Update July 17, 2015

The Multiple Sclerosis Scientific Research Foundation is seeking applications for projects investigating the gut microbiome in pediatric multiple sclerosis population

The Multiple Sclerosis Scientific Research Foundation (MSSRF) is pleased to launch a request for applications (RFA) that will invite academic investigators to apply for funding to specifically study the gut microbiome in collaboration with a larger, multi-site pediatric multiple sclerosis (MS) study.

Background and Purpose

The role of the gut microbiome in MS pathogenesis is a rapidly emerging area of study in the MS field. Microorganisms that reside in the gut interact extensively with the immune system, and perturbations of the gut microbiome have been implicated in a number of autoimmune diseases. Multiple lines of evidence indicate that disruptions to the community structure of gut bacteria are linked to disease severity in rodent models of MS. At the same time, people with MS have generally exhibited an intestinal microbiome composition that favours immunogenic over anti-inflammatory taxa of bacteria; this imbalance is partly corrected by treatment with disease-modifying therapies, which suggests a potential role for the gut microbiome in MS.

Resident intestinal microbes in the pediatric population are believed to play a fundamental role in the functional development of immunity during childhood; however, any potential alterations or disturbances in the gut microbiome of pediatric MS patients are poorly understood. This request for applications (RFA) stems from the urgent need to address this gap in our knowledge, and to generate information that will provide clues about the gut microbiome in MS. The selected project will be conducted in conjunction with an existing collaborative study led by Dr. Brenda Banwell (The Hospital for Sick Children - SickKids and Children's Hospital of Philadelphia - CHOP). Dr. Banwell and her team (Lead Team) will evaluate clinical and health-related quality of life, early loss of brain integrity, and accelerated immunological senescence in the pediatric MS population. A key component to the study is identifying the contributions of environmental risk factors to pediatric MS, particularly vitamin D status, which has been shown to be an important mediator of gut microbiome homeostasis.

Successful applicant(s) to this RFA will work collaboratively with the Lead Team to collect and archive stool samples from study participants for gut microbiome profiling, and will help to adapt the study design to align the goals of both the larger collaborative study and the gut microbiome study. Investigators will also have the unique opportunity to leverage the extensive expertise, resources, and patient recruitment capacity of the Canadian Pediatric Demyelinating

Disease Network and its comprehensive dataset.

Description of Canadian Pediatric Demyelinating Disease Study

The Canadian Pediatric Demyelinating Disease Study is led by Dr. Banwell and Co-Investigators:

- Dr. Ann Yeh, SickKids, clinical medicine
- Dr. Amit Bar-Or, McGill University, neuro-immunology
- Dr. Doug Arnold, McGill University, neuroimaging
- Dr. Ruth Ann Marrie, University of Manitoba, epidemiology and biostatistics

Study administration and the national database are housed at SickKids (Banwell). The Experimental Therapeutics Program biorepository (Bar-Or) and the neuroimaging core (Arnold) are housed at the Montreal Neurological Institute. Genetic studies have been partnered with the Canadian Collaborative Project on Genetic Susceptibility to MS (Dr. Dessa Sadovnick, University of British Columbia) as well as performed in collaboration with partners at Harvard, in the UK and the Netherlands. The integrated statistical analyses have been led by Dr. Marrie. The Table of Collaborators (see Appendix) lists the Sub-Investigators that have stewarded key study aspects, and the many scientists with whom they collaborate.

The Canadian Pediatric Demyelinating Disease Network is comprised of 23 Canadian sites, including all 17 pediatric health care institutions in Canada and 6 additional Canadian sites in locations distant from a formal pediatric hospital. The site investigators and co-ordinators at each site have regularly attended in-person and teleconference meetings over the last 10 years, with 19 of the original 23 sites remaining actively engaged (the four smallest sites – Sherbrooke QC, Windsor ON, Sudbury ON and Mississauga ON elected to refer patients to larger regional centers). One additional adult centre at University of British Columbia now follows patients who transitioned to adult care under the provision of Dr. Anthony Traboulsee, who serves as a site investigator. CHOP joined the Network in 2012, with partnered funding that has enabled the launch of the full program in Philadelphia. All sites have utilized standardized clinical case report forms, enabled by detailed training and shared practices, which have been entered centrally into the web-enabled comprehensive database. Clinical and MRI data are all analyzed centrally to ensure rigorous standardization.

