RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE ON DRUG ABUSE

Federal Award Date: 06/14/2018

Grant Number: 5R01DA025267-09 REVISED
FAIN: R01DA025267

Principal Investigator(s):
LANCE R MCMAHON, PHD

Project Title: Nicotine dependence: neuropharmacology in monkeys

Youngers, Jane
Asst Vice Pres for Resrch Admn
University of Texas Hlth Scis Center
7703 Floyd Curl Drive, MSC 7828
San Antonio, TX 782293900

Award e-mailed to: nihgrants@uthscsa.edu

Period Of Performance:
Budget Period: 07/01/2017 – 08/16/2017
Project Period: 07/01/2008 – 08/16/2017

Dear Business Official:

The National Institutes of Health hereby revises this award to reflect a decrease in the amount of $206,911 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Drug Abuse of the National Institutes of Health under Award Number R01DA025267. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Pamela G. Fleming
Grants Management Officer
NATIONAL INSTITUTE ON DRUG ABUSE

Additional information follows

SECTION I – AWARD DATA – 5R01DA025267-09 REVISED

Award Calculation (U.S. Dollars)

Federal Direct Costs	$115,118
Federal F&A Costs	$57,046
Approved Budget	$172,164
Total Amount of Federal Funds Obligated (Federal Share)	$172,164
TOTAL FEDERAL AWARD AMOUNT	$172,164
AMOUNT OF THIS ACTION (FEDERAL SHARE)	($-206,911)

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
9	$172,164	$172,164

Fiscal Information:

CFDA Name:	Drug Abuse and Addiction Research Programs
CFDA Number:	93.279
EIN:	1741586031A3
Document Number:	RDA025267B
PMS Account Type:	P (Subaccount)
Fiscal Year:	2017

IC	CAN	2017
DA	8472629	$172,164

NIH Administrative Data:
PCC: PC/RRR / **OC**: 414E / **Released**: eRA Commons User Name 06/13/2018
Award Processed: 06/14/2018 12:03:02 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01DA025267-09 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01DA025267-09 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V,

Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01DA025267. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

This award is not subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the eRA Commons (Commons) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) quarterly cash transaction data. A final quarterly federal cash transaction report is not required for awards in PMS B subaccounts (i.e., awards to foreign entities and to Federal agencies). NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures or quarterly federal cash transaction reporting. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level. If the grantee submits a final expenditure FFR but does not reconcile any discrepancies between expenditures reported on the final expenditure FFR and the last cash report to PMS, NIH will close the award at the lower amount. This could be considered a debt or result in disallowed costs.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51,

R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience*.

NIH strongly encourages electronic submission of the final invention statement through the Closeout feature in the Commons, but will accept an email or hard copy submission as indicated below.

Email: The final invention statement may be e-mailed as PDF attachments to: NIHCloseoutCenter@mail.nih.gov.

Hard copy: Paper submissions of the final invention statement may be faxed to the NIH Division of Central Grants Processing, Grants Closeout Center, at 301-480-2304, or mailed to:

National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and should be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Additional Costs

SECTION IV – DA Special Terms and Conditions – 5R01DA025267-09 REVISED

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

REVISION #_1__ - CHANGE OF INSTITUTION
This award has been revised to relinquish this grant on **08/11/2017**. This action is in accordance with the revised relinquishing statement from **UNIVERSITY OF TEXAS HLT SCI CTR** dated **12/19/2017**. Support for this project will continue under 7 **R01 DA025267-10** at the **UNIVERSITY**

OF FLORIDA. The revision supersedes the Notice of Award (NoA) issued **06/13/2017**. Future year(s) have been deleted accordingly.

DIVERSITY SUPPLEMENT

This award included support under the Research Supplements to Promote Diversity in Health-Related Research Program for Redacted by agreement Funds in the amount of $3,160 are restricted for the above purpose only and may not be transferred to any other individual. Funds awarded are available for carryover for awards given carryover authority as reflected in section III of this award notice. However, the funds remain restricted for the individual and the purpose for which the supplement is awarded.

