2022 Young Investigator Award Fellowship

REQUEST FOR APPLICATIONS

Phelan-McDermid Syndrome Foundation/Developmental Synaptopathies Consortium

We are seeking highly qualified postdoctoral applicants with an MD, PhD, or MD/PhD, for the Phelan-McDermid Syndrome Foundation/Developmental Synaptopathies Consortium Young Investigator Fellowship.

The ideal candidate has a clinical and/or research background in psychiatry, psychology, or neurology with a focus on neurodevelopmental disorders, and seeks to complement their expertise to become a leader in this growing field.

The fellow will help characterize neuropsychiatric phenotypes in patients with Phelan-McDermid syndrome (PMS). PMS is a rare genetic condition caused by a deletion or other structural change of the terminal region of chromosome 22 or a disease-causing sequence variant of the *SHANK3* gene. PMS is commonly associated with hypotonia, intellectual disability, and delayed or absent speech. Data is emerging that a subset of individuals with PMS experience devastating psychiatric symptoms, such as regression, bipolar disorder, and catatonia. The goal of this fellowship is to deeply characterize these psychiatric symptoms and/or explore their biological underpinnings.

The fellow will work within the NIH-funded Developmental Synaptopathies Consortium (DSC), a Rare Disease Clinical Research Network, under the training of leaders in the field with a pre-established infrastructure for recruiting and phenotyping large numbers of individuals with this rare disorder.

The training environment afforded by the Consortium includes access to PMS investigators, clinicians, and affected individuals, as well as interaction with other groups working on related genetic disorders - Tuberous Sclerosis Complex and PTEN Hamartoma Tumor Syndrome. **Priority will be given to fellows motivated to utilize the rich datasets that have been generated by the DSC, including genetic, behavioral phenotyping, electrophysiological studies, neuroimaging and biosample collections. Although the primary research focus should be PMS, cross-comparison of datasets within the disorders is encouraged.** Areas of

potential research include, but are not limited to, mechanistic studies of neuropsychiatric decompensation and regression in PMS, deep phenotyping of neuropsychiatric symptoms in PMS, development of clinical guidelines for assessment and care of people with PMS who experience neuropsychiatric decompensation, and outcome measure development for use in clinical trials in PMS. **Details describing the research resources available through the DSC are described in Appendix 1 of this document**.

Funding Mechanism Available in 2022

Fellowship Details:

- Two years in duration, MD/PhD level candidates.
    - Includes salary, fringe and research stipend up to $110,000 per year ($100,000 direct costs, $10,000 indirect)
- **Eligibility:** This opportunity is open to all early career investigators working in a relevant field (neurology, psychiatry, or psychology, and/or a focus in neurodevelopmental disorders or rare disorders). Funding is not restricted to US residents or citizens.

- **Mentorship Requirement:** The fellow will work closely with a Developmental Synaptopathies Consortium (DSC) mentor during the fellowship and is required to connect with a mentor ahead of time to express interest, discuss qualifications, and receive a letter of recommendation. Applicants already eligible to work at one of the five PMS DSC sites, including **Boston Children's Hospital, National Institute of Mental Health, Rush University Medical Center, Stanford University, and Seaver Autism Center at Icahn School of Medicine at Mount Sinai,** should contact a mentor at that site. Applicants from outside of these institutions are still eligible to apply and are required to receive a letter of recommendation from a DSC mentor at any site who the applicant feels is a good match for their proposed work. **A full list of DSC sites and mentors are provided in Appendix 1 of this document (section D).** If the applicant is having trouble connecting with a mentor, please contact DSC leadership at TNC@childrens.harvard.edu for help.

- **Application components:**

A complete application should be compiled as one PDF and emailed to the Phelan-McDermid Syndrome Foundation's Scientific Director: kate@pmsf.org. Applications require the following components:

- Applicant CV
- CV of any additional co-investigators mentioned in the research strategy or budget as providing expertise (if applicable)
- Lay abstract of the proposed project
- Cover Letter

- Career Plan
- Research Plan
- Budget
- Budget Justification

Detailed instructions on each of these components, including page limits, can be found in Appendix 2 of this document.

