Autism Speaks Clinical Research on GI and Neurobehavioral Processes
Request for Applications

Submission, Review, & Notification Schedule (subject to change):

RFA release date: March 11, 2014
Letter of Intent due: April 16, 2014, 8:00 PM Eastern
LOI notifications sent: Early May, 2014
Application due: June 18, 2014, 8:00 PM Eastern

Peer review panels: Summer, 2014
Notifications: Mid-September, 2014
Earliest Grant start date: November, 2014

Introduction

ASD is often associated with medical co-morbidities that can affect multiple organ systems. When these co-morbidities are untreated, they not only compromise physical health, but also can affect behavior, development, and educational outcomes. Treating these medical conditions is critical, but even identifying them is complicated by the communication impairments that characterize ASD. Furthermore, the underlying biology of ASD may affect the manifestations of these conditions, and their response to treatment.

The gastrointestinal (GI) system is a frequent site of co-morbidity, with constipation, diarrhea, digestive abnormalities and other pathologies reported with a higher prevalence than in the general population. It is generally understood that untreated GI pathology may be associated with pain, discomfort, and other distress that can give rise secondarily to behavioral difficulties, ranging from inattentive or irritable behaviors to self-injury. GI morbidity is often undiagnosed in patients with ASD because of their communicative impairments, with the result that patients sometimes receive treatments that are directed at the secondary behavioral manifestations rather than at the underlying GI pathology. Despite the awareness of the prevalence of GI problems and their neurobehavioral complications, there has been no systematic study of the neurobehavioral effects associated with the alleviation of GI pathology. Furthermore, no algorithm or practice pathway has been established for the evaluation of possible GI or other medical morbidity when an individual with ASD presents with behavioral problems of new onset.

In addition to the secondary effects of GI pain and discomfort on the neurobehavioral presentation of ASD, it is hypothesized that gut-based processes also may have a more direct pathophysiologic role in ASD. Several potential mechanistic pathways have been implicated. One hypothesis holds broadly that gut-based inflammatory processes may result in neuroinflammation and consequent alterations in brain function. An alternative hypothesis is that changes to the gut microbiota and the associated metabolome may alter neurobehavioral function. Dietary and nutritional mechanisms may also be implicated in the relationship between GI and CNS function. These various mechanisms linking the GI and nervous systems may not be independent of each other, and the direction of causality (gut to brain, or vice versa) is largely untested, even in animal models.
Autism Speaks recognizes the urgent need for a better understanding of the relationship between GI and CNS processes in ASD, of the best clinical approaches for evaluating GI and other medical co-morbidity in individuals with ASD who present with new-onset behavioral issues, and of the potential for GI-targeted treatments to improve the neurobehavioral manifestations of ASD. Studies to address these questions will ideally be performed in a timely manner, be robust statistically, and generate results that are generalizable to the broad ASD community.

**Key Objectives**

This RFA seeks proposals for clinical research that will elucidate the relationship of gut-based processes to the neurobehavioral manifestations of ASD, the potential for treatments directed at GI pathology to affect neurobehavior positively, and best clinical approaches to the evaluation of gut and other medical co-morbidity in patients presenting with new neurobehavioral concerns. Proposals should advance the clinical management of GI and associated neurobehavioral problems in ASD, either by performing clinical assessment research, clinical intervention research, or by studying pathophysiologic mechanisms that are amenable to clinical translation in the very near term. Applications may include proposals to perform pilot studies on the safety and efficacy of therapeutic interventions, or larger-scale confirmatory trials if sufficient scientific justification for such trials already exists.

Possible research aims include, but are not limited to, the following:

- Identifying indicators of GI and other medical co-morbidity in non-verbal individuals with ASD;
- Defining a practice pathway for the medical evaluation of individuals with ASD, and providing evidence in support of that pathway;
- Examining the impact of ASD and associated medical co-morbidity on nutritional status;
- Elucidating the pathophysiologic mechanisms that link GI and CNS processes in individuals with ASD;
- Demonstrating the potential to correct or ameliorate abnormalities in nutritional status, gut microflora, or gut inflammation in patients with ASD;
- Examining the potential neurobehavioral consequences of effectively addressing GI co-morbidity in patients with ASD.