GRADUATE STUDENT CAP

The maximum amount NIH will award for the support of a graduate student on a research grant or a cooperative agreement is tied to the National Research Service Award (NRSA) zero-level stipend in effect at the time the grant award is issued on the Federal award date. The schedule for NRSA stipends can be found at http://grants.nih.gov/training/nrsa.htm. Consistent with cost principles for Institutions of Higher Education (IHEs) described in 45 CFR 75.431(j) and 75.466, the compensation of graduate students supported by research grants must be reasonable. These operating principles associated with the compensation of students performing necessary work on NIH funded research projects are described in detail in the *NIH Grants Policy Statement* at http://grants.nih.gov/policy/nihgps/index.htm. The amount provided for compensation includes salary or wages, fringe benefits, and tuition remission.

NIDA TERMS

In conjunction with the Acknowledgment of Federal Funding Requirement (as specified in the NIH Grants Policy Statement, Appropriation Mandates- http://grants.nih.gov/policy/nihgps/index.htm), in order to most effectively disseminate research results, advance notice should be given to NIDA that research finds are about to be published so that we may coordinate accurate and timely release to the media. This information will be embargoed until the publication date. Any press notification should be coordinated with the NIDA Press Officer who can be reached at (301) 443-6245.

The National Institute on Drug Abuse (NIDA) encourages data harmonization to increase comparability, collaboration, and scientific yield of research on drug abuse. Towards that end, NIDA strongly encourages human-subject studies to incorporate a series of measures from the Substance Abuse and Addiction Core and Specialty collections, which are available in the PhenX Toolkit (www.phenxtoolkit.org>>>>;;;;). For more information about NIDA's data harmonization efforts, please see NOT-DA-12-008 at http://grants.nih.gov/grants/guide/notice-files/NOT-DA-12-008.html.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Debra Battle-dudley
Email: ddudley@nida.nih.gov **Phone**: 301 827 6698

Program Official: Rao Rapaka
Email: rr82u@nih.gov **Phone**: (30l) 435-1304

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01DA025267-09 REVISED

A. COVER PAGE

Project Title: Nicotine dependence: neuropharmacology in monkeys	
Grant Number: 5R01DA025267-09	**Project/Grant Period:** 07/01/2008 - 06/30/2019
Reporting Period: 07/01/2016 - 06/30/2017	**Requested Budget Period:** 07/01/2017 - 06/30/2018
Report Term Frequency: Annual	**Date Submitted:** 05/22/2017
Program Director/Principal Investigator Information: LANCE R MCMAHON , PHD **Phone number:** (210) 567-0143 **Email:** mcmahonl@uthscsa.edu	**Recipient Organization:** UNIVERSITY OF TEXAS HLTH SCIENCE CENTER 7703 FLOYD CURL DR SAN ANTONIO, TX 782293901 **DUNS:** 800772162 **EIN:** 1741586031A3 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: CHRIS G GREEN 7703 Floyd Curl Dr., MSC 7828 San Antonio, TX 782293900 **Phone number:** 210-567-2340 **Email:** grants@uthscsa.edu	**Signing Official:** CHRIS G GREEN 7703 Floyd Curl Dr., MSC 7828 San Antonio, TX 782293900 **Phone number:** 210-567-2340 **Email:** grants@uthscsa.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Nicotine dependence: neuropharmacology in monkeys

Smoking-related diseases (cancer, heart, and lung) are leading preventable causes of death. This proposal focuses on the subjective effects of smoking cessation aids and nicotinic acetylcholine receptor (nAChR) drugs in non-human primates. Nicotine replacement products (patch, gum, nasal spray) and varenicline (Chantix) are only marginally effective smoking cessation aids (i.e., no more than 2 out of 5 individuals remain continuously abstinent for 1 year). Varenicline has lower efficacy (i.e., intrinsic activity) than nicotine at a nAChR subtype implicated in nicotine abuse (i.e., α4β2). However, the extent to which a difference in nAChR efficacy contributes to clinical effectiveness has been difficult to assess given that most behavioral assays fail to detect a robust difference in the effects of nicotine and varenicline.

