SETBP1-HD MICROGRANT PROGRAM

SETBP1 Society offers grants to help enable investigator-led research to broaden our understanding of SETBP1 LOF biology and develop safe and transformative therapies for SETBP1 haploinsufficiency disorder.

INTRODUCTION

SETBP1 haploinsufficiency disorder (SETBP1-HD) is a monogenetic neurodevelopmental disorder characterized by expressive language delay, autistic traits/autism, attention deficits, and intellectual disability. DNA changes that lead to a decreased amount of the SETBP1 protein are associated with SETBP1-HD. The DNA changes are typically de novo. There are currently no approved therapies or standard of care.

The SETBP1 gene (also known as SEB), located on chromosome 18q12.3, codes for the protein SET-binding protein 1. SETBP1 codes for 2 isoforms, with the largest and most commonly studied being 1596 amino acids long. The SETBP1 protein is a transcription factor that binds to and transcriptionally regulates or controls the expression of different genes. The protein has many other functions including helping nerve cells grow, divide and move to their proper location during early brain development, interacting with SET protein, which is involved in histone methylation, cell proliferation, neuronal development and function, epigenetic regulation, cancer pathogenesis, and others. SETBP1 is not only a part of the SET complex, but also the INHAT complex, the PP2A complex, and is linked to Wnt/β-catenin signaling. Variants or deletions in the SETBP1 gene are associated with 3 neurodevelopmental disorders, 2 of which are SETBP1 haploinsufficiency and SETBP1-related disorders, which are linked to global neurodevelopmental delay, intellectual disability, attention-deficit/hyperactivity disorder, hypotonia, and autism. Pathogenic variants for SETBP1-HD and related disorders can occur throughout the SETBP1 gene - though there are some variants that affect 3 or more individuals with missense or nonsense variants. Current therapies are multidisciplinary and consist of speech therapy to address motor speech and language delays, physical and occupational therapies to address behavioral and locomotor problems, and medications to help impulsivity, focus, sleep, and behaviors; unfortunately, these interventions are minimally effective.

SETBP1 Society is an internationally-focused 501(c)3 non-profit organization based in the US with a mission to provide support to individuals with SETBP1 haploinsufficiency and related disorders and their families, to promote discussion and fund research, and to bring awareness and education to the public. SETBP1 Society supports a wide range of research activities including patient registries, natural history studies, and basic and clinical research.

OBJECTIVE AND AREAS OF INTEREST

The purpose of this funding opportunity announcement is to support novel research investigating altered molecular pathways, including the unknown role of phosphorylation and the identification of

potential treatments for SETBP1-HD. Through the support provided with this microgrant, the SETBP1 Society expects to address critical knowledge gaps underlying SETBP1 loss-of-function while facilitating research studies for the ultra-rare SETBP1-HD and fostering new scientific collaborations within the community.

Proposals should focus on:

1. **Uncovering molecular pathways** at the tissue or cellular level altered in SETBP1 loss-of-function contributing to neurodevelopmental phenotypes in SETBP1-HD.
2. **Identifying novel drug candidates** or treatments for SETBP1-HD.

Some examples of submissions that might be considered for this RFA include, but are not limited to:

- Proposals with a focus on the currently understudied role of phosphorylation in SETBP1-HD at the tissue or cellular level within the context of the brain.
- The use of existing publicly available RNA-sequencing data paired with signature reversion, drug repurposing, or drug-gene interaction studies.
- Studies leveraging existing cell lines, models, and samples for molecule screens to identify novel drug candidates.

Datasets, Models, and Materials Available (not all-inclusive):

Datasets:

- Publicly Available RNA-sequencing data from Cardo et al. Molecular Autism 2023

Cell Lines:

- Human SETBP1 LoF iPSC through Simons Searchlight, McGill University through Carl Ernst, or Max Planck Institute in Nijmegen through Simon Fisher

Samples:

- Human whole blood at Simons Searchlight

Models:

- Setbp1 conditional knock-out [tm1c] (#066873-JAX) at Jackson Laboratories

ELIGIBILITY

The SETBP1 Society microgrant program is open to research investigators affiliated with an academic institution, hospital system, non-profit institution, or other accredited research institutions based in the United States (U.S.) or internationally. Eligible applicants include postdoctoral fellows, clinical fellows, researchers, physicians, or other associated research professionals with faculty appointments or research positions.

GRANT DETAILS

SETBP1 Society currently is funding microgrants which are intended to fund small proof-of-concept studies aimed at collecting supportive data for subsequent research initiatives and funding. Applicants may request up to $25,000 direct costs to be expended within a 12-month period.

SETBP1 Society does not support indirect costs for Grants.

Current Deadline for Letter of Interest (LOI): Friday, August 2nd, 2024
Notification of LOI Acceptance by Friday, August 9th, 2024
Current Deadline for Full Application: Monday, September 16th, 2024
Grant Award Announcement by Friday, October 25th, 2024

APPLICATION INSTRUCTIONS

There will be a two-stage peer-review application process:

1. In the first stage, applicants will submit a Letter of Intent (LOI) summarizing the intended research.
2. The SETBP1 Society will review LOIs to advance and notify applicants if they have been selected to submit a full proposal.

Letter of Intent
All applicants must submit a one-page maximum LOI to the Foundation. Only select applicants will subsequently submit a full proposal. The LOI should consist of the following components.

1. **Title**: A succinct descriptive title of the project.
2. **Applicant/PI Information**: Name, title, position, institution, mailing address, email address, and telephone number.
3. **Brief Project Description**: This should include a description of the scientific aims for the project, how the project will advance the goals of SETBP1 Society, and a brief description of how the research will be accomplished.
4. **Amount Requested**: The requested award amount should be $25,000 or less.

LOIs should be submitted by email as PDF files to research@setbp1.org.

Full-length Application
Full-length applications will be invited from meritorious LOIs selected by SETBP1 Society. SETBP1 Society will supply the applicant with a Full Grant Application, which will be used for submission.

REVIEW MECHANISM

All proposals will undergo rigorous peer review by SETBP1 Society, composed of experts in SETBP1-HD and diverse areas of research as appropriate. Applications will be scored according to Key Selection Criteria including, but not necessarily limited to, (i) significance of the research to SETBP1-HD; (ii) innovation of the project; (iii) approach and feasibility of the proposed methods; (iv) investigators and environment; (v) prospect of long term funding; and (vi) potential impact of the project on SETBP1-HD. SETBP1 Society will provide summaries of reviewer critiques or evaluations to applicants. Depending on peer review and SETBP1 Society's program priorities, the Society may work with applicants to modify the submitted work plan and/or budget prior to award execution.