Dr. Banwell leads weekly teleconferences focused on study administration and progress between SickKids and CHOP. The 5 study PIs as well as the study teams engage in weekly teleconferences (twice monthly pathobiology, twice monthly neuroimaging) and meet in-person three times annually (once per year supported by the grant, and twice in conjunction with conferences). It is noteworthy that all of the study PIs and co-investigators have remained committed to the Canadian Pediatric Demyelinating Disease study; all remain inspired to pursue further work, which reflects the collective belief that the study of MS is invaluably enhanced through study of the youngest patients, and by the highly collegial manner in which such work has been achieved.

Eligibility

Interested applicants must be eligible under the policies of their host institution to submit an application. The following is a list of appropriate personnel who may apply to the competition:

- **The Principal Investigator (PI):** The PI is listed as the primary grant applicant and is responsible for overseeing the research conducted as part of the proposal. The RFA is open to PIs who hold a faculty appointment at either a Canadian or an international institution. The PI is autonomous regarding their research activities, and has the means to pursue the proposed research, supervise trainees and publish research activities.
- **Co-Principal Investigator (Co-PI):** The Co-PI is an individual who shares responsibility for the direction of the proposed research project with the PI and meets the eligibility criteria of a PI.
- **Collaborator:** A Collaborator is an individual external to the research team whose role is to provide a specific service to support and advance the proposed research (e.g. access to equipment, training in a specialized technique, statistical analysis etc.).

Term and Amount

Total funding available is up to $500,000 CAD for one project for up to three years.

Application Process

Interested applicants must apply online using the grant administration database Easygrants. Applications must include the following:

a) **Brief project description**: In 100 words or less, provide a brief project description of the proposed research project.

b) **Lay summary:** In 200 words or less, provide a lay summary of your research project.

c) **Relevance to MS description:** In 200 words or less, describe the relevance of your research project to MS.

d) **Other personnel:** List the names and institutions for the PI, any Co-PI(s), Collaborator(s).

e) **Budget:** Budget categories are divided into Research Staff, Materials, Supplies, Services, Travel and Equipment. You may apply for a maximum of 3 years of funding. Use the budget notes section to provide details and justification of all budget items relative to the proposed research. You may include electronic copies of quotations and other information useful to the reviewers in the Appendix.

The following documents are to be uploaded as part of the application. **Format:** Page limits indicated for each section below, 12-font size, page margins of at least 0.75 inches.

f) **Scientific research proposal summary:** Provide a scientific summary of the research proposal. Maximum 1 page.

g) **Detailed scientific research proposal:** Provide a detailed research proposal. Describe the background, objectives, hypothesis, scientific questions, budget, personnel and methodology. In the study design include descriptions for sample acquisition, sample processing and comparative analyses with other biological samples. Include any applicable pilot data and describe the feasibility and appropriateness of methods. Justify how the proposal will integrate and align with the Canadian Pediatric Demyelinating Disease Study, and how the successful PI will work collaboratively with the Lead Team. Maximum 10 pages.

h) **References and supplementary data:** Include references, supplementary tables, figures, charts that are referred to in the scientific research proposal etc. If applicable include patient data, questionnaires and analytical approach with power analysis. No page limit.

i) **Project plan:** List scientific milestones and key deliverables that will be achieved during the duration of the grant. Explain how each milestone will contribute to the overall goals of the study. A MSSRF Milestones Chart must be used (see Appendix). The successful PI will refine milestones and key deliverables in collaboration with the Lead Team and create a final project plan that is subject to approval. Maximum 1 page, plus Milestones Chart.

j) **Sustainability plan:** Describe any long-term objectives for the study and how the PI intends to achieve them beyond the duration of the grant term. Maximum 1 page.

k) **CV:** Provide the CV of the PI, Co- PIs and Collaborators. The MSSRF endorses the Common CV and requests that all applicants working at a Canadian Institution submit a Common CV, the template for which can be found at https://ccv-cvc.ca/indexresearcher-eng.frm, please choose MS Society as the agency.

l) **Required signatures:** The following signatures are required (template provided online)**:**

- The PI and Co-PIs
- Head of Department of Institution for PI and each Co-PI
- Dean of Faculty or Director of Institution for PI and each Co-PI

m) **Appendix:** Upload any additional supporting documents, publications. No page limit.

