele (associated with higher cholesterol) may be associated with a lower PD risk.

Aim 2 Progress: Testing the hypothesis that peripheral cholesterol-APOE status affects the metabolism and or central entry of toxicants that can cause Parkinson's like damage.

The working hypothesis was that cholesterol status influences the metabolism and/or distribution of trace toxicants to which PD-susceptible people are exposed, or alternately, that

cholesterol status influences the distribution of such toxicants, permitting greater entry into the brain. The model toxicants we selected were rotenone (modestly dopamine-neuron selective) and MPTP (highly dopamine-neuron selective). As we noted in a prior progress report, we had to develop assays for cholesterol and also determine how long mice had to be on their diet to achieve meaningful differences in cholesterol. In experiment 1, we established two groups of mice: one fed a high-cholesterol diet and one fed a low-cholesterol diet. We had purchased commercial kits for cholesterol measurements from Biovision because they required only 2 µL of serum per assay, but as noted, this experiment-limiting test was problematic. Biovision worked with us and improved the kits, and after confirming values with the Penn State Hershey Medical Center clinical laboratory, we intoxicated the animals as planned.

Experiment 1 had started with only 24 animals (six cells of four animals each), and several were lost due to unrelated events (fighting with other mice; etc.) because of the long-time period that was required to work out suitable cholesterol measurements. Because of the loss of animals, and because this was a pilot experiment, we eliminated the control only group. Although unusual, the primary hypothesis was that high cholesterol would be protective against one or both of the toxicants, and although not ideal, this could be tested without a control group. Thus, the effects of MPTP and rotenone were examined in groups of mice with high (296 mg/dL) and low cholesterol (124 mg/dL) treatments. A summary of the results of this experiment is shown in Figure 1. Despite the profound difference in plasma cholesterol, the only significant difference was that depletion of dopamine was actually greater in the high cholesterol group challenged with MPTP. These preliminary data do not support the working hypothesis of Aim 2.

We repeated this study in its entirety, but began with adequate numbers of mice such that we could accommodate for attrition due to causes noted earlier. In addition, because of the issues noted above, the cholesterol dietary treatments ran for more than 7 months in the first experiment, and we had to shorten this to complete the experiments before the end of the grant period. We therefore chose a pre-treatment period of 105 (112 days until the animals were euthanized and studied). In this case all groups had 5-6 animals, except for the high cholesterol control group in which N =4. An unexpected finding in Experiment 2 was that the high cholesterol group was less elevated than controls (185 ± 16 vs. 140 ± 7 mg/dL) compared to experiment 1; the high cholesterol mice also were markedly heavier (39.4 ± 1.1 versus 33.4 ± 0.5 g). Despite these differences, there is remarkable consistency with the results of experiment 1 as shown in the summary data from the neurochemical analyses in three different brain regions (Figures 2-4). Again, these data refute the working hypothesis. We conclude that the consistent clinical findings that we (and now others) have made (see data from Aim 1 and earlier publications) are not due to either of the two hypotheses we proposed that primarily relate to metabolism and distribution of toxicants as affected by cholesterol. Although “negative”, these are very important data as they now suggest the involved mechanism is likely related to neuronal response or repair, and not simply toxicant concentration.

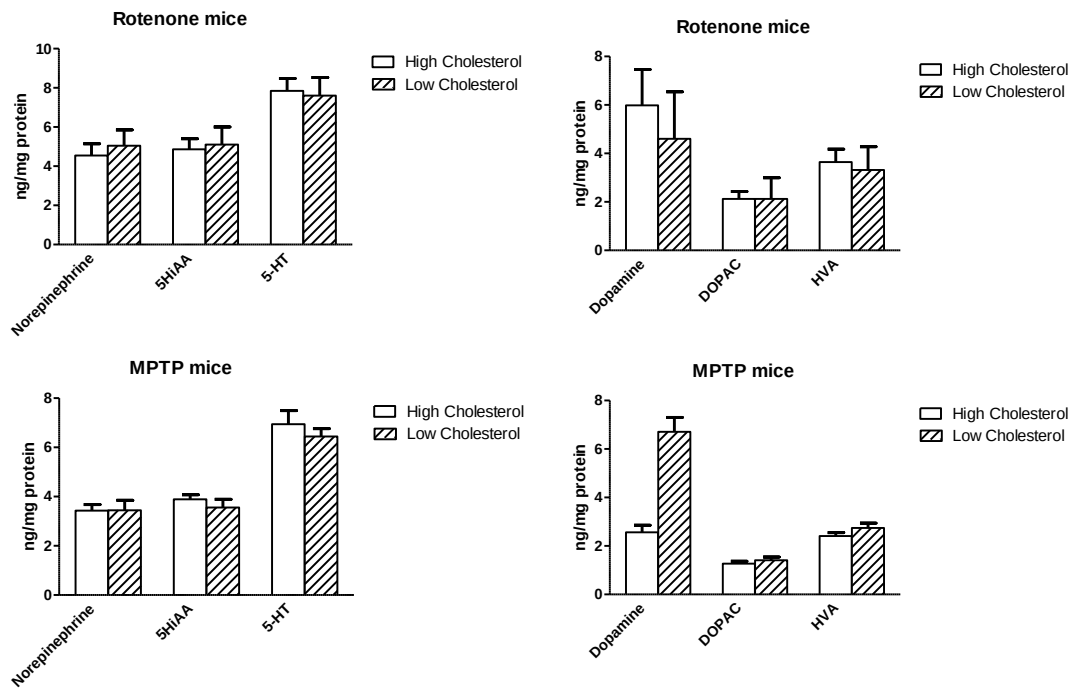

Figure 1. Neurochemical effects on C56/bl mice fed normal and cholesterol-supplemented diets for more than 6 months.

