Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov))

Components of Participating Organizations

National Institute on Drug Abuse (NIDA (http://www.nida.nih.gov))

Funding Opportunity Title

Extracellular Vesicles and Substance Use Disorders (R21)

Activity Code

R21 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r21&Search.x=0&Search.y=0&Search_Type=Activity) Exploratory/Developmental Research Grant

Announcement Type

Reissue of PAR-15-284 (https://grants.nih.gov/grants/guide/pa-files/PAR-15-284.html)

Related Notices

- September 20, 2017 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-114.html) - Updates to Active Funding Opportunity Announcements to Prepare for Policy Changes Impacting Due Dates On or After January 25, 2018. See NOT-OD-17-114 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-114.html).
- August 01, 2017 (//grants.nih.gov/grants/guide/notice-files/NOT-DA-17-050.html) - Notice of Change to Key Dates, PAR-17-242.See Notice NOT-DA-17-050 (//grants.nih.gov/grants/guide/notice-files/NOT-DA-17-050.html).
- May 10, 2017 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-062.html) - New NIH "FORMS-E" Grant Application Forms and Instructions Coming for Due Dates On or After January 25, 2018. See NOT-OD-17-062 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-062.html).

Funding Opportunity Announcement (FOA) Number

PAR-17-242

Companion Funding Opportunity

PAR-17-250 (https://grants.nih.gov/grants/guide/pa-files/PAR-17-250.html), R01 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r01&Search.x=0&Search.y=0&Search_Type=Activity) Research Project Grant

Number of Applications

See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.279

Funding Opportunity Purpose

The purpose of this FOA is to encourage research projects that investigate the interplay between extracellular vesicles (EVs) and substance use disorders (SUDs). In particular, NIDA is interested in the potential utility of EVs with respect to understanding neuroplastic mechanisms relevant to SUDs or as biomarkers or therapeutics.

Key Dates

Posted Date

April 4, 2017

Open Date (Earliest Submission Date)

July 15, 2017

Letter of Intent Due Date(s)

30 days prior to the application due date

Application Due Date(s)

New Dates November 3, 2017, March 3, 2018, November 3, 2018, March 3, 2019, November 3, 2019, March 3, 2020 , by 5:00 PM local time of applicant organization. All types of applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

AIDS Application Due Date(s)

New Dates November 3, 2017, March 3, 2018, November 3, 2018, March 3, 2019, November 3, 2019, March 3, 2020, by 5:00 PM local time of applicant organization. All types of applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

Scientific Merit Review

February/March 2018, June/July 2018, February/March 2019, June/July 2019, February/March 2020, June/July 2020

Advisory Council Review

New Dates May 2018; October 2018; May 2019; October 2019; May 2020; October 2020

Earliest Start Date

July 2018; December 2018, July 2019; December 2019; July 2020; December 2020

Expiration Date

New Date March 4, 2020 per issuance of NOT-DA-17-050 (//grants.nih.gov/grants/guide/notice-files/NOT-DA-17-050.html). (Original Expiration Date: January 16, 2020)

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/)). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

   Apply Online Using ASSIST

2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and eRA Commons to track your application. Check with your institutional officials regarding availability.

3. Go to Grants.gov to download an application package to complete the application forms offline or create a Workspace to complete the forms online; submit your application to Grants.gov; and track your application in eRA Commons.

Learn more about the various submission options (http://grants.nih.gov/grants/ElectronicReceipt/preparing.htm#2).

Table of Contents

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Background

Secreted extracellular vesicles (EVs) play roles in many biological processes. In some cases these vesicles appear to travel through the body and fuse with specific cell types to deliver nucleic acid, protein or other cargoes that may alter cellular phenotypes. In the nervous system, EVs may function in neuronal-glial communication, synaptic plasticity, immune surveillance, or as endocannabinoid carriers. However the role of EVs in CNS disorders and SUDs is not well characterized.

In addition, EVs from body fluids such as blood, cerebrospinal fluid, urine, saliva, semen, breast milk, and amniotic fluid could provide useful biomarkers for a variety of human diseases including CNS disorders. Understanding EV dynamics and cargoes across the trajectory of addiction may help to identify useful biomarkers for diagnosing: 1) drug use history (the type, quantity, and/or frequency of drug use), 2) the stage/trajectory of addiction (e.g. escalation, withdrawal, incubation, craving, relapse), or 3) both. Also EVs may be useful for in vivo targeting of cargoes such as nucleic acids or small molecules of therapeutic value to specific organs or cell types.