Online Application Procedures

Interested applicants must create a profile on Easygrants to complete the application process. Templates for required documents can be downloaded from Easygrants, completed and uploaded in their profile. All required components must be fully completed and required

documents must be uploaded on Easygrants prior to the due date for the application to be considered. Please ensure that contact information (name of institution, primary address, phone number and e-mail) is accurate and up to date. It is the applicant's responsibility to ensure the submitted application contains all required components. To review the completed application, select "View PDF" on the "Review and Submit" page BEFORE final submission.

You will receive a confirmation e-mail of your submission. If you DO NOT receive this e-mail after submitting your application you MUST contact msresearchgrants@mssociety.ca as soon as possible.

Evaluation of Applications

Applications will be reviewed and ranked by a non-conflicted committee comprising of scientific experts, Lead Team PIs Drs. Brenda Banwell and Amit Bar-Or, and a lay member from the community who is affected by MS. A Chair will be appointed to lead the review.

For details on the MSSC general review process please visit the MS Society's Website.

Review Criteria

Applications will be evaluated based on the following criteria:

- **Significance**: Will this bring new, relevant knowledge to the field and enhance understanding of the role of the gut microbiome in MS?
- **Investigator(s):** Do the lead PI and co-PIs have the necessary experience and expertise as well as appropriate leadership and team structure to carry out the proposed research?
- **Approach:** Are the overall scope, methodology, and analyses appropriate and feasible to accomplish the specific aims of the study?
- **Integration:** Will the proposed project integrate cohesively with, and contribute important knowledge to, the Lead Team study?
- **Environmen**t: Are there adequate resources and support to facilitate the proposed research and is the budget justified?

Notification and Funding

Following review, the selected applicant(s) will meet with the Lead Team to further develop and synchronize milestones and finalize the project plan during a meeting in September (see Timeline). This meeting is mandatory for the selected applicant(s). The final project plan is subject to review by the MS Society of Canada's Medical Advisory Committee (MAC) and approval by the MSSRF. Upon approval, the successful applicant will be advised of the term and amount of the grant awarded, and a letter of agreement will be issued and fully executed prior to the release of funds. Applicants who were not selected will also be notified following review.

Timeline

- RFA launch: June 15, 2015
- Q&A teleconference with Dr. Brenda Banwell: July 7 at 16:00-17:00 EDT and July 23 at 11:00- 12:00 EDT ~~and July 29 July 7 at 16:00-17:00 EDT~~. * The July 29th teleconference has been rescheduled for July 7th at 16:00-17:00 EDT. Click here for country dial in details, Passcode: 548692
- Deadline for applications: August 7, 2015 at 16:00 EDT
- Notification of selected applicant: September 2, 2015
- Meeting with Lead Team and finalize project plan: September 21, 2015 *****
- Notification of approval: November 18, 2015
- Anticipated project start date: December 1, 2015

*** This meeting is mandatory for the selected applicant(s)**

Support

For any questions or assistance, please contact:

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About the MSSRF

The MS Scientific Research Foundation was established in 1973 with an initial investment of $1,000. Over the years with financial support primarily from generous donations to the MS Society of Canada, the Foundation has become the largest fund in the world dedicated strictly to MS research. The goal for the Foundation is to support innovative and transformative research in multiple sclerosis (MS) beyond the scope of the MS Society of Canada's regular granting program. In particular, the focus is on multi-site, interdisciplinary research studies which foster collaboration and accelerate fundamental advances in understanding and treating MS.

Appendix

Full Description of Canadian Pediatric Demyelinating Disease Study Overview

Resources and Description of Participants

Full list of PIs, Co-PIs and Collaborators

Lancet Neurology 2011; 10:436-45 Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study

Milestones Chart

~~Operating Grant~~ Policies and Program Guide *

***This is an international RFA, eligibility criteria may differ from documents provided.**