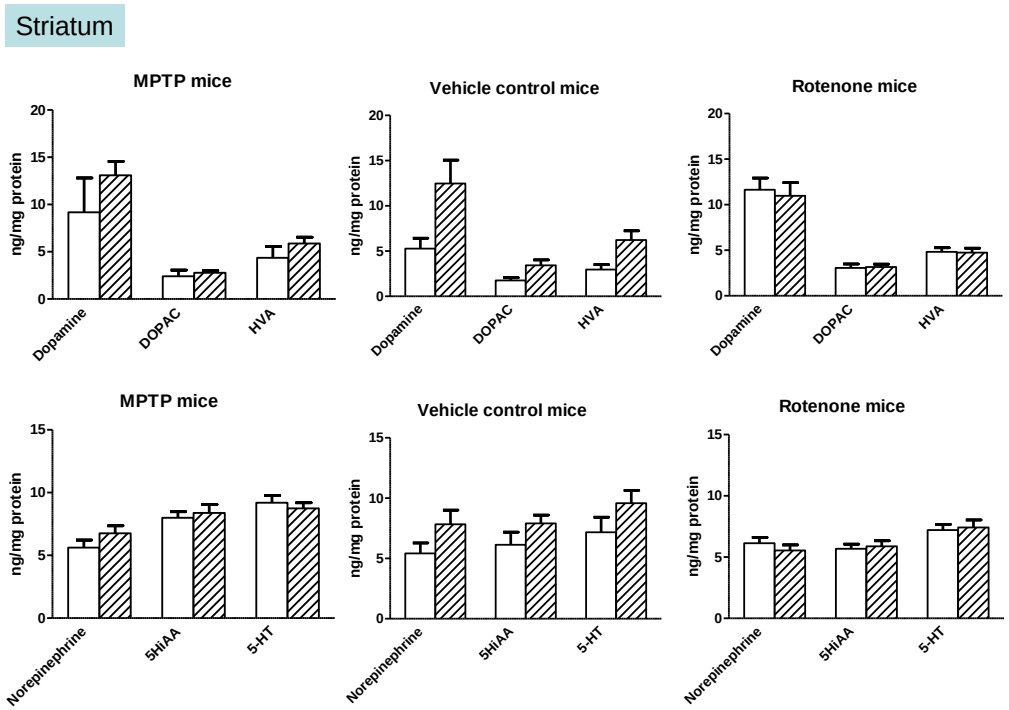

Figure 2. Effects of toxicants on striatal monoamine neurochemistry of mice on high and low cholesterol diets