Non-human primate assays of subjective effects developed under this grant detected a marked difference between nicotine and varenicline. Two groups of rhesus monkeys discriminated nicotine base (1.78 mg/kg s.c.) from saline in the morning. One group received additional chronic nicotine (8.9 mg/kg s.c.) during the day, but not during the night; monkeys in this group were deprived of nicotine for 15 h at the time that nicotine was discriminated. Discriminating nicotine after 15 h of deprivation from chronic treatment has face validity for the effects of the first cigarette of the day. The reinforcing effectiveness of the first cigarette of the day is a strong predictor of nicotine dependence. Whereas varenicline was able to fully share discriminative stimulus effects with nicotine in monkeys not receiving chronic nicotine, varenicline was unable to substitute for nicotine in the group receiving chronic nicotine, i.e., did not produce the “first cigarette of the day” effect. Aim 1 examines the pharmacology responsible for nAChR agonists to produce the “first cigarette of the day” effect.

Allosteric nAChR modulators bind separately from and modify the binding affinity and/or efficacy of orthosteric nAChR agonists (e.g., nicotine, varenicline, and acetylcholine). Without an orthosteric agonist, allosteric modulators by themselves are ineffective and thus under some conditions might have a more favorable in vivo profile than orthosteric ligands. During the previous funding period, the positive allosteric nAChR modulator and acetylcholinesterase (AChE) inhibitor galantamine was demonstrated to share discriminative stimulus effects with nicotine in monkeys not receiving chronic treatment. Aim 2 uses nicotine discrimination assays in monkeys to examine both positive and negative allosteric nAChR modulators for their capacity to modify the effects of nicotine.

Aim 1. Examine nAChR mechanisms responsible for the “first cigarette of the day” effect in monkeys. During the previous funding period, varenicline shared discriminative stimulus effects with nicotine (1.78 mg/kg s.c.) in a group of monkeys not receiving chronic nicotine treatment, but did not share discriminative stimulus effects with nicotine in a separate group of monkeys after 15 h of deprivation from chronic nicotine (8.9 mg/kg/day). Aim 1 tests the hypothesis that relatively high efficacy is necessary for nAChR agonists to produce the “first cigarette of the day” effect. Whereas all nAChR agonists are expected to substitute for nicotine in the absence of chronic nicotine treatment, only α4β2 nAChR agonists with relatively high efficacy (epibatidine, RTI-36, and RTI-76) are expected to retain their effectiveness in mimicking the effects of nicotine in monkeys receiving chronic nicotine treatment, whereas the low efficacy α4β2 nAChR agonists RTI-102 and cytisine are expected not to produce the “first cigarette of the day” effect. This aim examines the extent to which α4β2 nAChR efficacy differentiates the effects of agonists under conditions with validity for smoking cessation treatment.

Aim 2. Examine the effects of allosteric nAChR modulators in monkeys discriminating nicotine. Preliminary data demonstrate that a positive allosteric nAChR modulator and AChE inhibitor (galantamine) substitutes for the discriminative stimulus effects of nicotine, suggesting that perhaps positive nAChR modulation is sufficient to mimic the effects of nicotine. This aim examines the effects of positive and negative modulators that vary in selectivity for α4β2 versus α7 nAChR. Aim 2 tests the hypothesis that positive allosteric nAChR modulators by themselves mimic the effects of nicotine, presumably via modulation of acetylcholine, and further hypothesizes that positive and negative nAChR modulators enhance or attenuate the effects of nicotine, respectively. Allosteric nAChR modulators that either substitute for or antagonize the effects of nicotine in these pre-clinical models would be of interest as potential novel smoking cessation aids.