Research Objectives

The purpose of this FOA is to encourage research projects that investigate the interplay between EVs and SUDs. In particular, NIDA is interested in the potential utility of EVs with respect to understanding neuroplastic mechanisms relevant to SUDs or as biomarkers or therapeutics.

Proposed projects are expected to meet the following two criteria: 1) the major thrust of the application should involve extracellular vesicles or EV biogenesis machinery; and 2) at least one aim or sub-aim should involve exposure to addictive substances, or analysis of samples from patients with substance use or SUDs. Addictive substances of interest include: nicotine, cocaine, stimulants, opioids, prescription drugs, cannabinoids, or use of multiple substances (including alcohol). Applications focused solely on alcohol exposure should not apply through this FOA.

Project teams should include researchers with expertise in both EVs and in SUDs.

The choice of biological system for the proposed investigations should be well justified. Applicants may propose studies that investigate body fluids or tissues from human patients, primates, or rodents. Primary cells, cell lines, organoids, or other systems may also be proposed for investigation, if appropriately justified. Patient samples should be well characterized for stage/trajectory of SUD, type(s) of drug used, co-occurring conditions, gender, and age.

Applicants focused on behavioral assessments in mammals should ensure that they include one or more behavioral assays of drug reward and/or reinforcement (e.g. conditioned place preference, self-administration, compulsive drug seeking, or drug seeking in the face of negative consequences). In addition to testing drug-seeking behaviors, applicants are encouraged to analyze other relevant behavioral phenotypes.

High risk/high payoff projects that lack preliminary data are most appropriate for this R21 FOA. Applicants with preliminary data may wish to apply to the companion R01 FOA.

Some relevant topics of investigation could include, but are not limited to, the following:

Extracellular Vesicles, Biological Processes And Chronic Drug Exposure

- How are CNS-derived EVs generated and transported? What are the molecular mechanisms by which they traffic and enter cells? What are the molecular mechanisms by which they influence target cell phenotypes? How does exposure to addictive substances influence these processes?
- What are the cargoes of CNS-derived EVs (e.g. miRNA, circRNA, lncRNA, lipids, proteins, or metabolites)? What are the pathways and/or covalent modifications involved in establishing these cargoes? How does exposure to addictive substance influence CNS-derived EV cargoes?
- Can tools or technologies be developed to enable classification or characterization of single EVs or small numbers of EVs? Can in vivo sensors be developed to follow CNS EV biogenesis, transport, uptake, or impact on target cells? How can we better understand SUDs using these tools?
- What are the physiological roles of EVs in the nervous system with respect to neuronal-glial interactions? How are these different in drug-reinforced animals?
- How do EVs impact the neuroimmune system or mediate neuroinflammatory or neuroprotective responses? Are they affected by exposure to addictive substances?
- What roles do EVs play in regulation of brain energetics, metabolism, or waste/toxin clearance? Does exposure to addictive substances influence these roles?
- What is the role of EVs in normal endocannabinoid signaling in the nervous system? Do addictive substances impact this signaling? Are endocannabinoids or other EV components involved in transducing molecular phenotypes in target cells?
- What is the role of extracellular vesicles or EV biogenesis in different phases of addiction or in other relevant neuroplastic processes?
- How do EVs influence brain development and/or developmental signaling pathways (e.g. Notch, Wnt, or Hedgehog)? Do addictive substances alter these processes?
- Do EVs play a role in transport of retrotransposons and is this influenced by addictive substances?
- Do EVs in the nervous system interact with peripheral tissues or vice versa? Do addictive substances impact these interactions?
- Do EVs play a role in the transmission of transgenerational phenotypes relevant to SUDs?
- What are the roles of EVs or EV biogenesis in HIV infection, transmission, latency, persistence, or disease progression? How might these roles be influenced by exposure to addictive substances?

Biosignature-Relevant

- Can EVs from body fluids serve as biosignatures for monitoring chronic exposure to addictive substances or for identifying the status of an individual along the trajectory of addiction?
- Can EVs derived from brain tissues be obtained from relatively accessible body fluids (e.g. serum or saliva) in order to facilitate the study of drug exposure or addiction trajectory?
- Does exposure to different quantities or types of addictive substances impact EV varieties, dynamics, cargoes, or functions? What is the influence of age or sex or stress?
- Are specific EV cargoes (e.g. miRNA, circRNA, lncRNA, lipids, proteins, metabolites) of particular utility as biosignatures for substance use disorders?
- Can EVs or subpopulations of EVs serve as potential pharmacodynamic biosignatures to evaluate safety and/or efficacy of a therapeutic response?

Therapeutic-Relevant

- Do endogenous or exogenously-modified EVs have therapeutic potential for the prevention of drug initiation or treatment of SUDs?

Special Considerations

National Advisory Council on Drug Abuse Recommended Guidelines for the Administration of Drugs to Human Subjects: The National Advisory Council on Drug Abuse (NACDA) recognizes the importance of research involving

the administration of drugs with abuse potential, and dependence or addiction liability, to human subjects. Potential applicants are encouraged to obtain and review these recommendations of Council before submitting an application that will administer compounds to human subjects. The guidelines are available on NIDA's Web site at http://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-administration-drugs-to-human-subjects.

Points to Consider Regarding Tobacco Industry Funding of NIDA Applicants: The National Advisory Council on Drug Abuse (NACDA) encourages NIDA and its grantees to consider the points it has set forth with regard to existing or prospective sponsored research agreements with tobacco companies or their related entities and the impact of acceptance of tobacco industry funding on NIDA's credibility and reputation within the scientific community. Please see http://www.drugabuse.gov/about-nida/advisory-boards-groups/national-advisory-council-drug-abuse-nacda/council-statements/points-to-consider-regarding- for details.

Data Harmonization for Substance Abuse and Addiction via the PhenX Toolkit: NIDA strongly encourages investigators involved in human-subjects studies to employ a common set of tools and resources that will promote the collection of comparable data across studies and to do so by incorporating the measures from the Core and Specialty collections, which are available in the Substance Abuse and Addiction Collection of the PhenX Toolkit (www.phenxtoolkit.org). Please see NOT-DA-12-008 (http://grants.nih.gov/grants/guide/notice-files/NOT-DA-12-008.html) for further details.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument

Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.

Application Types Allowed

New
Resubmission

The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Clinical Trials Not Allowed for due dates on or after January 25, 2018: Only accepting applications that do not propose clinical trials

Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

Funds Available and Anticipated Number of Awards

The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.

Award Budget

The combined budget for direct costs for the two year project period may not exceed $275,000. No more than $200,000 in direct costs may be requested in any single year.

Award Project Period

Applicants may request a project period of up to two years.

NIH grants policies as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

  - Hispanic-serving Institutions
  - Historically Black Colleges and Universities (HBCUs)
  - Tribally Controlled Colleges and Universities (TCCUs)
  - Alaska Native and Native Hawaiian Serving Institutions
  - Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.
Foreign components, as defined in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications (//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) (http://fedgov.dnb.com/webform) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (https://www.sam.gov/portal/public/SAM/) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
    - NATO Commercial and Government Entity (NCAGE) Code (//grants.nih.gov/grants/guide/url_redirect.htm?id=11176) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123) - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=82300) – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see NOT-OD-11-101 (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)).

Section IV. Application and Submission Information

1. Requesting an Application Package

Buttons to access the online ASSIST system or to download application forms are available in Part 1 of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), including Supplemental Grant Application Instructions (https://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf) except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications (//grants.nih.gov/grants/guide/url_redirect.htm?id=41137).

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

By the date listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent to: NIDALetterofIntent@mail.nih.gov (mailto:NIDALetterofIntent@mail.nih.gov).

Applicants are encouraged to send the letter of intent by email to the email address above but as an alternative the letter may also be sent to:

Office of Extramural Policy and Review
National Institute on Drug Abuse/NIH/DHHS
6001 Executive Boulevard, Suite 4243, MSC 9550
Bethesda, MD 20892-9550

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits (//grants.nih.gov/grants/guide/url_redirect.htm?id=11133) must be followed.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R or Modular Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Applicants should ensure their applications contain sufficient information for reviewers to assess the following questions:

Will the proposed project dramatically improve our understanding of the role of extracellular vesicles in substance abuse disorders?

If use of extracellular vesicles as a biomarker for chronic drug exposure or other SUD relevant phenotypes is proposed, does the proposed biomarker have the potential to dramatically change the way we diagnose or treat substance abuse?

If use of extracellular vesicles as a therapeutic to treat SUDs is proposed, does the proposed therapeutic have the potential to dramatically change the way we diagnose or treat substance abuse?

Does the investigative team have expertise in extracellular vesicles?

Does the investigative team have expertise in substance use disorders?

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan.

Appendix:

Do not use the Appendix to circumvent page limits. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Inclusion Enrollment Report

When conducting clinical research, follow all instructions for completing PHS Inclusion Enrollment Report as described in the SF424 (R&R) Application Guide.