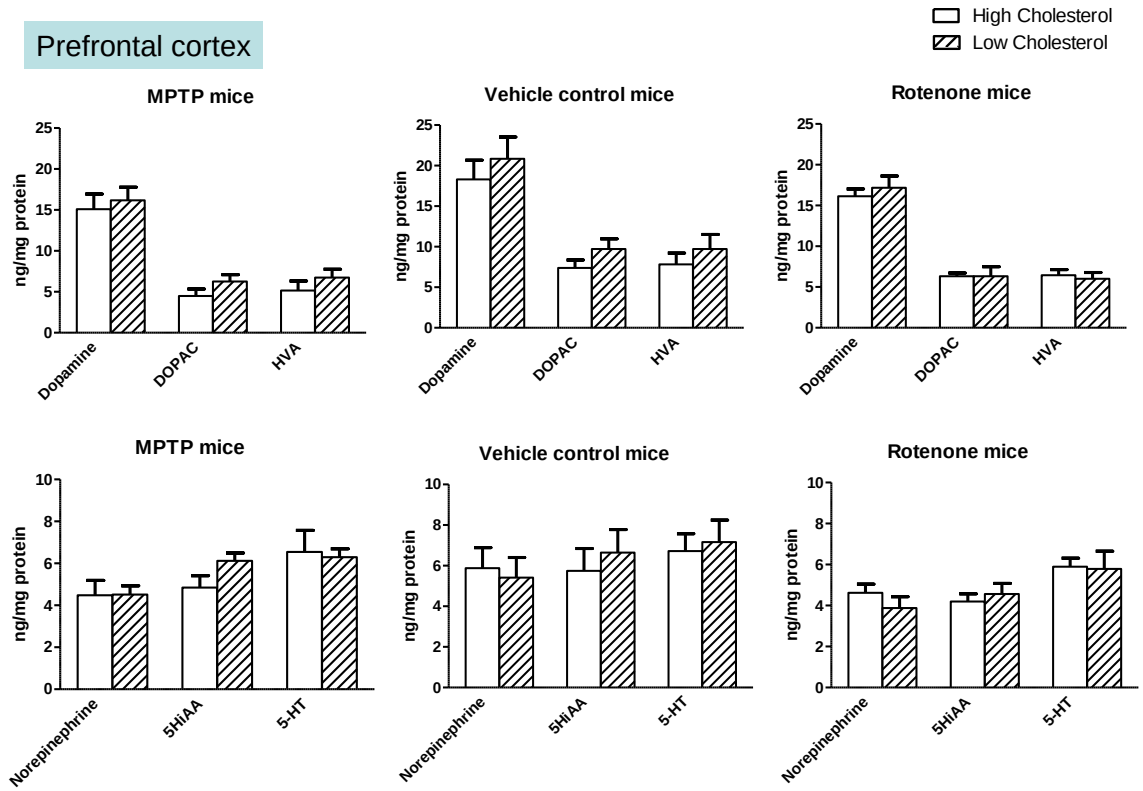

Figure 3. Effects of toxicants on prefrontal cortical monoamine neurochemistry of mice on high and low cholesterol diets

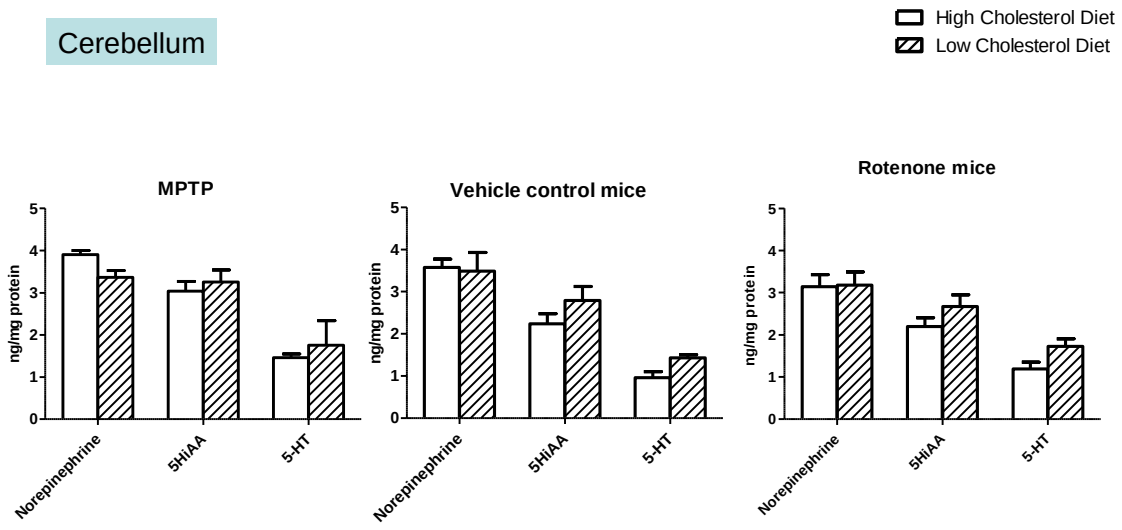

Figure 4. Effects of toxicants on cerebellar monoamine neurochemistry of mice on high and low cholesterol diets

The results above led to the need to now focus on brain mechanisms, specifically those related to genetic factors that influence whether an individual has high LDL-cholesterol and the associated lower risk of PD, and contributed to Dr. Huang receiving funding as the PI of a new NINDS-funded biomarker project that seeks to determine structural or biochemical markers of Parkinson's disease. This also led us to need access to NextGen Sequencing capacities not previously available at the Penn State College of Medicine to search for potential genetic markers. While there have been many GWAS studies reported for PD, few have attempted to test specific hypotheses, and those that have were focused on genes known to cause the rare familial PD. Through Dr. Huang's funded U01 project, we shall have the unique opportunity to access to extensive numbers of patient samples and controls gathered under stringent conditions that will allow us to examine those genes that are linked to LDL-cholesterol (e.g., biosynthetic and degrading enzymes, processing enzymes using cholesterol as precursor, carrier proteins like apolipoproteins, etc.). With NextGen sequencing capacities purchased to advance this and other projects at the College of Medicine, it is now feasible to research which of these genes are related to both high-LDL cholesterol and lower risk of PD, something not previously possible.

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
__X__No

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

_____Yes
__X__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

Note: Studies that fall dramatically short on recruitment are encouraged to

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

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

Gender:
_____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
__X____No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

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

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, 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):**
Apolipoprotein E genotypes and the risk of Parkinson disease.	Gao J, Huang X, Park Y, Liu R, Hollenbeck A, Schatzkin A, Mailman RB, Chen H	Neurobiol Aging. (2011) 32(11):2106. e1-6.	Dec 2010	☐Submitted ☐Accepted ☒Published

Serum cholesterol and the progression of Parkinson's disease: results from DATATOP	Huang X, Auinger P, Eberly S, Oakes D, Schwarzschild M, Ascherio A, Mailman R, Chen H, Parkinson Study Group DATATOP Investigators.	PLoS One. (2011) 6(8):e22854	April 2011	☐Submitted ☐Accepted ☒Published
Serum Cholesterol and Nigrostriatal R2* Values in Parkinson's Disease	Du G, Lewis MM, Shaffer ML, Chen H, Yang QX, Mailman RB, Huang X	PLoS One (2102) 7 (4) e3539720	Oct 2011	☐Submitted ☐Accepted ☒Published

(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:

There will be a publication from the ARIC cohort as well as a short communication on the animal results that will be submitted in 2013.

