SFARI

Genomics of ASD: Pathways to Biological Convergence and Genetic Therapies – Request for Applications

Grants awarded through this request for applications (RFA) are intended to improve our understanding of the molecular and cellular consequences of genetic risk for ASD, and to provide a foundation for the development of new therapies. Special emphasis is placed on the use of scalable methods, especially as applied to genes that are suitable targets for genetic therapies.

There are three budget tracks, depending on the scope of the project: an Explorer track of up to $400,000 over a period of up to two (2) years; an Expansion track of up to $1,500,000 over a period of up to three (3) years; and a Collaboration track of up to $750,000 per lab over a period of up to three (3) years. All budget figures are inclusive of 20 percent indirect costs.

Policies and Procedures
RFA Informational Session
July 5, 2022

Maximum Budget

Explorer Track
$400,000 over a period of up to two (2) years

Expansion Track
$1,500,000 over a period of up to three (3) years

Collaboration Track
$750,000
per lab
over a period of up to three (3) years

Important Dates

Application Available

June 21, 2022

RFA Informational Session
July 5, 2022

Application Deadline
August 18, 2022

Award Notification
December 2022

Award Start Dates
March/April 2023

RFA How To Apply FAQ Past Awards

SFARI Mission

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

Background and Objectives

Grants awarded through this request for applications (RFA) are intended to advance our understanding of the genetic basis of ASD and the molecular and cellular consequences of genetic risk, and to provide a foundation for the development of treatments for select genetically defined forms of the condition.

Over the past decade, the scientific community has identified more than 100 highly penetrant risk genes for ASD, owing in part to analyses of SFARI-sponsored cohorts such as SPARK, Simons Searchlight and the Simons Simplex Collection. Although important progress has been made in leveraging these genetic findings to better understand the biological underpinnings of ASD, much remains to be done.

In this RFA we seek proposals in three different areas, with the common goal of identifying new possibilities for intervention. The first will do so by identifying possible points of biological convergence among multiple genetic risk factors, which might then

suggest new therapeutic targets. The second will continue SFARI-supported efforts to characterize the full range of functional variation in genes associated with neurodevelopmental disorders, again with an eye toward informing translational efforts. And the third area will focus on the development of genetically based therapies for selec forms of ASD. We also encourage applicants to familiarize themselves with resources tha SFARI supports that may accelerate projects, such as our resource of iPS cells, mouse, ra and zebrafish models.

Grants awarded under the 2021 version of this RFA, which had slightly different areas of emphasis, can be found here.

Focus Area 1: Integrative Analyses of Multi-omic ASD Data

A group of recent preprints has established a new high-water mark for our understandin of the genetic basis of ASD and the ways in which rare *de novo* variation, rare inherited variation and common variation come together to explain the presentation of ASD in affected individuals[1–7]. In addition, initial studies have identified neurogenesis as one possible point of convergence for at least a subset of genetic risk factors (see here for a summary). Although these studies constitute important progress, a deeper understandin of how different classes of genetic susceptibility and different ASD risk genes converge o overlapping biological networks remains an important goal for the field.

To address this gap in knowledge, this focus area will prioritize integrative analyses that leverage available genomic data on tens of thousands of individuals with ASD, including 70,487 exomes (34,164 with ASD) and 11,628 genomes (3,199 with ASD) from SPARK, a well as many other available genome-wide multi-omic datasets.

A specific goal is to better understand how ASD-associated alleles perturb the regulation of DNA accessibility, transcription factor binding, mRNA splicing and protein-protein interactions, ultimately leading to convergent changes in signaling pathways in critical ce types at critical developmental stages. In particular, we encourage studies that capitalize on recent advances in genome-wide resources that are now available, including the reference map of the human protein interactome, ENCODE data and binding sites for 27 transcription factors (some of which are high-confidence ASD risk genes), among many other resources.

We are also eager to receive applications that address areas that were underrepresented in the previous iteration of this RFA, including assessments of the ASD proteome, the contribution of inherited genetic variation to ASD-associated biology and the possible contribution of mitochondrial genetic variation and biology. A summary of a recent SFAR

workshop on mitochondria and ASD can be found here, which highlighted, among many other issues, the need to evaluate mitochondrial function in cellular and animal models carrying ASD-associated risk variants.

Focus Area 2: Functional Analysis of Associated Variants

We invite proposals to study the functional effects of any class of variant associated with ASD susceptibility, including but not limited to missense, splicing and regulatory variants as well as repeat expansions and contractions. Variants to be analyzed may come from any autism cohort for which high-quality exome and/or genome sequences are available. Toward this end, assessment of variants as either loss-of-function or gain-of-function will be of special interest, as will information about molecular and/or cellular phenotypes that are particularly well suited to being used as a readout of the effectiveness of gene-based rescue experiments. Proposals that are complementary to previous SFARI awards in this area will also be of particular interest.