PHS Human Subjects and Clinical Trials Information

Form only available in FORMS-E application packages for use with due dates on or after January 25, 2018.

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered "Yes" to the question "Are Human Subjects Involved?" on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or a **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information
All instructions in the SF424 (R&R) Application Guide must be followed.

Delayed Onset Study: All instructions in the SF424 (R&R) Application Guide must be followed.

PHS Assignment Request Form

All instructions in the SF424 (R&R) Application Guide must be followed.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11137), and procedures for foreign institutions described throughout the SF424 (R&R) Application Guide.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday (http://www.opm.gov/Operating_Status_Schedules/fedhol/2010.asp), the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11128) (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123), NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must

be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)

6. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11143).

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically (//grants.nih.gov/grants/guide/url_redirect.htm?id=11144). If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Guidelines for Applicants Experiencing System Issues (//grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines). For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See Section III of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See more tips (//grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review, NIH. Applications that are incomplete or non-compliant will not be reviewed.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy (//grants.nih.gov/grants/guide/url_redirect.htm?id=82299).

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149), all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

The R21 exploratory/developmental grant supports investigation of novel scientific ideas or new model systems, tools, or technologies that have the potential for significant impact on biomedical or biobehavioral research. An R21 grant application need not have extensive background material or preliminary information. Accordingly, reviewers will focus their evaluation on the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications; however, they may be included if available.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? Will the proposed project dramatically improve our understanding of the role of extracellular vesicles in substance abuse disorders? If use of extracellular vesicles as a biomarker for chronic drug exposure or other SUD relevant phenotypes is proposed, does the proposed biomarker have the potential to dramatically change the way we diagnose or treat substance abuse? If use of extracellular vesicles as a therapeutic to treat SUDs is proposed, does the proposed therapeutic have the potential to dramatically change the way we diagnose or treat substance abuse?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project? Does the investigative team have expertise in extracellular vesicles? Does the investigative team have expertise in substance use disorders?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad

sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects? How well does the application utilize advances in our understanding of extracellular vesicles or EV biogenesis machinery to investigate a question exploring neuroplastic processes relevant to substance abuse?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models

and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

Not Applicable

Revisions

Not Applicable

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: (1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); (2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and (3) Genomic Data Sharing Plan (GDS) (//grants.nih.gov/grants/guide/url_redirect.htm?id=11153).

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by CSR, in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_redirect.htm?id=11154), using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

Applications will be assigned to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications . Following initial peer review, recommended applications will receive a second level of review by the National Advisory Council on Drug Abuse. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11156).

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to terms and conditions found on the Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities

(//grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html (http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html); and http://www.hhs.gov/ocr/civilrights/understanding/index.html (http://www.hhs.gov/ocr/civilrights/understanding/index.html). Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html (http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html). Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html (http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html) or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53 (http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53).

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

Cooperative Agreement Terms and Conditions of Award

Not Applicable

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161).

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11171) for additional information on this reporting requirement.

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 from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported 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 FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)
Finding Help Online: http://grants.nih.gov/support/ (//grants.nih.gov/support/) (preferred method of contact)

Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (//grants.nih.gov/grants/guide/url_redirect.htm?id=82301) (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact Center Telephone: 800-518-4726

Email: support@grants.gov (mailto:support@grants.gov)

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Email: GrantsInfo@nih.gov (mailto:GrantsInfo@nih.gov) (preferred method of contact)

Telephone: 301-945-7573

Scientific/Research Contact(s)

John Satterlee Ph.D.
National Institute on Drug Abuse (NIDA)
Telephone: 301-435-1020
Email: satterleej@nida.nih.gov (mailto: satterleej@nida.nih.gov)

Peer Review Contact(s)

Carole Jelsema, Ph.D.
Center for Scientific Review (CSR)
Telephone: 301-435-1248
Email: JELSEMAC@csr.nih.gov (mailto: JELSEMAC@csr.nih.gov)

Financial/Grants Management Contact(s)

Aida Vasquez
National Institute on Drug Abuse (NIDA)
Telephone: 301- 480-2154
Email: vasquez@mail.nih.gov (mailto:vasquez@mail.nih.gov)

Section VIII. Other Information

Recently issued trans-NIH policy notices (//grants.nih.gov/grants/guide/url_redirect.htm?id=11163) may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11164). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?04-07-17)
NIH Funding Opportunities and Notices (/grants/guide/index.html)