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.

During the course of this project, an article appeared (Drug Discovery & Development - June 29, 2010) entitled "Cholesterol Drugs For The Healthy Still Debatable". It summarized a current controversy about whether healthy people with low cholesterol take a pill to lower their cholesterol even more in hopes of preventing heart problems. Although Crestor® was approved by the FDA for this purpose in 2008, the data underlying our research (now supported by our DATATOP study) suggest that statins may neither be neuroprotective nor innocuous in otherwise healthy people. It is premature to make a clear judgment about this, but if our hypotheses are correct, it would argue against use of cholesterol lowering drugs in otherwise healthy individuals. This could result in decreased morbidity, as well as cost savings from unnecessary or harmful use of such drugs in otherwise healthy people.

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.

As we have summarized earlier, the studies conducted under the auspices of Aim 1 now have provided additional evidence in a variety of different types of clinical studies (above and beyond the ARIC cohort that was originally noted) showing the association of high cholesterol with a lower incidence of PD. Moreover, the secondary analysis of the DATATOP trial provides the first evidence that higher total serum cholesterol concentrations is also associated with a slower clinical progression of PD. It is established, however, that brain cholesterol is synthesized in situ, and is not dependent on peripheral cholesterol. This preliminary finding needs confirmation from larger prospective studies.

What has not been clarified by our work is the mechanism that relates high cholesterol to lower incidence of PD. Essentially, our studies indicate that altered cholesterol status, at least in the mouse, does not affect the central availability of dopamine neurotoxicants. Although our data refuted our working hypotheses, the information is critical to allow us to proceed on to other mechanisms that may actually be related to PD.

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.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Richard Bernard Mailman	Professor and College of Medicine Distinguished Senior Scholar
eRA COMMONS USER NAME (credential, e.g., agency login) RMAILMAN	

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
Rutgers University, New Brunswick, NJ	B.S.	05/1968	Chemistry/Food Science
North Carolina State University, Raleigh	M.S.	05/1972	Physiology/Toxicology
North Carolina State University, Raleigh	Ph.D.	05/1974	Physiology/Toxicology
North Carolina State University, Raleigh	Post-doc.	06/1974- 1/1976	Drug metabolism
University of North Carolina, Chapel Hill	Post-doc.	02/1976- 1/1978	Neurobiology

A. Personal Statement

My lab has had a decades-long interest in the design and discovery of novel dopamine receptor ligands. In the process, we were also the first to discover, elaborate, and name (in 1994) the major pharmacology research front now called functional selectivity (how drugs acting at a single receptor differentially activate or block selected signaling pathways of that receptor). Our current research uses both dopamine D1 and D2 receptors as our model system and our targets for drug discovery.

We are especially interested in discovery of ligands with agonist properties at the D_1 receptor. There is a large body of animal data, and some early human data, showing that D1 agonists can provide useful therapy in mid- and late-stage Parkinson's disease, for improving deficits in cognition and memory, for ADHD, and even possibly for and Huntington's disease. The function of dopamine D_1-like receptors and the discovery and development of novel ligands for these receptors has been a singular focus of mine for more than 30 years. Through the 1980's, my lab was the first to show the modulating effects of D_1 receptors on D_2 function, and the first to radiolabel SCH23390 and map D_1 receptors in brain. We published the first computational modeling study on D_1 ligands, and discovered the first high affinity, centrally available D_1 agonist dihydrexidine. Our current research in this area is focused on typical agonists with improved drugability, on functionally selective D_1-like ligands, and the discovery of D_1 or D_5 selective ligands. We recently have identified a lead compound that is a potential clinical candidate and for which we have already demonstrated antiparkinson efficacy in non-human primates. Our second focus is on "functional selectivity" of the D2 receptor. Here, we are interested in how small changes to drug-induced/selected conformations of the D2 receptor cause major differences in the signaling profiles of the receptor, and how resulting models may help design and discover functionally selective D2 ligands.

As this brief description may suggest, by its nature the lab's work for the past several decades is what is now termed "translational." My lab has played a major role in the understanding of aripiprazole (Abilify) pharmacology and in the path that brought it to the clinic. Moreover, the only D1 agonists currently available for clinical experimentation was discovered and developed by our group. I have active collaborations with the Parkinson's disease research group here headed by Dr. Xuemei Huang (a Department Joint appointee) and have collaborated on both human pharmacological and etiological studies related to PD.