Applicants should also ensure that two letters of recommendation are sent separately to kate@pmsf.org, one from a current or previous mentor of the applicant, and one from a DSC mentor. These letters, and all other documents, should be received before the application deadline on January 14th, 2022. Once all required documents are received, a confirmation email will be sent to the applicant.

- **Application review:** Applications will be evaluated by a review committee led by PMS research leadership and the DSC leadership. Priority will be given to applications that **leverage the resources being developed within the DSC, especially those proposals that bridge the three diseases in the consortium (Phelan-McDermid syndrome, PTEN Hamartoma Tumor Syndrome, and Tuberous Sclerosis Complex). All DSC resources can be found in Appendix 1.**

This fellowship award is intended to provide funding for a project directly relevant to PMS. The award is intended to fund the applicant's salary and some of the laboratory supplies or tools necessary to conduct the proposed research. The award is not intended to fund technical support for the project or to purchase equipment in the mentor's laboratory. The trainee applicant is considered to be the "Principal Investigator" for the purpose of postdoctoral fellowship awards

Key Dates

- Deadline for proposals: January 14, 2022 at 11:59 p.m. US EDT
- Earliest project start date: April 1, 2022

For Grant-Related Inquiries, Contact: TNC@childrens.harvard.edu

Appendix 1: Available Resources of the Developmental Synaptopathies Consortium

Since its inception in 2014, the Developmental Synaptopathies Consortium (DSC) has a detailed data collection and management system for the study of three rare neurogenetic disorders, Tuberous Sclerosis Complex, PTEN Hamartoma Tumor Syndrome and Phelan McDermid Syndrome.

A substantial amount of data has been collected from each cohort in the first phase of the DSC I (2014-2019) as described below. Additional data will be collected in the second phase of the DSC II (2020-2024). Cross-comparison of datasets is encouraged.

A) Tuberous Sclerosis Complex

DSC I Data:

N= 95 complete datasets (ages 3-21 years)

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test – 4 (PPVT-4)
- Expressive Vocabulary Test – 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview – Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological samples:
DNA samples: 91 patients, 121 parents (stored at University of Texas at Houston with PI Hope Northrup, MD)
RNA samples: 82 patients, 102 parents (stored at Van Andel Research Institute as part of TS Alliance collection)

Longitudinal data set of advanced diffusion tensor MRI including serial imaging for patients with Tuberous Sclerosis (performed yearly for 3+ years for 95 patients) and 54 healthy controls. We implemented a strict quality assurance platform in order to standardize the acquisition and analysis of these images.

DSC II Data:

We propose to study a total of 195 children ages 18 months and older (at the time of enrollment) with TSC and suspected or diagnosed ASD, ID, or combined ASD/ID.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5 or Mullen Scales of Early Learning
- Wechsler Processing Speed Index Subtests
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test – 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT-3 or K-CPT-2)
- Autism Diagnostic Observation Schedule (ADOS)
- Autism Diagnostic Interview – Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Caregiver report (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC-2)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Child/Individual & Family Quality of Life Measure (CFQL-2 or IFQL)
- Regression Interview

- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History to be collected over 3-5 years, collection of MR images done on a yearly basis clinically, collection of clinical EEGs

Yearly collection of TAND Questionnaire:
Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Blood sample collection for RNA and DNA (stored at Van Andel Research Institute as part of TS Alliance collection), optional consent for additional tissues/blood samples.

Neurophysiology:
A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

B) PTEN Hamartoma Tumor Syndrome

DSC I Data:

N= 32 PTEN positive without ASD ages 3-21 years
N= 44 PTEN positive with ASD diagnosis ages 3-21 years
N= 33 Macrocephaly with ASD, no PTEN ages 3-21 years
N= 33 Healthy Controls ages 3-21 years

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test – 4 (PPVT-4)
- Expressive Vocabulary Test – 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview – Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)

- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological Samples:
96 patients provided biomaterial including DNA, plasma, RNA, WBC, LCL, microbiome urine, oral and fecal (stored at Cleveland Clinic with PI Charis Eng, MD).