Proposals most likely to be funded under this RFA will exhibit the following qualities:

- Be based on compelling scientific rationale, derived either from preclinical or preliminary clinical research;
- Address the heterogeneity of ASD etiology and presentation, either by restricting enrollment to specific, well-justified subgroups within the ASD spectrum, or by a scientific plan that seeks to identify markers of stratification within the ASD spectrum;
- For interventional research, include examination of the mechanisms or mediators through which neurobehavioral effects are achieved;
- Include a power analysis demonstrating a likelihood of producing statistically- and clinically-meaningful results;
- Have a proven capacity to enroll an adequately-sized cohort of subjects in a timely manner. Smaller, pilot studies should be completed within a shorter period of time than larger-scale trials. This quality is most likely to be found in multi-site networks or consortiums of investigators.
Awards

Autism Speaks will make a limited number of awards based on the quality of the submissions and available financial resources. Awards are limited to a period of 3 years and an amount up to $500,000 per year, inclusive of 10% indirect costs.

Eligibility

Investigators holding full-time tenured or tenure-track faculty appointments or equivalent full-time non-tenure track appointments at accredited academic, medical or research institutions are eligible to apply.

- Applications will NOT be accepted from individuals or from proprietary organizations to support the research and development of products for profit.
- As Principal Investigator or Co-Investigator, all applicants are restricted to one submission per review cycle. Multiple submissions will be returned.

Preparing the Letter of Intent

NOTE: Applications or Letters of Intent that do not meet submission criteria will be returned without further review.

1. Access to the Autism Speaks Science Grants System. The applicant should go to http://science.grants.autismspeaks.org and register with your institutional email address (or log in if you have an ID). Complete your profile information.

2. Complete a Letter of Intent. Log in and click Applications at the top of the profile page or ‘Go to Applications’ at the bottom. Choose ‘Start a new LOI or application’, then ‘GI and Neurobehavior’ from the Award Type drop down and finally “Start new letter of intent…” The Letter of Intent (LOI) includes two web pages.

   a. Basic Information Page includes:
      i. Title: Enter less than 100 characters, spaces included
      ii. Scientific Abstract. 1500 characters, spaces included. Provide a summary of the research project to be conducted.
      iii. Brain Tissue Sources, as applicable
      iv. Enter Key Personnel: Name expected Co-Investigators and collaborators (hint: start by entering the last name). Many researchers are in our database. If you need to add someone new, you must use their institutional email address. It is important to enter all participants you expect, even if they change later.
      v. Name the Responsible Official (RO). First check the drop down list for officials from your institution already in the system. If need be, add a new person using their institutional email address. The RO will be copied on the confirmation email but has no responsibilities until it is time to submit the application. The RO can view the LOI or application at any time.
      vi. Choose the keywords which describe this project.
      vii. All this information will be available for editing/adding at the application stage.

   b. Letter of Intent Form includes:
      i. Letter of Intent Narrative: Two page maximum. Should include:
         1. A concise description of the proposed project including: specific aims, methods and expected results
2. A clear justification for the relevance and potential significance of the project to the priority research area for this RFA described in the introduction
3. Any references must be included in the 2 pages.
4. The LOI should be specific enough to be screened for scientific merit and fidelity to the purpose of this RFA.
   ii. PI biosketch: NIH format not to exceed 4 pages. More recent publications and those with greater relevance to the grant submission should be listed. Information on history of research funding including related current, pending and past awards should be included.
   iii. Biosketches for Co-investigators and research collaborators, NIH format not to exceed 4 pages per person. While not required, biosketches for consultants are recommended. Combine biosketches into one file for upload.
   iv. Eligibility letter: (optional) - Clear documentation for postdoctoral fellows, medical residents, clinical fellows, or part-time faculty members, etc. stating that appointment to a full-time faculty position will be in effect by the start date of the grant

Preparing the Application

1. Application requirements/Procedures: Applications are limited to the items listed below. No other supporting documents than those listed below will be accepted. All applications must be submitted online through the Autism Speaks Science Grants system.
   a. Review/edit entries on the Basic Information Page. Remaining items here are on the Application Form page.
   b. Research Narrative: (10 pages maximum) The research plan should address the evaluation criteria below:
      i. Impact in terms of potential to improve the lives of persons struggling with Autism Spectrum Disorders
      ii. Relevance to the RFA
      iii. Innovation – describe how the project is novel and has the potential to move the field forward
      iv. Research Strategy, including specific aims, participant exclusion/inclusion criteria, recruitment strategy, methods and procedures, and statistical analyses, including power analyses, to address specific aims
   c. Figures: you may include a maximum of two pages of relevant images, figures and graphics. Images uploaded here will not be counted towards the 10-page limit.
   d. References: include complete literature citations including titles and all authors
   e. Budget Form: download and complete the template. The budget may include:
      i. Personnel Costs (not to exceed the percent effort committed to the proposed project)
      ii. Principal Investigator and/or Co-Investigator salaries and benefits
      iii. Technical research assistant salary and benefits
      iv. Research Assistant or fellow stipends and benefits are allowed (NOTE: Tuition reimbursement is not allowed).
      v. Research supplies, services and related expenses
      vi. Essential equipment.. A vendor estimate is required for a single item of equipment costing more than $5000.
      vii. Consultants
viii. Travel to professional meetings
ix. Publication and data analysis costs
x. Indirect costs: An amount not to exceed 10% of direct costs may be included for the Sponsoring Institution’s indirect (overhead) costs. The total grant cannot exceed $500,000 per year
xi. Collaborations: If you are collaborating with a second site, put their total amount in a “Subcontract” row and include a separate budget sheet for the subcontract site(s) as well as an appropriate explanation in the budget justification section. Total indirect costs for both sites cannot exceed the maximum allowed.

f. **Budget Justification** (4 pages max) Provide an explanation for all lines in the budget for all years. Include explanations for subcontract budgets as appropriate.

g. **Human Participants and/or Vertebrate Animals**: Applications that use human participants or vertebrate animals must address issues of protections. If no ethics approval is needed for the proposed research, please upload a memo to that effect. Note that ethical approvals from the applicant organization are required before an award will be made. These approvals do not serve in lieu of the information requested below.

i. **HUMAN PARTICIPANTS** (defined as living individuals)
   - Scientifically justify the involvement of human participants in the proposed research.
   - Describe in detail the plan for the involvement of human participants in the proposed research.
   - Describe in details the potential risks to participants and measures to be taken to protect participants from those research risks.
   - For clinical trials, describe plans for data and safety monitoring, including the description of a data and safety monitoring board if necessary.

ii. **VERTEBRATE ANIMALS**
   - Describe in detail the proposed use of the animals, including species, strains, ages, sex and number to be used
   - Justify the use of animals, choice of species and numbers to be used
   - Provide information on the veterinary care of the animals
   - Describe procedures for ensuring discomfort, distress, pain and injury is minimized. Please include the method of euthanasia and the reasons for its selection.

h. **Consent form and consent procedures**: Please attach any consent forms that are to be used in the study, along with a summary of the procedures surrounding how consent will be obtained. Make a note if the forms have not yet been approved.

i. **Resources and research environment**: (1 page max) describe the resources and environment that will support the successful completion of the project. If the project will be utilizing existing samples and/or collecting samples, it should be specified how and when they will be used and shared with the autism community following the end of the project.

j. **Letters of Collaboration**: Appropriate letters of collaboration and support will be required to demonstrate sustainability and partnership. These letters should also outline what the collaborators are willing to contribute in terms of time, effort, and resources and infrastructure. Those who need a percent effort should be included in the budget. Combine multiple letters into one file for upload.
k. **Biographical Sketches:** for the Principal Investigator, named Co-Investigators and collaborators in NIH format (4 pages max each). Indicate education, complete citations (including title) of publications relevant to the proposed research, and briefly describe currently and pending grant support. While not required, biosketches for consultants are recommended. Biosketches must be combined into one file for upload.

l. **Supporting files:** other documents that are relevant to the application must be referenced in the research plan and may be uploaded to “Additional Materials.” Multiple documents should be combined into one file for upload.

m. **Peer reviewed research publications:** a maximum of 2 (including manuscripts accepted for publication) will be accepted; however, manuscripts not yet accepted for review, review articles, book chapters, popular press articles and meeting abstracts will NOT be accepted. Publication files MUST NOT be locked or protected in any way.

2. **Submission/Institutional approval** – When the applicant is ready, they should click the ‘Ready for RO’ link at the bottom of the application form page. The system will send an email to the Responsible Official (RO) who will then be able to submit the application. The RO can view the application at any time. The RO can also revert the application to draft if there is anything they want the applicant to change. The applicant would then make the change(s) and click ‘Ready for RO’ again.

**Other Information**

**Human Subjects and Vertebrate Animal Certifications** must be documented with a copy of an official letter of approval (or equivalent for non-US applicants), which identifies the Principal Investigator, project title as submitted to Autism Speaks and date of approval, and is signed by the Review Committee Chair or equivalent responsible institutional/government official. Prior certification for another project cannot be substituted but can be officially amended to include the proposed project (identified by project title). IMPORTANT NOTE: IRB, IACUC or equivalent ethical certification are NOT required at the time of applying; however, such ethical certification must be submitted as soon as possible following official notification of an award. Autism Speaks will NOT issue a grant contract or any form of funding until appropriate certifications are received.

**Projects using postmortem tissue** must provide documentation that the necessary tissue is or will be available at the research site at the time of the award. Applications without proper documentation will be returned without review.

**Contacts**

**Grants Administration/Online Application/Budget Questions:**
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**Application Development:**
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