B. Positions and Honors

Positions

At the Pennsylvania State University College of Medicine

2008-present Professor and College of Medicine Distinguished Senior Scholar in Pharmacology and Neurology

At the University of North Carolina School of Medicine at Chapel Hill

2008-present Adjunct Professor, Department of Psychiatry
1988-2008: Professor, Departments of Psychiatry, Pharmacology, and Medicinal Chemistry
1987-1988: Associate Professor (tenured), Departments of Psychiatry and Pharmacology
1978-1986: Research Assistant/Research Associate Professor, Department of Psychiatry and Pharmacology

Honors

Eugene Hargraves Award in Mental Health Research (1999); Burroughs-Wellcome Fund Travel Award (1999); 1st Distinguished Alumni Speaker, North Carolina State University (1998); Burroughs-Wellcome Scholar in Toxicology (1987-1992); Early Training Awards: Early admissions, Rutgers University; New Jersey State Scholarship (Full Tuition); Rutgers College Dean of Men's Grant; ASBC-Brand Travel Grant, 1974.

Federal and Other Advisory Group Memberships

NIH ZRG1 MDCN-L (2001-6); NIMH MATRICS Project (2003); NIMH Neuroscience of Mental Health Advisory Panel, 1993 (Neuropsychopharmacology Redbook); NIH Reviewers Reserve (1991-1995); NIH Toxicology Study Section (1987-1991); EPA Science Review Panel for Health Research (1985-1989); NIMH Special Research Review Committee (1985-1987); Frequent Consultant or ad hoc for NIH agencies, etc.

Current Editorial Board Activities

The Journal of Molecular and Biochemical Toxicology (1992-present); Current Opinion in Investigational Drugs (1998-present); Neuroscience.Net (1995-present) [Past service on eight other journals]

Professional Memberships:

American College of Neuropsychopharmacology (Fellow); Society for Neuroscience; American Society of Neurochemistry; International Society for Neurochemistry; American Society for Pharmacology and Experimental Therapeutics; Society of Toxicology; American Chemical Society; American Association for the Advancement Science

C. Selected Peer-reviewed Publications (Last 3 years plus examples of earlier drug discovery papers from total of >175 peer-reviewed papers, >50 chapters, 2 books; 6 issued patents)

1. Charifson PS, Wyrick SD, Hoffman AJ, Simmons RM, Bowen JP, McDougald DL, Mailman RB. Synthesis and pharmacological characterization of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as dopamine receptor ligands. J Med Chem 1988; 31(10):1941-6.
2. Charifson PS, Bowen JP, Wyrick SD, Hoffman AJ, Cory M, McPhail AT, Mailman RB. Conformational analysis and molecular modeling of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as D1 dopamine receptor ligands. J Med Chem 1989; 32(9):2050-8.
3. Lovenberg TW, Brewster WK, Mottola DM, Lee RC, Riggs RM, Nichols DE, Lewis MH, Mailman RB. Dihydrexidine, a novel selective high potency full dopamine D-1 receptor agonist. Eur J Pharmacol 1989; 166(1):111-3.
4. Brewster WK, Nichols DE, Riggs RM, Mottola DM, Lovenberg TW, Lewis MH, Mailman RB. trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine: a highly potent selective dopamine D1 full agonist. J Med Chem 1990; 33(6):1756-64.

5. Taylor JR, Lawrence MS, Redmond DE, Jr., Elsworth JD, Roth RH, Nichols DE, Mailman RB. Dihydrexidine, a full dopamine D1 agonist, reduces MPTP-induced parkinsonism in monkeys. Eur J Pharmacol 1991; 199(3):389-91.
6. Mottola DM, Brewster WK, Cook LL, Nichols DE, Mailman RB. Dihydrexidine, a novel full efficacy D1 dopamine receptor agonist. J Pharmacol Exp Ther 1992; 262(1):383-93.
7. Watts VJ, Lawler CP, Gilmore JH, Southerland SB, Nichols DE, Mailman RB. Dopamine D1 receptors: efficacy of full (dihydrexidine) vs. partial (SKF38393) agonists in primates vs. rodents. Eur J Pharmacol 1993; 242(2):165-72.
8. Wyrick SD, Booth RG, Myers AM, Owens CE, Kula NS, Baldessarini RJ, McPhail AT, Mailman RB. Synthesis and pharmacological evaluation of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as ligands for a novel receptor with sigma-like neuromodulatory activity. J Med Chem 1993; 36(17):2542-51.
9. Minor DL, Wyrick SD, Charifson PS, Watts VJ, Nichols DE, Mailman RB. Synthesis and molecular modeling of 1-phenyl-1,2,3,4-tetrahydroisoquinolines and related 5,6,8,9-tetrahydro-13bH-dibenzo[a,h]quinolizines as D1 dopamine antagonists. J Med Chem 1994; 37(25):4317-28.
10. Brewster WK, Nichols DE, Watts VJ, Riggs RM, Mottola D, Mailman RB. Evaluation of cis- and trans-9- and 11-hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridines as structurally rigid, selective D1 dopamine receptor ligands. J Med Chem 1995; 38(2):318-27.
11. Knoerzer TA, Watts VJ, Nichols DE, Mailman RB. Synthesis and biological evaluation of a series of substituted benzo[a]phenanthridines as agonists at D1 and D2 dopamine receptors. J Med Chem 1995; 38(16):3062-70.
12. Snyder SE, Aviles-Garay FA, Chakraborti R, Nichols DE, Watts VJ, Mailman RB. Synthesis and evaluation of 6,7-dihydroxy-2,3,4,8,9,13b-hexahydro-1H-benzo[6,7]cyclohepta[1,2,3-ef][3]benzazepine, 6,7-dihydroxy- 1,2,3,4,8,12b-hexahydroanthr[10,4a,4-cd]azepine, and 10-(aminomethyl)-9,10- dihydro-1,2-dihydroxyanthracene as conformationally restricted analogs of beta-phenyldopamine. J Med Chem 1995; 38(13):2395-409.
13. Wyrick SD, Booth RG, Myers AM, Owens CE, Bucholtz EC, Hooper PC, Kula NS, Baldessarini RJ, Mailman RB. 1-Phenyl-3-amino-1, 2, 3, 4-tetrahydronaphthalenes and related derivatives as ligands for the neuromodulatory sigma 3 receptor: further structure-activity relationships. J Med Chem 1995; 38(19):3857-64.
14. Mailman RB, Nichols DE, and Tropsha A “Molecular Drug Design for Dopamine Receptors” The Dopamine Receptors, K. Neve and R. Neve (eds.), Humana Press, pp. 105-133, 1996.
15. Ghosh D, Snyder SE, Watts VJ, Mailman RB, Nichols DE. 9-Dihydroxy-2,3,7,11b-tetrahydro-1H-naph[1,2,3-de]isoquinoline: a potent full dopamine D1 agonist containing a rigid-beta-phenyldopamine pharmacophore. J Med Chem 1996; 39(2):549-55.
16. Mottola DM, Laiter S, Watts VJ, Tropsha A, Wyrick SD, Nichols DE, Mailman RB. Conformational analysis of D1 dopamine receptor agonists: pharmacophore assessment and receptor mapping. J Med Chem 1996; 39(1):285-96.
17. Negash K, Nichols DE, Watts VJ, Mailman RB. Further definition of the D1 dopamine receptor pharmacophore: synthesis of trans-6,6a,7,8,9,13b-hexahydro-5H-benzo[d]naphth[2,1-b]azepines as rigid analogues of beta-phenyldopamine. J Med Chem 1997; 40(14):2140-7.
18. Mailman RB, Nichols DE, Lewis MM, Blake B, and Lawler CP. “Functional Effects of Novel Dopamine Ligands: Dihydrexidine and Parkinson’s Disease as a First Step”. Dopamine Receptor Subtypes: From Basic Science to Clinical Application. P. Jenner & R. Demirdemar (eds.), IOS Press. Pp. 64-83. 1998.

19. Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, Gonzalez AM, Sibley DR, Mailman RB. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacol. 20:612-627, 1999.
20. Doll MK, Nichols DE, Kilts JD, Prioleau C, Lawler CP, Lewis MM, and Mailman RB. Synthesis and dopaminergic properties of benzo-fused analogues of quinpirole and quinelorane. J. Med. Chem. 42:935-940, 1999.
21. Hoffman B, Cho SJ, Zheng W, Wyrick S, Nichols DE, Mailman RB, Tropsha A. Quantitative structure-activity relationship modeling of dopamine D(1) antagonists using comparative molecular field analysis, genetic algorithms-partial least-squares, and K nearest neighbor methods. J Med Chem 1999; 42(17):3217-26.
22. Gulwadi AG, Korpinen CD, Mailman RB, Nichols DE, Sit SY, Taber MT. Dinapsoline: characterization of a D1 dopamine receptor agonist in a rat model of Parkinson's disease. J Pharmacol Exp Ther 2001; 296(2):338-44.
23. Huang X, Lawler CP, Lewis MM, Nichols DE, Mailman RB. D1 dopamine receptors. Int Rev Neurobiol 2001; 48:65-139.
24. Mailman R, Huang X, Nichols DE. Parkinson's disease and D1 dopamine receptors. Curr Opin Investig Drugs 2001; 2(11):1582-91.
25. Miyamoto S, Mailman RB, Lieberman JA, Duncan GE. Blunted brain metabolic response to ketamine in mice lacking D(1A) dopamine receptors. Brain Res 2001; 894(2):167-80.
26. Montague DM, Striplin CD, Overcash JS, Drago J, Lawler CP, Mailman RB. Quantification of D1B(D5) receptors in dopamine D1A receptor-deficient mice. Synapse 2001; 39(4):319-22.
27. Andersson C, Hamer RM, Lawler CP, Mailman RB, Lieberman JA. Striatal volume changes in the rat following long-term administration of typical and atypical antipsychotic drugs. Neuropsychopharmacology 2002; 27(2):143-51.
28. Kilts JD, Connery HS, Arrington EG, Lewis MM, Lawler CP, Oxford GS, O'Malley KL, Todd RD, Blake BL, Nichols DE, Mailman RB. Functional selectivity of dopamine receptor agonists. II. Actions of dihydrexidine in D2L receptor-transfected MN9D cells and pituitary lactotrophs. J Pharmacol Exp Ther 2002; 301(3):1179-89.
29. Mottola DM, Kilts JD, Lewis MM, Connery HS, Walker QD, Jones SR, Booth RG, Hyslop DK, Piercey M, Wightman RM, Lawler CP, Nichols DE, Mailman RB. Functional selectivity of dopamine receptor agonists. I. Selective activation of postsynaptic dopamine D2 receptors linked to adenylate cyclase. J Pharmacol Exp Ther 2002; 301(3):1166-78.
30. Leonard SK, Anderson CM, Lachowicz JE, Schulz DW, Kilts CD, Mailman RB. Amygdaloid D1 receptors are not linked to stimulation of adenylate cyclase. Synapse 2003; 50(4):320-33.
31. Qandil AM, Lewis MM, Jassen A, Leonard SK, Mailman RB, Nichols DE. Synthesis and pharmacological evaluation of substituted naphth[1,2,3-de]isoquinolines (dinapsoline analogues) as D1 and D2 dopamine receptor ligands. Bioorg Med Chem 2003; 11(7):1451-64.
32. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28(8):1400-11.
33. Gay EA, Urban JD, Nichols DE, Oxford GS, Mailman RB. Functional selectivity of D2 receptor ligands in a Chinese hamster ovary hD2L cell line: evidence for induction of ligand-specific receptor states. Mol Pharmacol 2004; 66(1):97-105.
34. Grubbs RA, Lewis MM, Owens-Vance C, Gay EA, Jassen AK, Mailman RB, Nichols DE. 8,9-dihydroxy-1,2,3,11b-tetrahydrochromeno[4,3,2,-de]isoquinoline (dinoxyline), a high affinity and potent agonist at all dopamine receptor isoforms. Bioorg Med Chem 2004; 12(6):1403-12.