Current smoking cessation aids do not work in a majority of individuals. The current proposal has the potential to identify orthosteric and/or allosteric nAChR ligands that either mimic or antagonize the effects of nicotine under conditions predictive of smoking cessation therapy. Given the widespread use of cigarettes, even small or modest improvements in smoking cessation therapy will save many lives and substantially decrease the public health burden of cigarette smoking.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Progress Report for Year 8.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

Yes

Revision/ Supplements #	Revision/ Supplements Title	Specific Aims	Accomplishments
3R01DA025267-07S1		Aim 1. Examine nAChR mechanisms responsible for the "first cigarette of the day" effect in monkeys. Aim 2. Examine the effects of allosteric nAChR modulators in monkeys discriminating nicotine.	Aim 1 Complete tests in separate groups of mice trained to discriminate nicotine, epibatidine, or varenicline, including antagonism tests with dihydro-betaerythroidine; write the manuscript describing the results of experiments conducted under Aim 1 Aim 2 Purchase subjects; train to discriminate nicotine or epibatidine; determine doseresponse curves for nicotine, epibatidine, and other nAChR agonists before and immediately after chronic nicotine treatment Complete studies of chronic nicotine treatment in mice discriminating either nicotine or epibatidine; write the manuscript describing the results of experiments conducted under Aim 2

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: McMahon IDP.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

During year 9, differences in nicotine and varenicline self-administration in monkeys will be identified. These studies are ongoing and are extended from the previous reporting period. The working hypothesis is that varenicline is self-administered to a lesser extent than nicotine; the α4β2 antagonist DHβE antagonizes self-administration of both. The approach, i.v. drug self- administration, is a new skill to be learned by the PI. The proposed studies are critically needed to gain insight into nAChR mechanisms mediating reinforcing effects and to provide a basis for identifying new drugs that decrease the reinforcing effects of nicotine.

Two adult rhesus monkeys press levers to obtain nicotine i.v. at levels significantly greater than pressing for i.v. saline. The nicotine dose range describing the inverted U shaped dose-response function is 0.001-0.01 mg/kg/infusion. Dose will be varied by adjusting the concentration and infusion duration. A dose of 0.0032 mg/kg/infusion will be available daily until the infusion number does not vary by more than ±20% from the 3-day running average, with no increasing or decreasing trends. Next, unit dose will be increased or decreased or nicotine will be replaced with saline. Sessions with i.v. saline will be conducted until responding is low, e.g., less than 5 infusions per session. If a unit dose maintains a significantly greater number of infusions than saline, then saline will be substituted until responding is low, followed by the next unit dose until responding at that dose is stable for 3 consecutive days, and so on until an entire non-monotonic dose- response function is generated. Next, a cocaine dose-response function will be generated, followed be a second determination of the nicotine dose-response function. Doses of varenicline to be studied will be equal to and greater than the nicotine doses, based on i.v. nicotine discrimination data generated during progress of the previous year. The nAChR mechanism(s) will be identified by administering mecamylamine and DHβE prior to nicotine and varenicline self-administration. Data will be analyzed as infusion number, responses per s, and total intake as a function of unit dose using repeated measures ANOVA and post-hoc Tukey-Kramer tests ($p<0.05$). To identify a change in dose-response function, individual dose-response data will be converted to area under the curve; area under the curve values will then be compared with paired t-test or repeated measures ANOVA. Parallel shifts in inverted U shaped dose-response functions will [Redacted by agreement] sessed by comparing ED50 values from linear regression of the ascending and descending portions of the dose-response function. nificant potency difference will be evidenced by 95% confidence limits of a potency ratio that do not include 1.

In two different nicotine discriminate assays (0.32 mg/kg s.c. nicotine and 0.0178 mg/kg i.v. nicotine) in rhesus monkeys, studies are being initiated with the highly selective α4β2 partial agonist ispronicline. We are collaborating with [Redacted by agreement] at the University of Maryland Baltimore School of Pharmacy [redacted] is synthesizing novel analogs of ispronicline to be studied in the nicotine discrimination assays.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

1) Major activities

Two pre-doctoral trainees and one research assistant have been engaged in collecting data from two different groups of rhesus monkeys described below. The research assistant was hired as part of this grant award and has been sufficiently trained to work independently in the non-human primate laboratory. Several abstracts and poster presentations have been generated from these studies and presented at 2016/2017 annual scientific meetings including Behavior, Biology, Chemistry: Translational Research in Addiction, Society for Neuroscience, and American Society of Pharmacology and Experimental Therapeutics at Experimental Biology.

2) Specific objectives

a) Aim 1: Examine nAChR mechanisms responsible for the "first cigarette of the day" effect in monkeys.
b) Aim 2: Examine the effects of allosteric nAChR modulators in monkeys discriminating nicotine.

3) Significant results

a) *Attenuated nicotine-like effects of varenicline but not other nicotinic ACh receptor agonists in monkeys receiving nicotine daily*. Chronic treatment can differentially impact the effects of pharmacologically related drugs that differ in receptor selectivity and efficacy. The impact of daily nicotine treatment on the effects of nicotinic ACh receptor (nAChR) agonists was examined in two groups of rhesus monkeys discriminating nicotine (1.78 mg·kg-1 base weight) from saline. One group received additional nicotine treatment post-session (1.78 mg·kg-1 administered five times daily, each dose 2 h apart; i.e. Daily group), and the second group did not (Intermittent group). Daily repeated nicotine treatment produced a time-related increase in saliva cotinine. There was no significant difference in the ED50 values of the nicotine discriminative stimulus between the Daily and Intermittent group. Mecamylamine antagonized the effects of nicotine, whereas dihydro-β-erythroidine did not. Midazolam produced 0% nicotine-lever responding. The nAChR agonists epibatidine, RTI-36, cytisine and varenicline produced >96% nicotine-lever responding in the Intermittent group. The respective maximum effects in the Daily group were 100, 72, 59 and 28%, which shows that the ability of varenicline to produce nicotine-like responding was selectively decreased in the Daily as compared with the Intermittent group. When combined with nicotine, both varenicline and cytisine increased the potency of nicotine to produce discriminative stimulus effects. Nicotine treatment has a greater impact on the sensitivity to the effects of varenicline as compared with some other nAChR agonists.

b) *The discriminative stimulus effects of i.v. nicotine in rhesus monkeys: Pharmacokinetics and apparent pA2 analysis with dihydro-β-erythroidine*. Quantitative analysis of antagonism is infrequently used to identify nAChRs mediating behavioral effects. Here, nicotine (0.032 mg/kg i.v.) was established as a discriminative stimulus in rhesus monkeys responding under a fixed ratio 5 schedule; pharmacokinetics and underlying nAChR mechanism(s) were examined. When measured up to 4 h in venous blood, the training dose resulted in the following mean pharmacokinetic parameters: nicotine Cmax = 71.7 ng/ml, t1/2 = 116 min, and clearance = 6.25 ml/min/kg; cotinine Cmax = 191 ng/ml; and 3OH-cotinine Cmax = 63 ng/ml. The ED50 value of nicotine to produce discriminative stimulus effects was 0.013 mg/kg. Epibatidine and varenicline increased drug-lever responding to 97% and 95%, respectively (ED50 values = 0.00015 and 0.031 mg/kg, respectively), whereas cocaine, midazolam, and morphine produced no more than 28% drug-appropriate responding. Mecamylamine and dihydro-β-erythroidine (DHβE) dose-dependently attenuated the discriminative stimulus effects of the nicotine training dose, whereas methyllycaconitine (MLA) did not. DHβE (0.1 and 0.32) produced rightward shifts of the nicotine and varenicline dose-response functions; Schild plots fitted through individual data resulted in slopes that were not different from unity; the apparent pA2 calculated for DHβE did not significantly differ in the presence of nicotine (6.58) or varenicline (6.45). Compared to human cigarette smoking, nicotine blood levels after 0.032 mg/kg nicotine i.v. took a similar time to reach maximal concentration, levels at Cmax were similar to smoking 2-3 cigarettes, while average nicotine levels were comparable to smoking 5-6 cigarettes.

c) *The contribution of α4β2 and non-α4β2 nicotinic acetylcholine receptors to the discriminative stimulus effects of nicotine and varenicline in mice*. The extent to which non-α4β2 versus α4β2* nAChRs contribute to the behavioral effects of varenicline and other nAChR agonists is unclear. The purpose of this study was to characterize the discriminative stimulus effects of varenicline and nicotine using various nAChR agonists and antagonists to elucidate possible non-α4β2 nAChR mechanisms. Separate groups of male C57BL/6J mice were trained to discriminate varenicline (3.2 mg/kg) or nicotine (1 mg/kg). Test drugs included mecamylamine; the nAChR agonists epibatidine, nicotine, cytisine, varenicline, and RTI-102; the β2-containing nAChR antagonist dihydro-β-erythroidine (DHβE); the α7 nAChR agonist PNU-282987; the α7 antagonist methyllycaconitine (MLA); the α3β4 antagonist 18-methoxycoronaridine (18-MC); and the non-nAChR drugs midazolam and cocaine. In nicotine-trained mice, maximum nicotine-appropriate responding was 95% nicotine, 94% epibatidine, 63% varenicline, 58% cytisine, and less than 50% for RTI-102, PNU-282987, midazolam, and cocaine. In varenicline-trained mice, maximum varenicline-appropriate responding was 90% varenicline, 86% epibatidine, 74% cytisine, 80% RTI-102, 50% cocaine, and 50% or less for nicotine, PNU-282987, and midazolam. Drugs were studied to doses that abolished operant responding. Mecamylamine antagonized the discriminative stimulus effects, but not the rate-decreasing effects, of nicotine and varenicline. DHβE antagonized the discriminative stimulus and rate-decreasing effects of nicotine but not varenicline in either the nicotine or varenicline discrimination assays. The discriminative stimulus, but not the rate-decreasing, effects of epibatidine were antagonized by DHβE regardless of the training drug.

4) Key outcomes

a) Varenicline differs from nicotine in its selectivity for multiple nAChR subtypes.

b) However, in monkeys discriminating a dose of nicotine equivalent to that delivered from smoking 5-6 cigarettes, apparent pA2 analysis with DHβE is consistent with nicotine and varenicline acting through the same nAChRs to produce discriminative stimulus effects.

c) α4β2* nAChRs differentially mediate the discriminative stimulus effects of nicotine and varenicline; varenicline has substantial non-α4β2 nAChR activity.

IDP for pre-doctoral students

My laboratory has twice weekly 1-hour lab meetings in which each graduate student formally presents his/her research progress. The goal of these presentations is to help students to enhance their presentation skills and critical thinking abilities. In addition, I meet individually with students at least three days out of the week and often daily. Students also attend monthly chalk-talk sessions that cover a range of topics (statistics, research design, professional development, career opportunities, ethics) as well a bi-weekly journal club that keeps them apprised of state of the science in drug abuse research.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Moerke MJ, de Moura FB, Koek W, McMahon LR. Effects of nicotine in combination with drugs described as positive allosteric nicotinic acetylcholine receptor modulators in vitro: discriminative stimulus and hypothermic effects in mice. European journal of pharmacology. 2016 September 5;786:169-78. PubMed PMID: 27238974; PubMed Central PMCID: PMC4980200.
Complete	de Moura FB, McMahon LR. The contribution of α4β2 and non-α4β2 nicotinic acetylcholine receptors to the discriminative stimulus effects of nicotine and varenicline in mice. Psychopharmacology. 2017 March;234(5):781-792. PubMed PMID: 28028600; PubMed Central PMCID: PMC5309148.
Complete	Moerke MJ, Zhu AZ, Tyndale RF, Javors MA, McMahon LR. The discriminative stimulus effects of i.v. nicotine in rhesus monkeys: Pharmacokinetics and apparent pA₂ analysis with dihydro-β-erythroidine. Neuropharmacology. 2017 April;116:9-17. PubMed PMID: 27940077; PubMed Central PMCID: PMC5385163.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period?

No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
eRA Commons User Name	Y	McMahon, Lance R	PHD	PD/PI	EFFORT					NA
	N	Redacted by agreement	BA,PHD	Graduate Student (research assistant)						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

No

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANTONIO	800772162	TX-021	7703 Floyd Curl Drive San Antonio TX 78229

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No