Linking Early Neurodevelopment to Neural Circuit Outcomes RFA

The Linking Early Neurodevelopment to Neural Circuit Outcomes RFA aims to bridge the gap in our understanding of whether and how developmental phenotypes caused by autism risk gene mutation lead to altered circuit formation and function. We strongly encourage proposals involving close collaboration between investigators of diverse expertise, such as developmental neurobiologists and circuit neuroscientists, in order to convincingly demonstrate causal links between disparate phenotypes in the chosen model(s).

Applicants may request up to $300,000 per lab with a maximum total annual budget of $900,000, inclusive of 20 percent indirect costs, over a period of three (3) to four (4) years To allow potential applicants sufficient time to identify appropriate collaborators and conceptualize their projects, we are publishing this RFA call now; we will begin accepting applications on June 11, 2024.

Policies and Procedures
Application available
June 11, 2024

Important Dates

Application available
June 11, 2024

Informational session
June 25, 2024

Application deadline
September 12, 2024

Finalist presentations
January 14, 15 or 16, 2025

Award notification
March 2025

Award start date

Awards may begin as early as June 1, 2025, but we encourage PIs to select a project start date that best accommodates the needs of their project. Funds are expected to be expended as requested during each annual budget period. Projects must begin on the first of the month.

RFA

SFARI Mission

The mission of the Simons Foundation Autism Research Initiative (SFARI) is to improve th understanding, diagnosis and treatment of autism spectrum disorders by funding innovative research of the highest quality and relevance.

Background and Objective

The last decade has seen the discovery and functional annotation of numerous high-confidence autism spectrum disorder (ASD) risk genes[1-3]. In the time since, much effort has been dedicated to understanding how these genes impact nervous system development. A consensus has emerged that many genes implicated in ASD susceptibilit impact early steps in neurodevelopment, such as the timing and execution of neural differentiation, migration and synaptogenesis, with such cellular phenotypes thought to b rooted in altered epigenomic and transcriptomic landscapes[4-9].

In parallel, SFARI has invested in efforts to characterize the impact of ASD risk gene mutation on the neural circuits underlying ASD-relevant phenotypes, with notable advances made in understanding the contribution of peripheral and central circuits to ASD-related sensory atypicalities, motor phenotypes, sleep disruptions and social behavioral deficits, among other phenotypes[10-13].

While progress has been made toward understanding early development and mature functional outcomes in isolation, studies causally linking disruptions of early neurodevelopment to alterations in ASD-relevant neural circuits remain rare. The objectiv

of this RFA is to bridge this critical gap in our understanding of how developmental event impact later processes of circuit formation and function in ASD.

We envision that this RFA will bring together scientists of diverse expertise, such as developmental neurobiologists and circuit neuroscientists, to collaboratively conduct thorough characterizations of how early developmental events result in alterations to ASD relevant neural circuitry in carefully chosen models.

Scientific Priorities and Scope

The Linking Early Neurodevelopment to Neural Circuit Outcomes RFA will support research that aims to directly connect neurodevelopmental changes to ASD-relevant circuit phenotypes in order to advance our understanding of how ASD risk genes contribute to the neurobiology of autism. We invite proposals that will elucidate the impact of well-defined developmental alterations on the structure, function and/or output of neural circuits relevant to ASD phenotypes. To this end, experimental endpoints need not be behavioral readouts, but should be phenotypes that would reasonably be expected to drive alterations in function at the organism level (e.g., changes in synaptic connectivit or plasticity, or altered local or mesoscale neural dynamics and/or coding, ideally assesse with cell-type specificity). To facilitate rigorous assessments of causality, we imagine that successful applications will connect phenotypes at adjacent biological scales (e.g., from neuronal migration defect to aberrant connectivity or from aberrant connectivity to altere neural dynamics), linking across as many levels of analysis as possible within the time an budget provided by the grant. Because the goal of this RFA is to establish causal links between temporally distant phenotypes, we encourage dense and/or longitudinal sampling whenever appropriate, in order to rigorously characterize the relative timing and stability of the phenotypes of interest.