35. Mailman RB, Gay EA. Novel Mechanisms of drug action: Functional selectivity at D2 dopamine receptors (a lesson for drug discovery). Med Chem Res 2004; 13(1-2):115-26.
36. Sit SY, Xie K, Jacutin-Porte S, Boy KM, Seanz J, Taber MT, Gulwadi AG, Korpinen CD, Burris KD, Molski TF, Ryan E, Xu C, Verdoorn T, Johnson G, Nichols DE, Mailman RB. Synthesis and SAR exploration of dinapsoline analogues. Bioorg Med Chem 2004; 12(4):715-34.
37. Oloff S, Mailman RB, Tropsha A. Application of validated QSAR models of D1 dopaminergic antagonists for database mining. J Med Chem 2005; 48(23):7322-32.
38. Padilla S, Marshall RS, Hunter DL, Oxendine S, Moser VC, Southerland SB, Mailman RB. Neurochemical effects of chronic dietary and repeated high-level acute exposure to chlorpyrifos in rats. Toxicol Sci 2005; 88(1):161-71.
39. Ryman-Rasmussen JP, Nichols DE, Mailman RB. Differential activation of adenylate cyclase and receptor internalization by novel dopamine D1 receptor agonists. Mol Pharmacol 2005; 68(4):1039-48.
40. Leonard SK, Ferry-Leeper P, Mailman RB. Low affinity binding of the classical D1 antagonist SCH23390 in rodent brain: potential interaction with A2A and D2-like receptors. Brain Res 2006; 1117(1):25-37. PMCID: PMC1945230
41. Lewis MM, Huang X, Nichols DE, Mailman RB. D1 and functionally selective dopamine agonists as neuroprotective agents in Parkinson's disease. CNS Neurol Disord Drug Targets 2006; 5(3):345-53.
42. George MS, Molnar CE, Grenesko EL, Anderson B, Mu Q, Johnson K, Nahas Z, Knable M, Fernandes P, Juncos J, Huang X, Nichols DE, Mailman RB. A single 20 mg dose of dihydrexidine (DAR-0100), a full dopamine D1 agonist, is safe and tolerated in patients with schizophrenia. Schizophr Res 2007; 93(1-3):42-50.
43. Huang X, Chen H, Miller WC, Mailman RB, Woodard JL, Chen PC, Xiang D, Murrow RW, Wang YZ, Poole C. Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. Mov Disord 2007; 22(3):377-81. PMCID: PMC1906875
44. Lewis MM, Slagle CG, Smith AB, Truong Y, Bai P, McKeown MJ, Mailman RB, Belger A, Huang X. Task specific influences of Parkinson's disease on the striato-thalamo-cortical and cerebello-thalamo-cortical motor circuitries. Neuroscience 2007; 147(1):224-35. PMCID: PMC1939944
45. Mailman RB. GPCR functional selectivity has therapeutic impact. Trends Pharmacol Sci 2007; 28(8):390-6. PMCID: PMC2958218
46. Mailman RB, Huang X. Dopamine receptor pharmacology. Handb Clin Neurol 2007; 83:77-105.
47. Mu Q, Johnson K, Morgan PS, Grenesko EL, Molnar CE, Anderson B, Nahas Z, Kozel FA, Kose S, Knable M, Fernandes P, Nichols DE, Mailman RB, George MS. A single 20 mg dose of the full D1 dopamine agonist dihydrexidine (DAR-0100) increases prefrontal perfusion in schizophrenia. Schizophr Res 2007; 94(1-3):332-41.
48. Ryman-Rasmussen JP, Griffith A, Oloff S, Vaidehi N, Brown JT, Goddard WA, 3rd, Mailman RB. Functional selectivity of dopamine D1 receptor agonists in regulating the fate of internalized receptors. Neuropharmacology 2007; 52(2):562-75. PMCID: PMC1855220
49. Urban JD, Clarke WP, von Zastrow M, Nichols DE, Kobilka B, Weinstein H, Javitch JA, Roth BL, Christopoulos A, Sexton PM, Miller KJ, Spedding M, Mailman RB. Functional selectivity and classical concepts of quantitative pharmacology. J Pharmacol Exp Ther 2007; 320(1):1-13.
50. Urban JD, Vargas GA, von Zastrow M, Mailman RB. Aripiprazole has functionally selective actions at dopamine D2 receptor-mediated signaling pathways. Neuropsychopharmacology 2007; 32(1):67-77.