Advanced diffusion tensor MRI for 18 patients with PHTS

Ongoing Clinical Trial with potential data to be analyzed:
The PTEN Everolimus Trial (clinicaltrials.gov NCT02991807) is ongoing to evaluate the safety of everolimus (RAD001) compared to placebo in patients with *PTEN* mutations, in addition to evaluating the efficacy of everolimus on neurocognition and behavior in ages 5-45 year olds who have a *PTEN* mutation compared to placebo as measured by standardized direct and indirect neurocognitive tools and behavioral measures. We have randomized 40 patients for a 6 month blinded phase (1 everolimus: 1 placebo) and 6 month open label phase with a data collection completion date of December 2020. Participating centers include Boston Children's Hospital, Cleveland Clinic and Stanford University.

DSC II Data:

Population will include patients 18 months and older at the time of consent who have documentation of a verified *PTEN* mutation from a medical or mental health professional.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5 or Mullen Scales of Early Learning
- Wechsler Processing Speed Index Subtests
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test – 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Wechsler Processing Speed Index Subtests (PSI)
- Connors Continuous Performance Test (CPT or K-CPT-2)

- Autism Diagnostic Observation Schedule (ADOS)
- Autism Diagnostic Interview – Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Caregiver report (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC-2)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Child/Individual & Family Quality of Life Measure (CFQL-2 or IFQL)
- Regression Interview
- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History over 3-5 years

Yearly Blood Sample Collection, optional consent for additional tissues/blood samples/microbiome(stored at Cleveland Clinic with PI Charis Eng, MD).

Yearly collection of TAND Questionnaire:
Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Neurophysiology:
A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

C) Phelan McDermid Syndrome

DSC I Data:

N= 97 full datasets for children ages 3-21 years

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test – 4 (PPVT-4)
- Expressive Vocabulary Test – 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview – Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological Samples:
N= 98 total patients
N= 189 parents and/or sibling
Of these, 58 are trios (stored at Mt Sinai with PI Alexander Kolevzon, MD).

For each of the patients and their respective family members, Peripheral Blood Mononuclear Cells (PBMCs), RNA, DNA, and plasma were collected.

Advanced diffusion tensor MRI for 18 patients with Phelan McDermid Syndrome

DSC II Data:

We propose to collect 190 subjects 18 months of age and older with pathogenic deletions or mutations of the *SHANK3* gene will undergo medical, genetic, behavioral, cognitive, language, sensory, and motor testing.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Differential Ability Scales (DAS-II)/Mullen Scales of Early Learning
- Psychoeducational Profile, Third Edition (PEP-III)2
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test – 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Autism Diagnostic Observation Schedule (ADOS)
- Sensory Assessment for Neurodevelopmental Disorders (SAND)
- Autism Diagnostic Interview – Revised (ADI-R)
- Repetitive Behavior Scale – Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Child/Individual & Family Quality of Life Measure (CFQL or IFQL)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Comprehensive Interview Form (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- MacArthur Bates Communication Development Inventory (MCDI)
- Pervasive Developmental Disorder Behavior Inventory (PDD-BI)
- Children's Sleep Habits Questionnaire
- Early Detection Screen for Dementia
- Waisman Activities of Daily Living Form
- Regression Interview
- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History over 3-5 years

Blood samples will be collected for whole exome sequencing and RNA extraction and other similar analyses to DSCI data (stored at Mt Sinai with PI Alexander Kolevzon, MD), optional consent for additional samples.

Yearly collection of TAND Questionnaire:
Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Neurophysiology:
A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

D) Study Site Information (PIs/Mentors)

Boston Children's Hospital (TSC, PTEN, and PMS):
PI – Mustafa Sahin, MD, PhD (Consortium Investigator)
EEG Lead – Chuck Nelson, PhD
MRI Lead – Simon Warfield, PhD
Biostatistician – Bo Zhang, PhD

Stanford University (TSC, PTEN, and PMS):
TSC PI – Brenda Porter, MD
PTEN PI – Antonio Hardan, MD
PMS PI – Jon Bernstein, MD

Cincinnati Children's Hospital Medical Center (TSC and PTEN):
PI – Darcy Krueger, MD, PhD (TSC Study Chair)
PI – David Ritter, MD, PhD

University of California at Los Angeles (TSC and PTEN):
TSC PI – Shafali Jeste, MD
PTEN PI – Julian Martinez, MD, PhD