Focus Area 3: Genetic Therapies

We invite proposals to develop gene-targeted therapies for severe neurodevelopmental conditions caused by mutations in high confidence autism risk genes. To that effect SFARI has prioritized a list of approximately 50 genes from the SPARK gene list as strong candidates for the development of translational programs. However, applications targeting other genes from the SPARK gene list will not be excluded *a priori*. Successful applications will provide convincing justification for the genes or mutational mechanisms prioritized for study. Therefore, we encourage applicants to reference the criteria applied to select the list of 50 prioritized genes ("Gene Selection Criteria" tab) for guidance on gene selection.

We expect that proposals will include molecular, cellular and/or animal model studies of the target gene(s) that will lead to the identification or validation of phenotypes which are suited to test the efficacy of the proposed targeted interventions. It will be of advantage to have at least preliminary data showing the existence of suitable phenotypes.

As individual genes may be candidates for diverse gene-targeting technologies, it is difficult to predict which approach will be best suited for translation. Therefore, we encourage collaborative applications around individual genes. For such projects, each collaborating lab may focus on the development or use of a different technology, but labs will share resources (e.g., mouse models) and data (e.g., cellular, molecular, behavioral phenotypes) suited to address phenotype reversal.

Please familiarize yourself with SFARI's current portfolio on gene targeting therapies and consider how your work may be able to complement or expand ongoing work.

Available Resources

SFARI has established multiple resources that may be helpful to studies proposed in response to this RFA that can be requested by application to SFARI Base:

Data:

- Both genomic and phenotypic data are available for more than 50,000 individuals participating in SFARI cohorts (SSC, SPARK and Searchlight) with about 50,000 whole-exome and about 15,000 whole-genome sequences.

Biospecimens:

- iPS cell resources
- Lymphoblastoid cell lines
- Fibroblasts

Level and Duration of Funding

To enhance support of projects all along the continuum of translation, SFARI now offers three tracks within this RFA solicitation: Explorer, Expansion and Collaboration. Applicant should select the track that best matches the maturity and goals of their research proposal, as review criteria will be appropriately tailored for each track. We encourage investigators to take advantage of the flexibility in budget and duration, tailoring the scop of the award as appropriate for their specific aims.

Funds are expected to be expended as requested during each annual budget period.

Explorer track

This track is appropriate for early-stage projects in which establishing feasibility and proo of-concept are the most relevant outcomes of the grant period. The total budget is $400,000 or less, inclusive of 20 percent indirect costs, over a period of up to two (2) years. Allowable indirect costs to the primary institution for subcontracts are not include in the $400,000 total budget threshold (see grant policies).

Expansion track

This track is appropriate for more mature projects with evidence of feasibility and preliminary validity. The total budget is $1,500,000 or less, inclusive of 20 percent indirec costs, over a period of up to three (3) years. Allowable indirect costs to the primary institution for subcontracts are not included in the $1,500,000 total budget threshold (see grant policies).

Collaboration track

This track is appropriate for multi-lab collaborative projects. Collaborative proposals should be built around transdisciplinary teams that link analyses across different levels of biological complexity — from gene to cells to networks to circuits. Ideally experimental modalities used by collaborating labs are complementary. In addition, we encourage cross-species model comparisons (i.e., human organoid and mouse). The total budget *pe collaborating lab* is $750,000 or less, inclusive of 20 percent indirect costs, over a period o up to three (3) years. Allowable indirect costs to the primary institution for subcontracts are not included in the $750,000 total budget threshold (see grant policies). We welcome applications from up to four collaborating principal investigators (PIs).

As with all SFARI-funded projects, it is at the foundation's discretion to modify final budgets and scientific scope as needed. Grant progress will be critically evaluated at the end of each annual funding period before support for the upcoming year will be approve

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.

Applications may be submitted by domestic and foreign nonprofit organizations; public and private institutions, such as colleges, universities, hospitals, laboratories, units of sta and local government; and eligible agencies of the federal government. There are no citizenship or country requirements.

Instructions for Submission

Applications must be completed electronically and submitted using forms provided at proposalCENTRAL. Please log in as an applicant, go to the grant opportunities tab, scroll

to "Simons Foundation," and click "Apply Now" for the "Genomics: Pathways to Biological Convergence and Genetic Therapies." For assistance, please call 800-875-2562 or email pcsupport@altum.com.

Details concerning application requirements and submission can be found in our instructions or on proposalCENTRAL. If you have other questions, please review our FAQs.

Informational Sessions for Potential Applicants

To answer questions about this RFA, SFARI will hold an informational Zoom meeting on July 5, 2022, at 1:00 p.m. EDT. 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. The foundation also funds programs directed at supporting scientists from disadvantaged backgrounds or underrepresented groups, often working closely with professional societies and other funding agencies.

References

1. Fu J.M. *et al. medRxiv* (2021) Preprint

2. Wang T. *et al. bioRxiv* (2021) Preprint

3. Zhou X. *et al. medRxiv* (2021) Preprint

4. Trost B. *et al. medRxiv* (2022) Preprint

5. Antaki D. *et al. Nat. Genet.* Epub ahead of print (2022) PubMed

6. Rolland T. *et al. medRxiv* (2021) Preprint

7. Warrier V. *et al. Nat. Genet.* Epub ahead of print (2022) PubMed

8. Rolland T. *et al. medRxiv* (2021) Preprint

9. Warrier V. *et al. medRxiv* (2020) Preprint

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE