GRANTS PROGRAM

The **STXBP1 Foundation** offers grants to help enable investigator-led research to broaden our understanding of STXBP1 biology and develop safe and transformative therapies for STXBP1 related disorders.

INTRODUCTION

The STXBP1 gene (also known as MUNC-18), located on chromosome 9q34.1, codes for the protein syntaxin-binding protein 1. The STXBP1 protein is an essential component of the SNARE complex, a composite of generally small proteins that mediate the fusion of synaptic vesicles to the neuronal cell membrane, and thus vital for neurotransmitter release. Mutations in the STXBP1 gene are associated with global neurodevelopmental delay, early onset epilepsy, movement disorders, and autism. The estimated incidence rate for STXBP1 disorder is 1:30,000 making it a leading cause of developmental epileptic encephalopathy. Pathogenic mutations can occur throughout the STXBP1 gene - though there are some 'hotspots' - and include missense, frameshift, splice site, nonsense, and intragenic and whole gene deletions; haploinsufficiency is sufficient for disease manifestation, though other pathogenic mechanisms may be involved. Current therapies are multidisciplinary and consist of symptomatic treatment of seizures, and physical and occupational therapies to address behavioral and locomotor problems; unfortunately, these interventions are minimally effective.

The STXBP1 Foundation is a non-profit advocacy organization dedicated to creating awareness and finding a cure for STXBP1 disorders. It supports a wide range of research activities including patient registries, natural history studies, and basic and clinical research.

OBJECTIVE AND AREAS OF INTEREST

The objective of the STXBP1 Foundation grant program is to identify promising research projects that address specific areas of interest to the Foundation. These areas include but are not limited to the following:

1. **Biomarkers and clinical endpoints development.** Biomarkers can be critical to the success of clinical trials for new drug therapies. Biomarkers can be used to assess target engagement, evaluate drug pharmacokinetics and pharmacodynamics, used to select and stratify trial participants, and serve as an indicator of drug efficacy. STXBP1 disorders lack reliable biomarker(s) that can be used for clinical drug development and the Foundation is extremely interested in identifying either CNS or non-CNS biomarkers. Potential biomarkers could include CNS imaging (e.g., PET for neurotransmitters, magnetic resonance spectroscopy) EEG, metabolomics, fluid biomarkers (e.g. genes and proteins found in blood or CSF), or others. Reductions in seizure activity and/or severity can be an important clinical endpoint for evaluating potential therapeutics; however, many patients do not experience seizures and in those that do, seizure activity naturally

varies over time. The development of clinical endpoints, other than seizure activity, will be necessary for future clinical trials.

2. **Neurodegeneration.** Mutations in the STXBP1 protein are associated with presynaptic dysfunction. While synaptic pathologies are associated with a range of neurodegenerative disorders, our understanding of the potential neurodegeneration associated with STXBP1 is limited, including basic mechanisms, the effects of age, interactions with other synaptic proteins, or the potential role of non-neuronal cells.
3. **Pathomechanisms of STXBP1 mutations and genotype-phenotype relationships.** Dysfunctional STXBP1 protein is known to adversely affect synapse function and that GABAergic synapses are particularly vulnerable; However, how STXBP1 mutations affect larger neurotransmitter and/or brain functional networks is not well understood or appreciated. This is especially relevant given the cognitive impairments associated with STXBP1 disorders. Additionally, how, or if, specific STXBP1 mutations are associated with specific pathophysiological processes or specific disease phenotypes is important to understand.
4. **Non-CNS functions.** STXBP1 protein is expressed in several tissues outside the CNS, including the intestine and the pancreas, and gastrointestinal problems such as constipation and reflux are common symptoms in STXBP1 disorders. There is a lack of understanding in how STXBP1 protein mutations affect non-CNS tissues and functions, such as gastric motility or endocrine release and how this impacts patients.
5. **Drug repurposing.** The ability to repurpose FDA-approved drugs for new indications is becoming more and more important and offers the opportunity to identify new therapies for the treatment of STXBP1 disorders and similar developmental encephalopathies. For example, the small molecule 4-phenylbutyrate, which is approved to treat urea cycle disorders, has been demonstrated to act as a molecular chaperone and enhance STXBP1 function, leading to a small clinical trial.

ELIGIBILITY

The STXBP1 Foundation grant 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 post-doctoral fellows, clinical fellows, researchers, physicians, or other associated research professionals with faculty appointments or research positions.

MECHANISMS OF SUPPORT

The STXBP1 Foundation funds multiple types of projects aimed at addressing diverse research needs in the STXBP1 field.

1. **Seed Grant.** Seed Grants 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.
2. **Trainee Grant.** Trainee Grants are intended to help cover the salary and/or research costs for promising Postdoctoral Fellows interested in pursuing basic and/or clinical

research in the STXBP1 field. Applicants may request up to $60,000 direct costs to be expended within a 12-month period. This grant may be renewed for a second year at the Foundation's discretion.

3. **Innovation Grant.** Innovation Grants are intended to fund projects with significant potential for pioneering discoveries that accelerate the mission of the Foundation. Applicants may request up to $100,000 direct costs to be expended within a 12-month period. This grant may be renewed for a second year at the Foundation's discretion.
4. **Clinical Grant.** Clinical Grants are intended to fund STXBP1-related clinical studies. The funding can be used to either fund a small study in its entirety or help to cover the costs of a larger clinical trial that is already partially funded. Applicants may request up to $150,000 direct costs to be expended within a 12-month period.

The STXBP1 Foundation does not support indirect costs for Grants.

APPLICATION INSTRUCTIONS

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

1. In the first stage, applicants will submit a Letters of Intent (LOI) summarizing the intended research.

2. The STXBP1 Foundation 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. **Mechanism of Support:** The type of grant mechanism for which the applicant is applying
4. **Brief Project Description:** This should include a description of the scientific aims for the project, how the project will advance the goals of the Foundation, and a brief description of how the research will be accomplished.

LOIs should be submitted by email as PDF files to grants@stxbp1disorders.org.

Full-length Application

Full-length applications will be invited from meritorious LOIs selected by the STXBP1 Foundation. The Foundation will supply the applicant with a 'Grant Application Instructions and Forms' package, which will be used for submission.

REVIEW MECHANISM

All proposals will undergo rigorous peer review by the STXBP1 Foundation, composed of experts in STXBP1 disorders 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 STXBP1 disorders; (ii) innovation of the project; (iii) feasibility of the proposed methods; (iv) investigators and environment; and (v) potential impact of the project on STXBP1 disorders. The Foundation will provide summaries of reviewer critiques or evaluations to applicants. Depending on peer review and the Foundation's program priorities, the Foundation may work with applicants to modify the submitted work plan and/or budget prior to award execution.