University of Alabama at Birmingham (TSC):
PI – Martina Bebin, MD

University of Texas Health Science Center at Houston (TSC):
PI – Hope Northrup, MD
Lead TSC Psychologist – Deborah Pearson, PhD

Cleveland Clinic (PTEN):
PI – Charis Eng, MD, PhD (PTEN Study Chair)
Lead PTEN Psychologist – Robyn Busch, PhD

Mount Sinai School of Medicine (PMS):
PI – Alex Kolevzon, MD (PMS Study Chair)
Director of Administrative Core – Joseph Buxbaum, PhD

National Institutes of Health (PMS):
PI and Lead PMS Psychologist – Audrey Thurm, PhD

Rush University Medical Center (PMS):
PI – Elizabeth Berry-Kravis, MD, PhD
PI – Latha Soorya, PhD

Consultant:
Lead Psychologist – Celine Saulnier, PhD

Appendix 2: Detailed Application instructions

For questions about the content of the application, please contact Kate Still, Scientific Director at the Phelan-McDermid Syndrome Foundation (PMSF): kate@pmsf.org.

The following application components should be sent as a single PDF file. Text should be single spaced, and no smaller than an 11-point font. The primary applicant's name must appear in the upper right-hand corner of each page.

CV for Key Personnel – For this fellowship, the Young Investigator is considered the PI and their CV is required. Because this is a training fellowship, a majority of support is meant to go to the PI. If collaborating investigators are needed to perform a specific technique, or provide expertise, and are mentioned in either the Research Strategy or Budget, their CV should also be included. Do not include laboratory staff or trainees who are directly supervised by the PI or by a collaborating PI. The budget for the fellowship is not to exceed $110,000 per year total in direct and indirect costs.

Lay Abstract (300 words max) –Please write a lay abstract summarizing your proposed research in a way that families of those with Phelan-McDermid syndrome (PMS) can understand. Please be advised that if the application is approved and an award is made, abstracts may become public information.

Cover Letter (1 page max) – Please include rationale for applying to this fellowship, including your investment in PMS specifically, or in neurodevelopmental disease and/or psychiatry.

Career Plan (1 page max) – No definitive format - but must include the applicant's short-term (2 years) and long-term (10 years) career goals. The career plan should also describe how this fellowship will support these goals and provide new skills or knowledge to the applicant. The applicant should also list other tools they are using to further their career (workshops, coursework, grant applications, etc.)

Budget (2 pages max) – Include a line-item budget for both years of the fellowship. Please break up the budget into the following categories (not all will be applicable): "Key Personnel" (including percentage effort, salary, and fringe benefits), "Supplies/Equipment" (Includes consumables, and anything related to research, including animal costs if applicable), "Recruitment costs" (related to human subjects), "Travel", "Subcontracted Services", "Publication/academic costs", and "Indirect Expenses." The first budget period will be 04/01/2022 – 03/31/2023 and the second budget period will be 04/1/2023 – 03/31/2024. ***Applications for shorter durations are acceptable*** provided that total costs do not exceed $110,000 in any 12-month period. Travel costs should not exceed $1500 and should be for a PMS-relevant meeting, such as the PMS Family Research Conference, American Epilepsy Society, Society for Neuroscience, American Society for Human Genetics, etc.

Budget Justification (2 pages max) – Each budget line-item should be justified (~a few sentences per item)**.**

Research Plan (3 page max not including references) - There is not a detailed template for the research plan. The plan itself should not exceed three pages (no limit on references) and should include background, a hypothesis, NIH-style Specific Aims, and detailed methods. This plan should be centered on studying neuropsychiatric phenotypes in PMS. Preference will be given to candidates who use DSC resources in their proposed research (Appendix 1). Cross comparison of datasets across PMS, Tuberous Sclerosis Complex, and PTEN Hamartoma Tumor Syndrome is encouraged.

Submitted separately by mentors:

Letters of Recommendation – Two mentors (a current/previous mentor, and a DSC mentor) should send letters of recommendation supporting the applicant to Kate@pmsf.org. To receive a letter of recommendation from a DSC mentor, please meet with the mentor virtually or in person, to discuss your background and your interest in the fellowship. Receipt of both letters is required by the application deadline.

Once all application materials including letters are received, a confirmation email will be sent to the applicant.