51. Huang X, Abbott RD, Petrovitch H, Mailman RB, Ross GW. Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study. Mov Disord 2008; 23(7):1013-8.
52. Mailman RB. Toxicant-Receptor Interactions: Fundamental Principles. *In* Hodgson E, Smart R, eds. Introduction to Biochemical and Molecular Toxicology. Hobocken, NJ: Wiley, 2008. pp. 359-88.
53. Brown JT, Kant A, Mailman RB. Rapid, semi-automated, and inexpensive radioimmunoassay of cAMP: application in GPCR-mediated adenylate cyclase assays. J Neurosci Methods 2009; 177(2):261-6. PMCID: PMC2717699
54. Lewis MM, Smith AB, Styner M, Gu H, Poole R, Zhu H, Li Y, Barbero X, Gouttard S, McKeown MJ, Mailman RB, Huang X. Asymmetrical lateral ventricular enlargement in Parkinson's disease. Eur J Neurol 2009; 16(4):475-81. PMCID: PMC2908273
55. Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, Umbach DM, Xu Q, Hollenbeck A, Schatzkin A, Blair A. Smoking duration, intensity, and risk of Parkinson disease. Neurology 2010; 74(11):878-84. PMCID: PMC2836869
56. Mailman RB, Murthy V. Ligand functional selectivity advances our understanding of drug mechanisms and drug discovery. Neuropsychopharmacology 2010; 35(1):345-6. PMCID: PMC2952437
57. Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des 2010; 16(5):488-501. PMCID: PMC2958217
58. Gao J, Huang X, Park Y, Liu R, Hollenbeck A, Schatzkin A, Mailman RB, Chen H. Apolipoprotein E genotypes and the risk of Parkinson disease. Neurobiol Aging. 2011;32(11):2106 e1-6. PMCID: PMC3172377.
59. Huang X, Auinger P, Eberly S, Oakes D, Schwarzschild M, Ascherio A, Mailman R, Chen H. Serum cholesterol and the progression of Parkinson's disease: results from DATATOP. PLoS One. 2011;6(8):e22854. PMCID: PMC3154909.
60. Lewis MM, Du G, Sen S, Kawaguchi A, Truong Y, Lee S, Mailman RB, Huang X. Differential involvement of striato- and cerebello-thalamo-cortical pathways in tremor- and akinetic/rigid-predominant Parkinson's disease. Neuroscience. 2011;177:230-9. PMCID: PMC3049982.
61. Boyd KN, Mailman RB. Dopamine receptor signaling and current and future antipsychotic drugs. Handb Exp Pharmacol. 2012(212):53-86.
62. Du G, Lewis MM, Shaffer ML, Chen H, Yang QX, Mailman RB, Huang X. Serum cholesterol and nigrostriatal R2* values in Parkinson's disease. PLoS One. 2012;7(4):e35397. PMCID: PMC3328461.
63. Fowler JC, Bhattacharya S, Urban JD, Vaidehi N, Mailman RB. Receptor conformations involved in dopamine D(2L) receptor functional selectivity induced by selected transmembrane-5 serine mutations. Mol Pharmacol. 2012;81(6):820-31. PMCID: PMC3362898.
64. Lewis MM, Du G, Kidacki M, Patel N, Shaffer ML, Mailman RB, Huang X. Higher iron in the red nucleus marks Parkinson's dyskinesia. Neurobiol Aging. 2013;34(5):1497-503. PMCID: PMC3570638
[Available on 2014/5/1]

D. Research Support

Ongoing Research Support

None

Completed Research Support (past 3 years)

U19 MH082441-05 (B. Roth-PI, R. Mailman-Subaward PI) 9/1/2007-8/9/2012
NIH/University of North Carolina

“Functional Selectivity: A Novel Approach for CNS Drug Discovery “, Project 2 (Mailman)
This project is studying the mechanisms of functional selectivity of selected dopamine and serotonin receptors, and use the resulting knowledge for the discovery of novel ligands.

SAP #4100047645 (Mailman, Richard B.) 4/20/2009-6/30/2011
PA Tobacco Settlement Fund/Dean's Feasibility
“The Interaction of Environmental Agents and LDL-Cholesterol in Parkinson's Disease”
This project is studying the mechanisms by which low cholesterol increases the potential risk of Parkinson’s disease.
Role: Co-PI

(Mailman, Richard B.) 3/16/2011-3/15/2012
Pfizer, Inc.
“Avoiding Rapid Tolerance with D1 Dopamine Agonists”
Contract
Role: P.I.