Competitive applications will provide strong evidence in support of the chosen phenotypi starting point(s) in the form of published or high-quality preliminary data, as well as a statement of the direct relevance of the proposed work to ASD.

While we envision many successful projects will take a “forward” approach (starting with a developmental phenotype and following it to circuit function), we are open to considering proposals adopting a “reverse” approach (starting with a later-manifesting phenotype and working backward to uncover its developmental underpinnings), provided that the motivating phenotype is well established and that there is a specific and well-supported hypothesis regarding its potential developmental origin.

Whenever possible, we encourage applicants to demonstrate evolutionary conservation o their chosen phenotypes. We also encourage, but do not require, that studies consider convergence in the function of ASD risk genes within their proposed framework. Because the work supported by this RFA is likely to be time-intensive and highly mechanistic in nature, the choice of experimental model(s) and risk gene(s) must be well justified.

SFARI recognizes the critical contributions of in vitro systems such as organoids and slice preparations to our understanding of neurodevelopment and circuit function. While we ar open to proposals utilizing such models, we feel that due to the inherent complexity of circuit formation and function in the intact nervous system, work in in vitro systems must be carefully justified and ideally accompanied by in vivo studies in order to achieve the goals of this RFA.

Collaboration Across Funded Groups

SFARI plans to facilitate coordination across projects funded through this RFA. While the details are yet to be determined, this may include periodic meetings among funded investigators to discuss challenges and share research findings. We hope that these serve as organic collaborative opportunities, with funded groups sharing protocols, data and reagents with other consortium members whenever applicable and with SFARI throughou the grant period. Adherence to an open-science ethos will be an important consideration in yearly assessments. Costs associated with attending any SFARI-initiated meetings will be covered separately by the Simons Foundation.

Level and Duration of Funding

Due to the multidisciplinary focus of this RFA, we strongly encourage collaborative applications involving multiple principal investigators (PIs); single PI applications will also be accepted. Each lab may request a maximum of $300,000, inclusive of 20 percent indirect costs, for each year of funding over a period of three (3) to four (4) years, up to an annual maximum of $900,000. Allowable indirect costs to the primary institution for subcontracts are not included in the total budget threshold (see grant policies). We encourage investigators to take advantage of the flexibility in budget and duration, tailoring the scope of the award as appropriate for their specific aims. As with all SFARI-funded projects, it is at Simons Foundation's discretion to modify final budgets as needed

Recognizing that different stages of a project may have different personnel and financial requirements, the primary PI may adjust PI membership during the funding period to reflect scientific needs, with SFARI approval.

Progress will be critically evaluated at two (2) years before support for the remainder of the funding period will be approved, bearing in mind the potentially high-risk nature of th funded work. Adherence to an open-science ethos will be an important consideration in this assessment.

Please note that in the event of budgetary or other considerations, The Simons Foundation, Inc. reserves the right to refer an application that has advanced through scientific review to The Simons Foundation International, Ltd. (SFI) for consideration and funding, in which case SFI's grant policies would apply.

Review Process

Applications will be evaluated by the SFARI science team, with a subset selected for further evaluation by an external review panel. Competitive applications will be invited to present their proposal via Zoom to the SFARI science team and invited scientists on January 14, 15 or 16, 2025.

Eligibility

All applicants and key collaborators must hold a Ph.D., M.D. or equivalent degree and have a faculty position or the equivalent at a college, university, medical school or other research facility.

SFARI recognizes the importance of diverse viewpoints for scientific advancement. As such, SFARI encourages the inclusion of researchers who span career stages and of groups historically underrepresented in science.

Applications may be submitted by domestic and foreign nonprofit organizations; public and private institutions, such as colleges, universities, hospitals, laboratories and units of state and local government; and eligible agencies of the federal government. There are nc citizenship or country requirements.

Instructions for Submission

The deadline for application submission is 12:00 p.m. (noon) Eastern Time on Thursday, September 12, 2024.

Applications must be submitted via the Simons Award Manager (SAM). Please click on the Funding Opportunities icon and navigate to the Autism Research – "Development to Circuits" call. Click the Create Application button to begin. Applications should be startec and submitted under the applicant's own account in SAM.

Application templates will be available in SAM beginning on Tuesday, June 11, 2024. Applications will include a Specific Aims page and a 6-page Proposal Narrative. Up to 10 figures may be included separately and do not count towards the page limit.

Informational videos on submitting applications in SAM can be found here.

Informational Session for Potential Applicants

To answer questions about this RFA, SFARI will hold an informational Zoom meeting on June 25, 2024 at 12 p.m. EDT. Interested applicants can register here.

Our Commitment to Diversity, Equity and Inclusion

Many of the greatest ideas and discoveries come from a diverse mix of minds, backgrounds and experiences. The Simons Foundation is committed to grantmaking that inspires and supports greater diversity and inclusiveness by cultivating a funding environment that ensures representation of all identities and differences and equitable access to information and resources for all applicants and grantees.

The Simons Foundation provides equal opportunities to all applicants for funding without regard to race, religion, color, age, sex, pregnancy, national origin, sexual orientation, gender identity, genetic disposition, neurodiversity, disability, veteran status or any other protected category under federal, state and local law. We also fund programs directed at supporting scientists from disadvantaged backgrounds or underrepresented groups, ofte working closely with professional societies and other funding agencies.

References

1. Satterstrom, F. *et al.* Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*. 180, 568-584 (2020). PubMed

2. Fu, J. *et al.* Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat. Gen*. 54, 1320-1331 (2022). PubMed

3. Rolland, T. *et al.* Phenotypic effects of genetic variants associated with autism. *Nat. Med*. 29, 1671-1680 (2023). PubMed

4. Schafer, S.T. *et al*. Pathological priming causes developmental gene network heterochronicity in autistic subject-derived neurons. *Nat. Neurosci*. **22**, 243-255 (2019). PubMed

5. Willsey, H.R. *et al.* Parallel in vivo analysis of large-effect autism genes implicate cortical neurogenesis and estrogen in risk and resilience. *Neuron* 109, 788-804 (2021). PubMed

6. Paulsen, B. *et al*. Autism genes converge on asynchronous development of shared neuron classes. *Nature* 602, 268-273 (2022). PubMed

7. Villa, C.E. *et al*. CHD8 haploinsufficiency links autism to transient alterations in excitatory and inhibitory trajectories. *Cell Rep*. 39, 110615 (2022). PubMed

8. Li, C. *et al*. Single-cell brain organoid screening identifies developmental defects in autism. *Nature* 621, 373-380 (2023). PubMed

9. Munz, M. *et al*. Pyramidal neurons form active, transient, multilayered circuits perturbed by autism-associated mutations at the inception of neocortex. *Cell* 186, 1930-1949 (2023). PubMed

10. Golden, C. *et al.* Disrupted circuits in mouse models of autism spectrum disorde and intellectual disability. *Curr. Opin. Meurobiol.* 48, 106-112 (2017). PubMed

11. Orefice, L. Peripheral somatosensory neuron dysfunction: emerging roles in autism spectrum disorders. *Neuroscience* 445, 120-129 (2020). PubMed

12. Monday, H. *et al.* Circuit-level theories for sensory dysfunction in autism: convergence across mouse models. *Front. Neurol.* 14:1254297 (2023). PubMed

13. Cording, K. and Bateup, H. Altered motor learning and coordination in mouse models of autism spectrum disorder. *Front. Cell. Neurosci.* 17:1270489 (2023). PubMed

Please find an extended list of literature describing early developmental phenotypes here.